Chapter 20
Cell Cycle Regulation During Proliferation and Differentiation of Mammalian Muscle Precursor Cells

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Abstract Proliferation and differentiation of muscle precursor cells are intensively studied not only in the developing mouse embryo but also using models of skeletal muscle regeneration or analyzing in vitro cultured cells. These analyses allowed to show the universality of the cell cycle regulation and also uncovered tissue-specific interplay between major cell cycle regulators and factors crucial for the myogenic differentiation. Examination of the events accompanying proliferation and differentiation leading to the formation of functional skeletal muscle fibers allows understanding the molecular basis not only of myogenesis but also of skeletal muscle regeneration. This chapter presents the basis of the cell cycle regulation in proliferating and differentiating muscle precursor cells during development and after muscle injury. It focuses at major cell cycle regulators, myogenic factors, and extracellular environment impacting on the skeletal muscle.

20.1 Introduction

Precise control of the cellular proliferation, differentiation, and also cell death is vital for the proper embryonic and postembryonic development. Despite a great variety of cell types, they utilize the same molecular machinery governing both the cell cycle progression and withdrawal. However, in each cell type analyzed cell cycle can be specifically tuned and its machinery is influenced by tissue-specific factors. Reciprocally, timing and the expression of these factors are effectively controlled by the cell cycle regulators. These mutual interactions can be studied in rapidly proliferating and differentiating embryonic tissues and organs and also in those of adult organisms. Mechanisms governing proliferation and differentiation of skeletal muscle cells can be analyzed at the level of developing embryo, and

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importantly can also be pinpointed in adult organisms, by studying activation, proliferation, and differentiation of satellite cells. These cells can be forced to reentry cell cycle either after muscle injury or after their isolation and in vitro culture. Analyses of these adult cells allowed deciphering molecular mechanism governing the quiescence, proliferation, and differentiation of muscle precursor cells. Some of them are common for both embryonic and adult cells localized within the muscle. In this chapter, we focus on the processes governing the cell cycles and differentiation of mammalian cells. However, it has to be emphasized that vast amount of data originated from the experiments first performed using model organisms such as amphibian and birds, or even invertebrates, and then confirmed in mammals.

20.2 Molecular Basis of Cell Cycle Regulation

The ascent of the cell cycle studies dates to the time of discovery of the activity controlling meiotic maturation of Rana pipiens oocytes, termed as maturation promoting factor (MPF) or M-phase promoting factor (Masui and Markert 1971; Smith and Ecker 1971; Masui 2001). Soon it was demonstrated that MPF operates not only in amphibian, but also in murine oocytes (Balakier and Czolowska 1977), and controls meiotic as well as mitotic divisions (Rao et al. 1977; Sunkara et al. 1980). Biochemical nature of MPF has been exposed after cloning and characterization of yeast kinases cdc2 and CDC28, i.e., CDK1 (cyclin-dependent kinase 1; Hartwell et al. 1974; Hindley and Phear 1984; Simanis and Nurse 1986; Lee and Nurse 1987; Hartwell 1991) and discovering the first cyclin (Evans et al. 1983). In the years to follow, several other CDKs, cyclins, and their positive and negative regulators were identified, and their role in the staging of the cell cycle of various organisms and cell types was revealed (for a review see e.g., Wong 1996; Ciemerych and Sicinski 2005; Malumbres and Barbacid 2005; Umeda et al. 2005; Gubbels et al. 2008; Doonan and Kitsios 2009). In addition, it has been proved that homologues or orthologues of these crucial factors were present and operational in plant, fungal, and animal cells. As a result, the Sèvres standard[1] of the cell cycle was designed, and the role of the cell cycle regulators has been assigned.

20.2.1 Sèvres Standard of Mammalian Cell Cycle Regulation[1]

The majority of mammalian cell types, except the blastomeres that build the preimplantation embryo, are under the influence of extracellular signals, such as

[1]International Bureau of Weights and Measures, located in Sèvres (France), kept the measurement standards of the International System of Units (SI): the standard kilogram, atomic clocks, and other metrological devices. The phase "Sèvres standard" can be used to emphasize that the described phenomena can be considered as a typical ones.

hormones and growth factors, which are commonly described as mitogens. These factors determine whether the cell will continue to proliferate, differentiate, undergo apoptosis, become senescent, or withdraw from the cell cycle, i.e., become quiescent. Highly specialized cellular mechanisms control and impact on the cellular reactions.

Decisive role in the regulation of both the quiescent state and cell cycle initiation is played by the members of the pocket family proteins, i.e., retinoblastoma protein (pRb), p107, and p130 (Grana et al. 1998; Adams 2001). pRb binds and inactivates the members of E2F transcription factors family preventing the expression of genes encoding cell cycle factors responsible for the progression through and beyond G1 phase (Classon and Dyson 2001; Blais and Dynlacht 2004). The E2F transcription factor family includes the transcriptional activators such as E2F1, E2F2, and E2F3a and repressors, i.e., E2F4, E2F5, and E2F6 (De Falco et al. 2006). E2F7 and E2F8 are also described as inhibitory ones (Moon and Dyson 2008). Interestingly, E2F3 locus encodes not only E2F3a but also E2F3b transcription factor (Leone et al. 2000). Each of the E2Fs is regulated by different pocket protein family members, i.e., E2F1, E2F2, E2F3a, and E2F3b are associated with pRb; E2F4 and E2F5 preferentially bind p107 and p130. E2F6 and E2F7 form transcriptional repressor complexes, but they are not associated with any pocket proteins (Cobrinik 2005). To fulfill their function E2Fs have to interact with their specific cofactors, i.e., DP proteins (DP1 and DP2).

In consistence with its anti-proliferative role, pRb protein was also shown to be a major player in the regulation of cellular differentiation (e.g., Korenjak and Brehm 2005; De Falco et al. 2006). Changes in the extracellular environment that stimulate the cell to resume or continue the cell cycle result in the pRb inactivation (Fig. 20.1). Mitogens acting on the cell can activate intracellular pathways, e.g., mitogen-activated protein kinase (MAPK) pathway, which in turn may lead to the synthesis of D-type cyclins that bind and activate G1-phase-specific CDKs – CDK4 and CDK6 (CDK4/6) (Sherr et al. 1992; Xiong et al. 1992). It has to be remembered, however, that activation of CDKs requires not only their interaction with appropriate cyclin but also removal of inhibitory phosphorylation, which is mediated by Cdc25 phosphatase (Russell and Nurse 1987; Gabrielli et al. 1992), and additional phosphorylation catalyzed by CDK-activating kinase (CAK, Kaldis 1999). CDKs activation also requires the removal/destruction of specific inhibitors. Activity of G1 controlling CDK4/6 is negatively controlled by INK4 family members – $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$, and $p19^{INK4d}$ (Serrano et al. 1993; Hannon and Beach 1994; Quelle et al. 1995; Guan et al. 1996, Fig. 20.1). Other CDKs, such as those that control S and G2/M-phase, i.e., CDK2 and CDK1, are blocked by the CIP/KIP inhibitors – $p21^{CIP1}$, $p27^{KIP1}$, and $p57^{KIP2}$ (Harper et al. 1993; Polyak et al. 1994; Lee et al. 1995, Fig. 20.1). Interestingly, cyclin D–CDK4/6 complexes also interact with members of CIP/KIP family. However, in such configuration CDK4/6 complexes not only remain active but also, by titrating CIP/KIP inhibitors, positively influence activity of CDK2 (La Baer et al. 1997; Cheng et al. 1999; Sherr and Roberts 1999; Geng et al. 2001; Tong and Pollard 2001). Upregulation of CDK inhibitors can be induced by cellular stress, e.g., $p21^{CIP1}$ expression is induced by

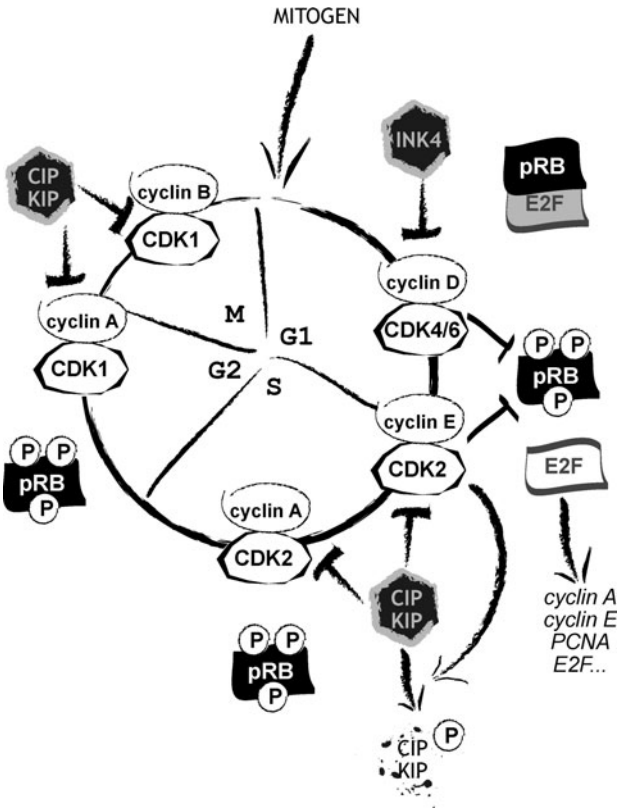

Fig. 20.1 Cell cycle regulation. Cell cycle progression is under control of periodically active cyclin–CDK complexes. During G0–G1 transition, in response to the mitogen stimulation, D-type cyclins become synthesized and activate CDK4/6, which phosphorylate and inactivate pRb. As a result, pRb releases E2F transcription factors and allows the transcription of cell cycle progression genes such as E- and A-type cyclin. In G1–S, E-type cyclins activate CDK2, further phosphorylate pRb, and also phosphorylate its own inhibitors CIP/KIP proteins, directing them for degradation and securing the S-phase progression. Further stages of S phase remain under control of cyclin A–CDK2 complexes, and initiation of M-phase requires the action of cyclin A-CDK1 and then cyclin B-CDK1. Upon degradation of A- and B-type cyclins, mitosis can be completed and the cell can either reenter the next cell cycle, or differentiate or become quiescent. In quiescent cells, CDK activity is negatively regulated not only by CIP/KIP inhibitors but also by the INK4 that inhibits CDK4/6

p53 transcription factor (Sharpless and DePinho 2002). Most importantly, however, expression of these inhibitors is characteristic for cell cycle withdrawal that accompanies cellular differentiation and can be mediated by the tissue-specific transcription factors.

Formation of active cyclin D–CDK4/6 complexes, which takes place during cell cycle reentry, leads to the phosphorylation and inactivation of pRb (Zarkowska and

Mittnacht 1997). Phosphorylated pRb is no longer able to interact and block E2F transcription factors (Fig. 20.1). As a result, E2F-dependent transcription of various cell cycle regulators, such as E-and A-type cyclins, is induced (Lees et al. 1993; Dimova and Dyson 2005). E-type cyclins interact and activate CDK2, which hyperphosphorylates pRb, further preventing its interaction with E2Fs (Lundberg and Weinberg 1998; Harbour et al. 1999; Fig. 20.1). Cyclin E-CDK2 also influences the function of its own regulators, i.e., it phosphorylates and activates Cdc25 phosphatase (Hoffmann et al. 1994), or marks its own inhibitor – $p27^{KIP1}$ for degradation (Sheaff et al. 1997; Furstenthal et al. 2001b). Among the targets phosphorylated by CDK2 are factors involved in the initiation of DNA replication (Krude et al. 1997; Arata et al. 2000; Zou and Stillman 2000; Furstenthal et al. 2001a; Geng et al. 2003, 2007), centrosome duplication (Okuda et al. 2000; Chen et al. 2002; Tarapore et al. 2002), or proteins required for histone biosynthesis, such as $p220^{NPAT}$ (Ma et al. 2000). During the further stages of the S-phase, CDK2 interacts with A-type cyclins (Fig. 20.1; Girard et al. 1991; Pagano et al. 1992; see also Fisher 2011), and by phosphorylating proteins involved in DNA replication, e.g., by Cdc6, these complexes play a crucial role in the regulation of their stability (Petersen et al. 1999; Coverley et al. 2000). At the G2–M transition cyclin A switches from CDK2 to CDK1 and controls the initiation of prophase (Furuno et al. 1999, Fig. 20.1). Notably, cyclin A degradation is a prerequisite step for the completion of the cellular division (Minshull et al. 1990; den Elzen and Pines 2001). Lastly, MPF, i.e., cyclin B-CDK1, directs various M-phase-associated processes such as reorganization of cellular cytoskeleton, cellular organella (e.g., Golgi cysterns), depolymerization of nuclear envelope lamina, formation of mitotic or meiotic spindle, or even chromatin condensation. Cyclin B degradation, leading to CDK1 inactivation, is required for the M-phase exit (see e.g., Gotoh et al. 2011). Importantly, not only timely activation and inactivation of CDKs, but all processes governing the cell cycle stages are precisely controlled by the checkpoint mechanisms ensuring proper completion of each of them and correction of possible mistakes (see de Medina Redondo and Meraldi 2011).

The real outbreak of the cell cycle studies, which also focused at cell cycle withdrawal during cellular differentiation, took place in the last two decades of the twentieth century. It resulted in a multitude of in vivo and also in vitro experiments involving analyses of various cells, including mammalian cell lines and tissues. Results of these projects led to the conclusion that many of major cell cycle regulators play indispensable role in the cell cycle progression. However, by the end of the twentieth century, due to the rapid development of molecular biology techniques allowing generation of genetically modified mice, crucial role of the vast majority of cell cycle regulators has been questioned (for a review, see e.g., Aleem et al. 2004; Sherr and Roberts 2004; Ciemerych and Sicinski 2005). Moreover, not only the redundancy of cell cycle regulators, but also the cell cycle modifications distinctive for specific cell types, such as embryonic cells, stem cells, or differentiating cells, have been revealed (see Momčilović et al. 2011).

20.2.2 Embryonic and Stem Cell Cycle Variants

"Sèvres standard" of the cell cycle described above *does* exist, but one has to be aware of the fact that each cell type can be portrayed by its custom tuned cell cycles. The cell cycles of early mammalian embryos can serve as one of the examples of the specific cell cycle machinery adjustment. During oogenesis maternal "information" (mRNAs and proteins) is synthesized and accumulated within the oocytes. However, majority of these factors become rapidly degraded at the two-cell stage of mouse embryo (Flach et al. 1982; Latham 1999). Thus, almost entire embryogenesis, except the one-cell stage, is governed by the products of embryonic genome. Interestingly, the maternal influence on the progression of the cell cycle of one-cell embryo seems to manifest in the specific regulation of the first mitotic division of such embryo. This particular mitosis, for yet unknown reasons, is as twice long as the second and the following ones (Ciemerych et al. 1999; Sikora-Polaczek et al. 2006; Kubiak et al. 2008), illustrating the notion that the tuning of the cell cycle regulation starts very early during mammalian development. Interestingly, preimplantation mammalian development occurs regardless of the presence of extracellular mitogens. Starting from the one-cell stage (zygote) up to blastocyst stage embryo can be cultured in the serum-free medium. The growth factor independency of cell cycles was shown to be possible due to the lack of the expression of pRb. Maternal stores of this protein become degraded at the early two-cell stage, and then its expression is resurrected at the blastocyst stage, i.e., at the time when embryo is about to implant and start differentiation processes (Iwamori et al. 2002). Moreover, these early cell cycles seem to be independent of p53 and $p21^{CIP1}$, what might be a part of the mechanism ensuring the unperturbed and environment-independent cleavage divisions of preimplantation embryo. Again, p53 and $p21^{CIP1}$ become important regulatory factors at the time of blastocyst implantation (Adiga et al. 2007a, b; Artus and Cohen-Tannoudji 2008; Houlard et al. 2009).

Preimplantation mouse embryo is not the only example of the cell cycle independency from pRb. It was also documented by the analyses of the embryonic stem cells (ES cells), which originate from inner cell mass, i.e., pluripotent cells, of blastocyst. These cells are characterized by very rapid cell cycles that take approximately 10 h (see Wang and Blelloch 2011). Similarly to preimplantation mouse embryo, also ES cell cycles are deficient of pRb activity. However, in contrast to embryos that cells fail to express pRb, this protein was shown to be synthesized by ES cells, but kept in the hyperphosphorylated, i.e., inactive, state (Savatier et al. 1994; Conklin and Sage 2009). Interestingly, lack of all three members of pocket proteins family, i.e., pRb, p107, and p130, does not influence the ES cell cycle progression (Dannenberg et al. 2000; Sage et al. 2000), strongly suggesting that this axis of cell cycle regulation is dispensable. In consequence, E2F-dependent genes, such as cyclins A and E, are stably expressed, which results in the lack of CDK2 activity oscillations (Stead et al. 2002; White and Dalton 2005). Moreover, ES cell cycles were suggested to occur either independently of cyclin D–CDK4/6 complexes (Savatier et al. 1996), or at least to be regulated by only one unique kinase, i.e., cyclin D3-CDK6, which in addition was shown to be resistant to $p16^{INK4a}$ inhibition (Faast et al. 2004). It seems highly

possible that these "special" cellular machinery modifications adapt ES cells to efficient propagation. Importantly, induction of ES cell differentiation "reverses" the cell cycle regulation to the canonical one, i.e., cyclin D expression rises and CDK4 activity becomes resurrected (Savatier et al. 1996), pRb status changes, and the expression of E2F-dependent targets, and their activity, resume oscillatory pattern (White and Dalton 2005; White et al. 2005).

In contrast to rapidly proliferating pluripotent ES cells, majority of the cells that underwent differentiation remain quiescent. This state is sustained by the high levels of hypophosphorylated pRb, INK4, and CIP/KIP inhibitors. However, along with quiescent terminally differentiated cells almost every mammalian tissue was shown to contain the subpopulation of so-called somatic stem cells. These cells are long living, retaining ability to self-renew, and thus, are essential for the renewal of the tissues in adult organisms. In contrast to embryonic cells and ES cells, somatic stem cells divide rarely and are predominantly found in the quiescent state (Cotsarelis et al. 1990; Potten et al. 1997; Li and Clevers 2010). Well-studied examples of adult stem cells are hematopoietic stem cells (HSCs). Different subpopulations of HSCs were reported to divide with various frequencies, e.g., very rarely every 4–5 months (Wilson et al. 2008; Foudi et al. 2009) or more frequently (Cheshier et al. 1999; Kiel et al. 2007). Skin stem cells divide every 200 h, and intestine epithelium, as being one of the "fastest" adult stem cells, every 9–10 h (Fuchs 2009; Li and Clevers 2010). Besides being able to constantly self-renew, adult stem cells are also ready to respond to the environmental cues and to differentiate. To avoid the abnormal development of tissues they reside in, the interplay between stem cell "machinery" controlling the cell cycle progression and differentiation has to be finely tuned. The well-studied examples of such tuning are processes associated with cellular proliferation and differentiation during embryonic and adult myogenesis.

20.3 Cell Cycle and the Developing Skeletal Muscle

Strict control of cell proliferation is particularly crucial for proper development of tissues and organs during embryogenesis. Formation of functionally and morphologically correct structures depends on the balance between sufficient propagation of precursor cells and their differentiation. During muscle development, first muscle precursor cells are singled out, and then satellite cells that can be considered as muscle stem cells are generated from them. Due to their ability to persist, self-renew within the adult muscle, and activate in response to the environmental changes, satellite cells are one of the excellent examples of the precisely tuned balance between quiescence, proliferation, and differentiation.

20.3.1 Outline of Mouse Embryo Myogenesis

In vertebrates nearly all body muscles are derived from epithelial structures, i.e., somites that are formed by segmentation of paraxial mesoderm localized along

axial structures of a developing embryo. During mouse embryogenesis, this process starts at approximately 8th day postcoitum (dpc) and is followed by gradual differentiation of somites into compartments containing precursor cells for several tissues and organs. Dorsal part of the somite develops into dermomyotome that will give rise to skeletal muscles, connective tissue of the skin, and to endothelium and smooth muscles of some blood vessels (Kardon et al. 2002; Ben-Yair and Kalcheim 2005). In many different groups of vertebrates, from amphibians to birds and mammals, specification and then determination of skeletal muscle cells are induced by signals released by structures adjacent to somites, i.e., notochord, neural tube, and embryonic ectoderm (Bryson-Richardson and Currie 2008). In response to Sonic Hedhehog (Shh) synthesized by notochord, or Wingless proteins (Wnts) secreted by neural tube and dorsal ectoderm, dermomyotome cells start to express the first markers of muscle precursor cells, i.e., Pax3 and Pax7 transcription factors. Shh itself is one of the very few factors that have been shown to influence proliferation of myogenic cells in mammals and other vertebrates such as birds. Experiments performed by Duprez et al. revealed that Shh increases proliferation rate of myogenic cells leading to hypertrophy of muscle in chick embryos (Duprez et al. 1998). The possible role of Shh as a regulator of cell divisions was further indicated by the phenotype of Shh-deficient mice. These mutants were characterized by the lack of both epaxial (associated with the vertebrae, ribs, and base of the skull) and hypaxial (abdominal and limb) muscles (Chiang et al. 1996). During unperturbed development Shh was shown to be involved exclusively in the formation of epaxial muscles; thus, ablation of hypaxial ones might result from decreased proliferation of precursor cells, as suggested by Parker et al. (2003). It has also been shown that Shh promotes cell division of muscle cells in adults (Koleva et al. 2005; Elia et al. 2007). Administration of cyclopamine, a specific chemical inhibitor of the Shh pathway, influences proliferation of primary cultures of satellite cells and myoblasts isolated from both chick and mouse. In regenerating muscles, inhibition of Shh pathway leads to reduced number of satellite cells at injury site, impaired activation of MyoD and Myf-5, and decreased level of IGF-I (Straface et al. 2009).

Various Pax proteins control development of many lineages during embryogenesis (Buckingham and Relaix 2007). Two of them, Pax3 and Pax7, are the key regulators of skeletal muscle formation, acting as the master regulators of this process. Despite that their myogenic role was analyzed in many studies (Maroto et al. 1997; Tajbakhsh et al. 1997; Borycki et al. 1999; Seale et al. 2000; Ridgeway and Skerjanc 2001; Relaix et al. 2004; Bajard et al. 2006; Buckingham and Relaix 2007), Pax3 and Pax7 target genes have only started to be identified (McKinnell et al. 2008; White and Ziman 2008; Sato et al. 2010). Among Pax3 and Pax7 direct or indirect targets are transcription factors known as early myogenic regulatory factors, e.g., Myf-5, MyoD (Tajbakhsh et al. 1997; McKinnell et al. 2008; Collins et al. 2009; Sato et al. 2010). In the mouse embryo, Pax3 is initially expressed in newly formed somites and then become restricted to dermomyotome, while Pax7 appears later in the central part of this compartment (Jostes et al. 1990; Goulding et al. 1994; Williams and Ordahl 1994; Buckingham and Relaix 2007). Expression of Pax genes is subsequently followed by the synthesis of factors responsible for

determination of the cell fate and the onset of myogenesis, i.e., MyoD and/or Myf-5 (Sassoon et al. 1989; Ott et al. 1991), which together with myogenin and MRF4 (Myf-6) belong to the MRFs. The common feature of MRFs is the presence of bHLH (basic helix-loop-helix) domain enabling their heterodimerization with E proteins (Olson and Klein 1994). In general, complexes of MRF and E protein regulate myogenic differentiation by recognizing and binding to E-box consensus sequences (CANNTG) present within the promoters of genes encoding muscle-specific proteins, such as myosin heavy chains (MyHCs) or muscle creatinin kinase (MCK) (Olson 1992; Olson and Klein 1994). Experimental overexpression of MRFs was shown to induce myogenic differentiation program and convert various types of cells into myogenic cells, including differentiated ones, such as neurons, chondroblasts, and fibroblasts (Braun et al. 1989; Edmondson and Olson 1989; Weintraub et al. 1989, 1991; Choi et al. 1990; Miner and Wold 1990; Lattanzi et al. 1998). Myotubes derived from MyoD-converted chondroblasts and fibroblasts were identical if compared to myotubes obtained from cells isolated from breast muscles, including localization of muscle sarcomeric proteins such as alpha-actinin, titin, MyHCs, and others (Choi et al. 1990). However, overexpression of MyoD, Myf-5, MRF4, and myogenin in NIH3T3 fibroblasts did not result in the full conversion into multinucleated myotubes (Russo et al. 1998). Thus, exogenous expression of MRFs can induce myogenic conversion of different cell lines, however, with variable success (see Sect. 20.4).

In dermomyotome, expression of Myf-5 has been shown to be induced by Pax3 via engagement of Dmrt2 transcription factor (Sato et al. 2010). Besides Myf-5, MyoD has also been identified as a target for both Pax3 and Pax7, emphasizing the role of Pax genes in orchestrating the progression from undifferentiated toward determined and then differentiating cell (Bajard et al. 2006; Hu et al. 2008; McKinnell et al. 2008). Expression of MyoD or Myf-5 induces the cells localized within dermomyotome to migrate downward and create the cellular layer called myotome (Parker et al. 2003). Once they become localized within the myotome, they stop to divide. Myotome, however, continues to extend gradually due to proliferation of cells localized in the medial part of dermomyotome, which do not activate expression of MRFs, but instead maintain synthesis of Pax3 and Pax7, and as a result of it continue dividing (Kassar-Duchossoy et al. 2005; Relaix et al. 2005). Besides Pax3- and Pax7-positive cells, precursor cells are also present in the hypaxial part of dermomyotome, localized at the level of forming limb buds. These cells retain ability to proliferate due to inhibition of Pax3-mediated expression of MyoD (Bendall et al. 1999). Divisions of these precursor cells enable their sufficient propagation during migration and homing within limb buds, where they undergo differentiation (Birchmeier and Brohmann 2000).

As it was signalized above, Pax3 influences proliferative state of muscle precursor cells. So far this factor is the best recognized regulator of muscle cell proliferation. Downregulation of Pax3 expression in dermomyotome of chick embryos resulted in the cell cycle arrest of muscle precursors (Amthor et al. 1999) and also led to the reduction of precursor cells population in dermomyotomes of mice lacking Pax3 (Franz and Kothary 1993). Importantly, Pax3 activity is crucial for the

survival of precursor cells migrating from dermomyotome toward limb buds (Bober et al. 1994; Goulding et al. 1994; Williams and Ordahl 1994). Linkage between Pax3 activity and cell proliferation was further supported by the fact that chromosomal translocation resulting in fusion of DNA binding domain of Pax3 or Pax7 genes with transcriptional activation domain of FOXO1a (FKHR) leads to uncontrolled division of the muscle cells and development of rhabdomyosarcomas (Barr 2001). Moreover, constitutive expression of Pax3 or Pax7 in in vitro cultured myoblasts results in their extensive proliferation; however, the mechanism of this phenomenon remains unknown (Collins et al. 2009). Identification of Pax3/Pax7 targets by microarray analyses (Khan et al. 1999; Mayanil et al. 2001; White and Ziman 2008) will undoubtedly help to understand how these proteins influence the cell cycle machinery.

Muscle precursor cells that reach the limb buds start to express MyoD approximately at 10.5 dpc, while Myf-5 is expressed between 10th and 12th dpc (Ott et al. 1991). In the meantime, cells present within the myotome undergo final differentiation manifested by their fusion and formation of multinuclear myotubes, and subsequently skeletal muscle fibers. During mouse embryo development, first wave of fiber formation is observed between 11th and 14th dpc and is followed by the formation of secondary fibers taking place between 14th and 16th dpc. Fiber formation remains under control of so-called late MRFs, i.e., myogenin and MRF4, as, for example, myogenin-null mice are characterized by the lack of secondary fibers, which is a consequence of myoblasts' inability to differentiate and fuse to each other (Venuti et al. 1995). The population of Pax3- and Pax7-positive cells, initially localized in the middle part of dermomyotome, which enters the myotome around 10th day of development, will serve as a source of skeletal muscle progenitor cells (Kassar-Duchossoy et al. 2005; Relaix et al. 2005). During the later stages of myogenesis progeny of these cells, characterized by the expression of Pax7, localize between muscle fibers and surrounding basal lamina (Kassar-Duchossoy et al. 2005; Relaix et al. 2005), and become satellite cells, i.e., so-called muscle stem cells, responsible for their growth and regeneration in adult organisms.

20.3.2 Some Lessons on Myogenesis from the Cell Cycle Mouse Mutants

Successful progression of myogenesis depends, to a great extent, on the unperturbed proliferation on muscle precursor cells, securing the generation of the sufficient pool of cells that will next differentiate into muscle fibers. Not surprisingly, interplay between cell cycle regulators, Pax proteins, and/or MRFs has to be perfectly tuned. Important lessons on the role of the cell cycle regulators in myogenesis were learned from experiments involving manipulation of the levels of cell cycle regulators in in vitro growing cells (see Sect. 20.4) or analyses of the mutant mice lacking genes encoding crucial elements of cell cycle machinery.

The role of pocket protein family member pRb in the differentiation of skeletal muscles has been documented by many studies, including analyses of knockout mice. Initial experiments leading to the generation of pRb-null mice showed that deletion of this gene causes embryonic lethality between 12th and 15th dpc, i.e., prior to the stage of terminal muscle differentiation (Clarke et al. 1992; Jacks et al. 1992; Lee et al. 1992; Morgenbesser et al. 1994). Two approaches allowed uncovering the role of pRb in muscle development. First one based on the observation that pRb-null embryos die due to severe anemia that might by caused by the placental abnormalities. Experiments involving "tetraploid complementation" technique allowed to generate mutant embryos developing within wild-type, i.e., "healthy," placentas (Wu et al. 2003). Second approach is based on the "construction" of conditional pRb knockout mice (de Bruin et al. 2003). Both experiments lead to the full-term development of pRb-deficient mice, i.e., long enough to allow the manifestation of the defects in skeletal muscle development. The rescued embryos were characterized by the presence of hypoplastic myofibers in several muscle types analyzed (intercostal and limb muscles, diaphragm, and tongue; de Bruin et al. 2003). Moreover, analyses of mice carrying pRb hypomorphic minigene, i.e., expressing low levels of pRb, uncovered similar phenotypes – dispersed myotubes within intercostal muscles (Zacksenhaus et al. 1996). In developing muscles of these mutant mice, myoblasts were undergoing apoptosis or aberrant DNA replication before they were able to initiate terminal differentiation. Myotubes were shorter, less abundant, contained fewer myofibrilles, and fail to express MRF4 (Zacksenhaus et al. 1996). Thus, on the basis of their own results, and experiments conducted by others, the authors concluded that in the absence of pRb terminal withdrawal from the cell cycle is obstructed, resulting in apoptosis or abnormal DNA endoreduplication (Zacksenhaus et al. 1996). However, they also noted that even in the absence of pRb some myogenic precursor cells (MPCs) are able to undergo activation and differentiate into myotubes. Moreover, myoblasts derived from pRb-null ES cells failed to preserve their terminal differentiation, i.e., nuclei present within the myotubes were able to resume DNA synthesis after mitogen stimulation (Clarke et al. 1992; Schneider et al. 1994).

Also p130 was suggested to play a role in the regulation of myogenesis. Histological analyses of 10.5 dpc p130-null embryos showed that they were characterized by the reduced number of myocytes within the differentiating myotome. However, this phenotype was only manifested when mutant mice were generated in Balb/cJ genetic background. C57BL/6J p130-deficient mice were viable with no detectable defects in myogenesis (LeCouter et al. 1998). Thus, it is likely that lack of pRb can be compensated by p107 and p130. However, possibility of such "replacement" could not be tested using mouse model due to the fact that double knockout mice, i.e., lacking pRb and p107, or pRb and p130, die at 11.5 dpc (Lee et al. 1996). However, experiments on triple knockout ES cells underscored the crucial role of pRb, p107, and p130 in the cellular differentiation (Dannenberg et al. 2000; Sage et al. 2000). Unlike wild-type ES cells that are introduced subcutaneously into nude mice differentiate into variety of cell lines including myoblasts, $pRb^{-/-}p107^{-/-}p130^{-/-}$ ES cells were able to differentiate only into primitive neuronal cells and

never gave rise to myoblasts (Dannenberg et al. 2000). Defects in muscle development were also manifested in mice lacking pRb and E2F1 (Tsai et al. 1998), or pRb and E2F3 (Ziebold et al. 2001). Concomitant deletion of E2Fs and their repressor, i.e., pRb, led to the prolonged survival of such double mutant embryos, and again allowed the demonstration of "muscle phenotype" of pRb-null mice.

Other players that were shown to be involved in the regulation of myogenic differentiation are the members of the Id family. They also carry bHLH domain and inhibit E proteins or MyoD–E protein complexes from binding DNA (Benezra et al. 1990a; Christy et al. 1991; Sun et al. 1991; Melnikova and Christy 1996). In particular, Id1 was shown to be a potent negative regulator of MyoD (Benezra et al. 1990b; Jen et al. 1992; Katagiri et al. 2002) and also to prevent the expression of $p21^{CIP1}$ (Prabhu et al. 1997). Besides Id1, Id2 was also shown to be synthesized in myogenic cells and to regulate their proliferation (Zhao and Hoffman 2004). Id2 ablation rescued the pRb phenotype, i.e., prolonged survival of mutant mice and influenced myogenesis, once again revealing crucial role of pRb in muscle development (Lasorella et al. 2000). It should be also mentioned that Id2 plays a role in the placental development (Janatpour et al. 2000); thus, it is possible that observed rescue can be attributed to the genetic interactions between pRb and Id2 within this organ.

The crucial role of pRb revealed during the analyses of various mice mutants has been emphasized by number of other studies, which documented that participation of pRb in myogenesis relies on its ability to bind crucial MRFs, i.e., myogenin and MyoD, as well as other transcription factor, MEF2 (myocyte enhancer factor; Gu et al. 1993; Novitch et al. 1996, 1999; Huh et al. 2004). Interestingly, reciprocal interactions between pRb and MRFs were also documented. MyoD was shown to induce the expression of pRb, and also of $p21^{CIP1}$, which ensures the effective cell cycle exit of the differentiating myoblasts (Martelli et al. 1994; Halevy et al. 1995; Rao and Kohtz 1995; de la Serna et al. 2001; Magenta et al. 2003). However, as mice lacking $p21^{CIP1}$ do not reveal any malfunctions in myogenesis, it is possible that $p21^{CIP1}$ can be replaced by other CDK inhibitors, i.e., $p27^{KIP1}$ or $p57^{KIP2}$ (Zabludoff et al. 1998; Zhang et al. 1999b). It has to be stressed that interaction between MyoD and pRb is crucial for proper expression of genes controlling formation of myotubes and fibers during final stages of differentiation (Gu et al. 1993; Novitch et al. 1996). However, more importantly, pRb displaces histone deacetylases (HDACs) from MyoD, enabling MyoD-dependent transcription and progress of differentiation in muscle cells (Puri et al. 2001; see Sect. 20.3.3). Differentiation promoting function of pRb was also shown to be associated with its ability to negatively regulate Ras activity (Lee et al. 1999; Takahashi et al. 2003). Importantly, the activity of MyoD was shown to be influenced by the Ras-family members, e.g., N-ras (Kong et al. 1995; Ramocki et al. 1997, 1998), and the interplay of N-ras, MyoD, and pRb was emphasized during the analysis of yet another mutant mice. Loss of N-ras resulted in the significant rescue of skeletal muscle development of pRb-null embryos (Takahashi et al. 2003).

The other cell cycle regulators that impact on the myogenic differentiation are D-type cyclins, which in addition to their growth promoting function play unique

roles in differentiation of specific cell types. The best studied so far is cyclin D1, the role of which in the regulation of transcription and differentiation of various tissues, e.g., retinas or mammary glands, is very well documented (Bienvenu et al. 2001, 2010). As far as differentiation of myoblasts is concerned, several lines of evidence engage D-type cyclins in this process. Differentiation of muscle cells is accompanied by the decrease in cyclin D1 level (Skapek et al. 1995; Guo and Walsh 1997). Analysis of mouse embryos documented that developing muscles express almost exclusively cyclin D3, but not D1 or D2 (Ciemerych et al. 2008). Expression of this cyclin is dramatically induced when myoblasts exit the cell cycle and fuse into myotubes (Kiess et al. 1995; Cenciarelli et al. 1999). Interestingly, cyclin D3 fails to accumulate in pRb-null myoblasts, in which it is subjected to rapid degradation (Cenciarelli et al. 1999). In wild-type mice, however, it was shown to associate with hypophosphorylated form of pRb and as a result to escape GSK3β-mediated phosphorylation, which is a prerequisite step for its degradation in proteosome (De Santa et al. 2007). pRb and cyclin D3 interaction was also proven to be crucial for the proper regulation of myogenic differentiation (Mariappan and Parnaik 2005). However, there is no hard data coming from the analyses of cyclin D-null mice proving their indispensability for the proper progression of myogenesis. Nevertheless, multiple lines of evidence coming from in vitro studies prove importance of this protein in the myoblast proliferation and differentiation (see Sect. 20.4).

20.3.3 Epigenetic Regulation of Proliferation and Differentiation of Muscle Precursor Cells

During myogenic differentiation, MyoD activates expression of several muscle-specific genes necessary for the myoblasts fusion and myotubes formation, such as myogenin or M-cadherin, and those responsible for generating force by skeletal muscles, such as MyHCs (Berkes and Tapscott 2005). For that reason, to prevent premature and uncontrolled differentiation of myoblasts, activity of MyoD must be inhibited in proliferating cells. The exact mechanisms leading to inhibition of MyoD activity still remain unclear. It is assumed, however, that inductive molecules/environmental cues released during embryogenesis, or serum-derived growth factors present in in vitro culture, activate some crucial cell cycle regulators (see Sect. 20.5). However, reciprocal interactions between MyoD and cell cycle machinery are much more complicated than presented so far. It is clear that the central role of MyoD in controlling these processes is possible only by its cooperation with many additional modulators. Despite a great gap in our knowledge, some of them have been already identified and characterized.

Activation or repression of any of the genes depends on chromatin conformation within these genes and surrounding sequences. Chromatin relaxation enabling gene expression is achieved inter alia by histone acetyltransferases (HATs) and chromatin remodeling factors such as SWI/SNF complex. While transferring acetyl groups

to lysine residues of histones increases transcription factors' access to DNA, activity of HDACs leads to the suppression of chromatin structure and repression of transcription (Strahl and Allis 2000). Modification of histones by methylation/demethylation also influences chromatin conformation and modulates its interactions with transcriptional machinery. Histone modifying enzymes, together with chromatin remodeling complexes, are engaged in the regulation of expression of genes encoding both cell cycle regulators and muscle-specific factors. Results of in vitro experiments documented that in proliferating C2C12 myoblasts, MyoD remains bound to HDACs and hence is unable to heterodimerize with E proteins and to drive transcription of muscle-specific genes such as MyHCs (Mal et al. 2001, Fig. 20.2). HDACs also inhibit the activity of MEF2 transcription factors that serve as MyoD cofactors and are crucial for the induction of MyoD-dependent transcription (Gossett et al. 1989; Molkentin et al. 1995; Dressel et al. 2001; McKinsey et al. 2001). In addition, in proliferating myoblasts, dimers of MyoD and HDACs are found within promoters of some genes normally expressed during myogenic differentiation, such as genes encoding myogenin or acetylcholine receptor (Liu et al. 2000; Mal and Harter 2003; Fig. 20.2). It is believed that expression of such genes is inhibited by HDACs activity before the onset of differentiation by deacetylation of histones within their regulatory regions and conversion of chromatin to transcriptionally silent form (Sartorelli and Caretti 2005).

Apart from HDACs chromatin repression is also sustained by the activity of histone methyltransferases (Fig. 20.2), such as Ezh2 (Enhancer of zeste homologue 2), of Polycomb family that methylates lysine 27 of histone H3 (H3K27) (Caretti et al. 2004). However, in proliferating myoblasts, unique pattern of deacetylation and methylation of repressed genes does not exist, as for example, promoter of repressed myogenin gene is characterized by methylation of lysine 9, while methylation of lysine 27 is detected within promoters of transcriptionally inactive MCK and MyHCs genes (Zhang et al. 2002; Caretti et al. 2004). As suggested by Forcales and Puri, distinct pattern of modifications within regions encoding genes and/or regulatory sequences repressed in proliferating myogenic cells may serve as an "indicator" for their proper expression during subsequent differentiation. In other words, genes that will be expressed earlier in differentiating myogenic cells (such as myogenin) are "marked" differently than those expressed at later stages of differentiation (such as MyHCs or MCK; Forcales and Puri 2005).

During myogenic differentiation, activation of many genes crucial for proper progression of this process is possible only after MyoD-mediated recruitment of chromatin-relaxing factors such as HATs, and chromatin remodeling complexes, for example SWI/SNF (Puri et al. 1997a, b; Sartorelli et al. 1999; de la Serna et al. 2001; Simone et al. 2004; Fig. 20.2). In differentiating myoblasts and myotubes, MyoD is found in a complex with p300 and PCAF acetylases being stably associated with muscle-specific genes. It is considered that recruitment of HATs by MyoD to its target genes leads to histone acetylation within such regions and subsequent expression of modified genes (Sartorelli and Caretti 2005). Presence of p300 and PCAF acetylases together with SWI/SNF complex is also necessary for the expression of pRb gene driven by MyoD in differentiating muscle cells

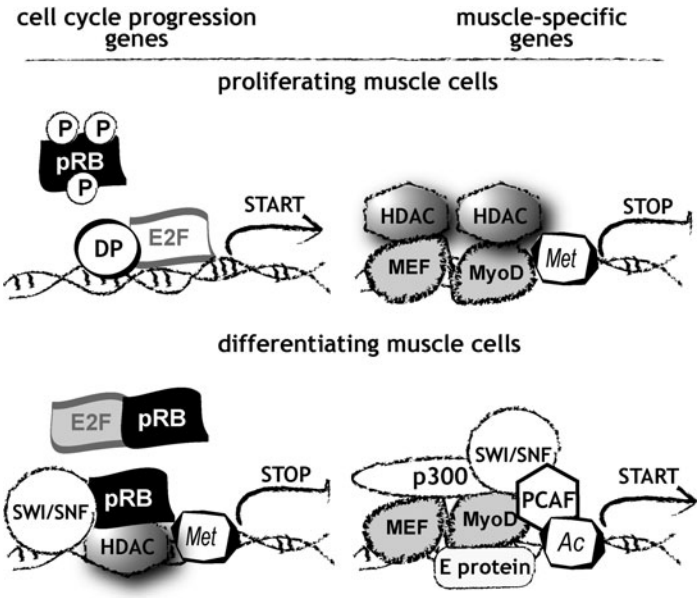

Fig. 20.2 Epigenetic regulation of gene expression in proliferating and differentiating muscle cells. In proliferating muscle cells, activation of muscle-specific genes is inhibited, while cell cycle progression genes are expressed. MyoD and MEF, cofactors necessary for MyoD-dependent transcription, stay bound to HDAC, and as a result remain inactive. Activity of HDAC leads to deacetylation of histones within muscle-specific genes preventing transcription of such modified DNA regions. Expression of muscle-specific genes is also repressed by the activity of histone methyltransferases (Met) converting chromatin into transcriptionally silent form. As a result of CDKs' action, pRb is hyperphosphorylated, and thus, becomes inactive and unable to bind E2F transcription factors. Active E2F/DP complexes promote expression of cell cycle progression genes. In differentiating muscle cells, activated pRb binds to E2F preventing transcription of cell cycle regulators. pRb also induces repression of these genes by recruitment of HDAC and SWI/SNF complex that together convert chromatin into transcriptionally inactive form. In contrast, chromatin within muscle-specific genes is relaxed due to activity of histone acetylases (HATs), such as p300 and PCAF, and chromatin remodeling complexes, such as SWI/SNF, all recruited by MyoD. Binding of MyoD–E protein dimers, together with MEF transcription factors, leads to the expression of muscle-specific genes

(Martelli et al. 1994; Magenta et al. 2003). Modulation of the action of p300, PCAF, or components of SWI/SNF complex by specific antibodies was performed in differentiating myoblasts or MyoD-overexpressing fibroblasts. It resulted in inhibition of MyoD-dependent expression of both pRb and muscle-specific genes, such as myogenin, MCK, and MyHCs (Eckner et al. 1996; Simone et al. 2004). Besides histones, MyoD was also shown to be a substrate of PCAF acetylase. Modification of MyoD by PCAF increases its transcriptional activity (Puri et al. 1997a, b; Sartorelli et al. 1999; Fig. 20.2).

As mentioned above, MyoD induces expression of pRb gene during myogenic differentiation. In return, active pRb releases MyoD from HDAC inhibition and

facilitates its interactions with MEF2, thereby promoting MyoD-dependent transcription (Gu et al. 1993; Novitch et al. 1999; Puri et al. 2001). However, the most important role of pRb is played through its interactions with E2F transcription factors (Macaluso et al. 2006), as described above. pRb was also shown to inhibit the expression of E2F target genes by the relocation of HDACs to such sequences, induction of histone deacetylation, and repressive chromatin conformation (Shin et al. 1995, Fig. 20.2). Repression of cell cycle genes is also achieved by pRb via recruitment of Ezh2 methyltransferase and/or SWI/SNF complexes to their promoters (Dunaief et al. 1994; Strober et al. 1996; Blais et al. 2007, Fig. 20.2). Activity of Ezh2 was shown to prevent expression of genes encoding CDK2 as well as MCM3 and MCM5, i.e., proteins that are crucial for proper DNA synthesis (Blais et al. 2007). Inhibition of transcription is achieved via Ezh2-processed trimethylation of lysine 27 of histone 3 (H3K27Me3) leading to repression of chromatin within modified region (Blais et al. 2007). Depletion of pRb in terminally differentiated myotubes by siRNA results in erasure of H3K27Me3 modifications, followed by reexpression of cell cycle genes such as CDK2, MCM3, MCM5, or BRCA1 and cell cycle reentry (Blais et al. 2007). Therefore, pRb plays a dual role during myogenic differentiation progression acting as both a repressor of cell cycle gene transcription and a coactivator of the muscle-specific gene expression, as it was shown that the lack of pRb results in perturbed expression of MyHCs and MCK genes, and impaired myoblasts fusion (Gu et al. 1993; Novitch et al. 1996).

Presented examples indicate interplay between cell cycle machinery, genes regulating differentiation of muscle cells, and epigenetic factors involved in the regulation of both these processes. Undoubtedly, the central role in triggering both cell cycle arrest and myogenic differentiation is played by MyoD. Surprisingly, mice devoid of this factor do not reveal any serious malfunctions of embryonic myogenesis, probably due to compensation by Myf-5 (Rudnicki et al. 1992; Kablar et al. 1999). However, lack of MyoD is manifested in adults, as satellite cells isolated from such mice are characterized by abnormalities in both the cell cycle withdrawal and myogenic differentiation (Sabourin et al. 1999; Yablonka-Reuveni et al. 1999).

20.4 Quiescence, Cell Cycle Reentry, and Differentiation of Adult Skeletal Muscle Precursor Cells

20.4.1 Satellite Cells and Their Function in Muscle Regeneration

Satellite cells were first identified by Mauro and Katz in 1961 (Katz 1961; Mauro 1961). In adult skeletal muscle, they remain quiescent until appropriate signals, e.g., injury or disease caused degeneration, induce them to reenter the cell cycle (Charge and Rudnicki 2004). Satellite cells, localized between myofiber and basal

lamina (Schultz et al. 1978), consist 3–8% of muscle nuclei (Schmalbruch and Hellhammer 1976, 1977; Gibson and Schultz 1982). After muscle injury they undergo activation, the first manifestation of which is the cell cycle reentry. At this stage, they are usually described as MPCs or myoblasts. Satellite cells number decreases with age, however, usually remains sufficient to support effective regeneration of muscles of healthy individuals (Renault et al. 2002; Shefer et al. 2006; Day et al. 2010). The decline in the cell number and their proliferative capacity is drastically enhanced in certain pathologies, such as muscular dystrophies. One of the intensively studied example of dystrophies is Duchenne muscular dystrophy (DMD) (Decary et al. 2000), which is caused by mutation in the gene coding dystrophin, i.e., protein responsible for linking myofiber cytoskeleton with basal lamina (Ryder-Cook et al. 1988; Sicinski et al. 1989; Emery 2002). Analyses of satellite cell number in the best-studied animal model of DMD, i.e., mdx mice, carrying mutation in dystrophin gene, revealed dramatic decrease in injured and regenerating skeletal muscles (Reimann et al. 2000). Thus, in the case of dystrophies, the population of satellite cells might be prematurely exhausted causing inability to regenerate the skeletal muscle and premature death (Chamberlain et al. 2007).

Our current knowledge on the progression of skeletal muscle regeneration allows clear description of the MPCs behavior during subsequent stages of this process. Briefly, skeletal muscle reaction to the injury covers satellite cell activation, intensive proliferation, differentiation, i.e., formation of first myotubes, and subsequently muscle fibers. Myoblasts' differentiation and fusion into myotubes, i.e., their terminal differentiation, are associated with the cell cycle withdrawal. Throughout the process of muscle regeneration, some of the proliferating myoblasts are "left aside," i.e., do not fuse, but localize within the specific niches, become quiescent, and as a result renew the satellite cells pool. The mechanisms controlling the choice between being cells that regenerate the muscle and that "regenerate" the satellite cell population are not precisely described yet. Also, the factors that control the satellite cell activation and influence the temporal expression of cell cycle regulators responsible either for cell cycle reentry or withdrawal are only partially understood.

Since the identification of satellite cells, many different approaches of analysis of their quiescence, cell cycle reentry, and differentiation have been designed. Among the "materials" that are intensively studied are in vitro cultured single myofibers (Rosenblatt et al. 1995; Rossi et al. 2010), satellite cells/MPCs isolated from skeletal muscles (Foucrier et al. 1999), and various cell lines, such as L8 (Yaffe and Saxel 1977a) and C2C12 (Yaffe and Saxel 1977b; Blau et al. 1985). Another approach covers the in vivo analyses involving skeletal muscle injury leading to satellite cell activation (Zimowska et al. 2001; Moraczewski et al. 2008; Brzoska et al. 2009), or various mouse models (e.g., mdx and SMN) (Banks and Chamberlain 2008; Park et al. 2010). It has to be noted, however, that behavior of in vitro cultured cells only partially "reflects" their differentiation accompanying regeneration of skeletal muscle. Nevertheless, isolated satellite cells and cultured MPCs are considered as a useful tool in the studies involving

biochemical and cytological analysis of the processes accompanying cellular proliferation and differentiation.

First studies focusing at the satellite cell population suggested relative homogeneity of their population. However, currently it is accepted that satellite cell niche is occupied by more than one population of cells. Characterization of the subpopulation of various satellite cells was possible, thanks to many research projects that proposed specific markers. Detection of the cells expressing these proteins allows to precisely subdivide the population of the satellite cells and to mark off the ones that are the most "potent" in supporting the regeneration. One has to remember, however, that the expression of some markers varies as the cells react to the changing environment, and as the "decisions" about the self-renewal vs. differentiation are made.

The cells that become predestined to form a pool of satellite cells during embryonic development express Pax7 transcription factor (Zammit et al. 2006). Pax7 and Myf-5 are among the proteins that are most frequently used as satellite cell markers (Seale et al. 2000). However, some satellite cells were shown to lack Myf-5 expression (Beauchamp et al. 2000). As a rule, satellite cells, i.e., quiescent ones, should not express early myogenic differentiation marker, i.e., MyoD (Fig. 20.5). Thus, the cells that express MyoD are usually excluded from the pool of satellite cells (Cornelison and Wold 1997; Kitzmann et al. 1998). Among the factors characterizing the quiescent satellite cells are also proteins involved in cell adhesion, such as M-cadherin mediating adhesion between these cells and the sarcolemma of adjacent muscle fiber (Irintchev et al. 1994), or integrin α7 subunit (LaBarge and Blau 2002; Gnocchi et al. 2009). The latter one is coexpressed with other markers, i.e., Myf-5 and hepatocyte growth factor (HGF) receptor – c-met (Cornelison and Wold 1997; LaBarge and Blau 2002). The list of satellite cell markers was also extended with syndecan-3 and syndecan-4 (Cornelison et al. 2001). However, it has to be noted that M-cadherin, integrin α7, syndecan-3, and syndecan-4 cannot be considered as perfect markers since their expression continues after the induction of satellite cell activation and differentiation (e.g., Brzoska et al. 2003; Xiao et al. 2003; Wrobel et al. 2007; Tanaka et al. 2009). Importantly, these proteins are widely accepted to be involved not only in the cell adhesion but also in the signal transduction. Last but not least, expression of HSC antigen, i.e., CD34, however, always together with other markers, e.g., Myf-5, is also employed to determine the population of quiescent satellite cells (Beauchamp et al. 2000; Ieronimakis et al. 2010). Presence of almost none of these markers is unique for satellite cells, although combined analyses of such markers as Pax7, integrin α7 subunit, and CD34, supplemented by the examination of cell localization, allow identification of satellite cells. Molecules listed above cannot be considered as "definitive" marker list as almost every year satellite cell population further loses its homogeneity and undergoes extensive "deconstruction".

The most wanted among the satellite cell population is the one that has the highest "regenerative" potential. In search for such cells, Tanaka et al. focused at so-called side population (SP) (Tanaka et al. 2009). These cells, present in many adult tissues and organs, including bone marrow (Goodell et al. 1996) or other adult tissues (Asakura and Rudnicki 2002), are characterized by the ability to exclude

vital dyes, e.g., Hoechst 33342. Analyses of satellite cells isolated from murine hindlimb revealed the presence of rare SP consisting of 0.05–0.5% cells, described by them as "satellite-SP cells." These cells express syndecan-4, Pax7, HSCs marker Sca-1, and also ABCG2 transporter responsible for the exclusion of Hoechst 33342 dye, and are characterized by high potential to participate in muscle regeneration (Tanaka et al. 2009). Other studies supported the idea of the satellite cell heterogeneity by defining two coexisting subpopulations of satellite cells, i.e., so-called low and high proliferating cells. Interestingly, both types of cells demonstrate diverse myogenic potential (Rossi et al. 2010). These findings strongly suggest that cells localized within the satellite stem cell niche differ not only in the proteins that they express, but also in their ability to resume the cell cycle in response to the changing niche, i.e., the environment that can force them to remain quiescent, self-renew, or activate.

20.4.2 Satellite Cells' Niche and Self-Renewal

The niche, an important "factor" influencing the behavior and fate of the satellite cell progeny, secures proper cellular environment protecting the balance between satellite cell renewal and differentiation. Unevenness of these processes may lead either to the premature exhaustion of satellite cells or to their uncontrolled, and thus possibly dangerous, overproliferation. The influence of the niche on satellite cells is based on their physical interaction with muscle fiber and basal lamina, presence of extracellular signals (e.g., Dahlqvist et al. 2003; Le Grand et al. 2009), or mechanical properties of the niche (e.g., Boonen et al. 2009).

Two different mechanisms controlling niche-residing satellite self-renewal have been proposed. One of them suggests that equal divisions of satellite cells generate identical progeny. Resulting daughter cells randomly choose their fate, i.e., some of them differentiate, others retain satellite cell characteristics (Kuang et al. 2008). Other scenario proposes that the presence of the cellular asymmetry results in the generation of two cells of various fates. One daughter cell will be determined to renew satellite cell population, the other will proliferate and differentiate into myotubes (Kuang et al. 2008). Indeed, the existence of the cellular asymmetry was supported by several lines of evidence. One of the tested theories was the "immortal strand hypothesis." It proposes that during stem cell division, segregation of DNA strands is nonrandom, i.e., one daughter cell, presumably the self-renewing stem cell, inherits sister chromatid built of the "older" DNA template strands. The "younger" DNA strand is passed to the cell that is committed to differentiate (Herreros and Giannelli 1967; Cairns 1975). The stem cell retains the old, i.e., "immortal," DNA strand that does not contain possibly dangerous replication errors. Such segregation was shown to accompany the satellite cell divisions. Self-renewing Pax7 and Sca-1 expressing cells inherit "older" DNA strand (Shinin et al. 2006, 2009; Conboy et al. 2007), and the cell that will differentiate, as predicted by the expression of muscle-specific protein – desmin, inherits the newly synthesized,

i.e., younger strand (Conboy et al. 2007). However, it has to be noted that only a subpopulation of satellite cells divides asymmetrically (Shinin et al. 2006; Conboy et al. 2007), which can be another illustration of the fact that population initially described as satellite cells is not homogenous.

Another manifestation of the satellite cells asymmetry is the localization of Numb protein. Numb protein can be inherited either by both "types" of daughter cells, i.e., the one that retains the ability to self renew and the one that will differentiate, i.e., myoblast (Conboy and Rando 2002; Shinin et al. 2006; Jory et al. 2009), or by only one daughter cell. Interestingly, in the case of asymmetric localization, the cell that takes over the Numb also inherits an old DNA strand and is considered a self-renewing one (Shinin et al. 2006; Jory et al. 2009). In the differentiating myoblasts, Numb action is crucial for the repression of Notch, i.e., the factor that was shown to be engaged in the stem-cell renewal via maintaining expression of Pax7 (Conboy and Rando 2002; Dahlqvist et al. 2003; Sun et al. 2008). Interestingly, the Notch ligand, delta-like 1 (DLL1), the expression of which leads to the increase in the expression of Pax7, is also asymmetrically distributed in dividing myoblasts. The cell that will differentiate inherits more DLL1, initiates Notch signaling pathway on the sister cell, and, via this action, promotes its self-renewal (Kuang et al. 2007). Interfering with proper DLL1 processing, i.e., its shedding, results in elevation of Notch signaling and expansion of Pax7-positive cells (Sun et al. 2008). Moreover, mutant mice carrying DLL1 hypomorph, and as a result expressing lower levels of this protein, are characterized by the premature differentiation of myoblasts and loss of muscle precursor cells (Schuster-Gossler et al. 2007). Notch activation was also documented to cause rapid induction of members of Hes family of transcription factors that function as transcriptional repressors, and MyoD was shown to be among the targets of Hes1 (Jarriault et al. 1998; Kuroda et al. 1999). Another Hes protein, i.e., Hes 6 was suggested to block the expression of $p21^{CIP1}$, and thus, support myoblast proliferation (Cossins et al. 2002). However, it has to be noted that Hes6 was also reported to promote the differentiation (Gao et al. 2001; Cossins et al. 2002). The switch from myoblast proliferation to differentiation correlates with transition from Notch to Wnt signaling (Brack et al. 2008). As it was described above, during embryogenesis, Wnt proteins produced by dorsal neural tube and surface ectoderm influence the somite differentiation and thus myogenesis. In adult organisms, Wnts are secreted by skeletal muscle fibers and are also able to influence the behavior of satellite cells. Besides Wnt proteins, other extracellular signals such as growth factors (e.g., IGF-I, HGF, epidermal growth factor [EGF], and TGFβ) or cytokines (e.g., IL-1) that penetrate to the satellite cell niche can also impact on their fate (see Sect. 20.5).

20.4.3 Maintaining Quiescence and Inducing Activation of MPCs

Quiescence is a state common for many cells within organism. However, in case of satellite cells, any in vitro studies of this process are highly difficult to conduct.

At the very moment, the satellite cells are isolated from myofibers; they become activated and reenter the cell cycle. Although, culture of whole myofibers gives a chance to follow quiescent satellite cells for few days and also to have an insight into their niche (Wozniak and Anderson 2005). Another approach allowing the analysis of satellite cells in G0 phase of the cell cycle includes the short and mild trypsinization of in vitro cultured myoblasts that already formed myotubes. Such treatment removes most myotubes, leaving only undifferentiated residual, reserve cells that can be considered as an "equivalent" of satellite cells. After proper stimulation, these cells can reenter the cell cycle (Kitzmann et al. 1998; Carnac et al. 2000). Moreover, the analyses can be conducted using various myogenic cells that were forced to withdraw from the cell cycle, such as cultured in serum-free conditions (e.g., Coller et al. 2006) or in that various signaling pathways were manipulated (e.g., Reed et al. 2007).

Elevated activity of Raf kinase was shown to induce the cell cycle arrest in several cell types studied. Thus, the mouse myoblasts expressing inducible Raf kinase can be used to study the cell cycle regulation during myogenic cells proliferation and differentiation. Importantly, they were shown to express Pax7 (Reed et al. 2007). Using such model system, Reed et al. showed that induction of G0 in Raf expressing mouse myoblasts was accompanied by the translocation of pRb and E2F5 into the nucleus. However, other pocket proteins – p107 and p130 retained their cytoplasmic localization (Reed et al. 2007). Analyses of the status of pocket proteins family members in in vitro cultured C2.7 myoblasts revealed that, similarly as in other cell types, pRb was active in nonproliferating reserve cells and myoblasts, and inactive only in proliferating cell (Carnac et al. 2000). In subpopulation of reserve cells, p130 was expressed and complexed with E2F transcription factors, while p107 was not detectable (Carnac et al. 2000). In agreement, overexpression of p130 in cycling C2 myoblasts led to the suppression of S-phase. It also led to the reduction of MyoD expression. Similar observation was made when p130 and MyoD were coexpressed in 10T1/2 fibroblasts; again the presence of this pocket protein resulted in reduction of MyoD level (Carnac et al. 2000). Thus, p130 inhibits both proliferation and myogenic differentiation program and could be a part of the pathway responsible for maintenance of reserve cell pool during differentiation. Global analyses of gene expression during the regeneration of injured mouse muscles documented that p130 expression changes concurrently with those of E2F1 and E2F2, i.e., factors responsible for the expression of the crucial cell cycle regulators, and is induced during the initial stages of regeneration (Yan et al. 2003). However, E2F1 but not E2F2 gene was shown to be necessary for correct regeneration of mice skeletal muscles. Moreover, concomitantly with the progress of skeletal muscle regeneration, the expression of E2F3, E2F4, and E2F5 increases. Expression of pRb, however, correlates with the cell cycle withdrawal and myoblast differentiation, which once again underlines the importance of pRb in the regulation of muscle differentiation (Yan et al. 2003).

Analysis of E2F1 expression in C2C12 cells showed that myoblasts differentiation is accompanied by its downregulation. On the other hand, overexpression of this transcription factor results in the decrease of myogenin levels and induction of

cyclin D1 expression, thus preventing myogenic differentiation (Wang et al. 1995). Another E2F family member – E2F3a and E2F3b, was previously shown to play opposite roles in the cell cycle regulation. E2F3a was expressed in proliferating cells, predominantly in S-phase, while E2F3b is active throughout the cell cycle and also in the G0 arrested cells (Leone et al. 2000). E2F3a was widely accepted to be a transcriptional activator, while in differentiated or quiescent cells E2F3b acts as transcriptional repressor (Kong et al. 2007). These proteins were also shown to play opposite role in myoblasts (Asp et al. 2009). E2F3a as well as E2F1 was shown to be downregulated during myogenic differentiation of C2C12 cells, but the level of E2F2, E2F4, and also E2F3b did not change (Asp et al. 2009). Asp et al. showed that in proliferating myoblasts E2F3a binds to the promoters activating certain subset of cell cycle genes, while in myotubes E2F3b interacts with the same regions repressing them. Moreover, these factors regulate subsets of specific genes. Among the E2F3a targets are genes involved in the regulation of the cell cycle proliferation-associated genes, while E2F3b is predominantly recruited to genes involved in differentiation (Asp et al. 2009).

Satellite cells maintain quiescent state balancing between cell cycle progression and differentiation. While analyzing MPCs, one has to remember that quiescence in contrast to terminal differentiation, apoptosis, and senescence is reversible (Coller et al. 2006). Conclusions drawn from the initial studies devoted to myoblast proliferation stated that only proliferating myoblast can be induced to differentiate (Nameroff and Holtzer 1969; Dienstman and Holtzer 1977; Yeoh and Holtzer 1977). If this holds true only the cycling, but not quiescent cells, would respond to the factors inducing myogenesis. Indeed, expression of MyoD in cycling human fibroblasts induced their myogenic differentiation (Coller et al. 2006). However, also the quiescent fibroblasts, which were cultured under serum-free conditions or subjected to contact inhibition, differentiated as a result of MyoD overexpression. Importantly, concomitant expression of MyoD and $p21^{CIP1}$ also led to myogenic differentiation, supporting the view that such cells do not need to transiently reenter cell cycle to differentiate (Coller et al. 2006).

20.4.4 Regulating Proliferation of MPCs

Satellite cells can be induced to reenter the cell cycle either by the muscle injury or after their isolation and in vitro culture. In regenerating muscles, the first cycling myoblasts were detectable as soon as 30 h, and intensive proliferation approximately 5 days after muscle injury (McGeachie and Grounds 1987). Increased levels of MyoD and myogenin expression occurs in mononuclear cells, i.e., activated satellite cells, 6 h after injury, and the numbers of MyoD-positive cells were augmented markedly by 24 h. MyoD expression declined to preinjury levels at approximately 8th day of regeneration (Grounds et al. 1992; Yan et al. 2003). However, as it was documented in analyses of injured skeletal muscles (Grounds et al. 1992; Yan et al. 2003), in vitro cultured murine MPCs (Yablonka-Reuveni

et al. 1999), or isolated mouse muscle myofibers (Zammit et al. 2004), MyoD upregulation is correlated with satellite cell activation and induction of differentiation. As long as the myoblasts proliferate, they synthesize high levels of cyclin D1 (Rao et al. 1994; Skapek et al. 1995), the expression of which is controlled by c-jun and c-fos transcription factors (Fig. 20.3). It should be mentioned that one of these factors – c-jun also binds to bHLH domain of MyoD. This interaction prevents the formation of MyoD–protein E complexes and in turn inhibits MyoD transcriptional activity (Bengal et al. 1992; Li et al. 1992a). In proliferating MPCs, increase in the cyclin D1 level promotes translocation of CDK4 to nucleus and interaction with MyoD (Fig. 20.3). MyoD bound through CDK4 to cyclin D1–CDK4 complex is unable to bind DNA and, therefore, cannot induce transcription (Li et al. 1992a; Zhang et al. 1999a). As a result of cyclin D1 degradation that accompanies cell cycle withdrawal, D1–CDK4 complexes are disassembled liberating MyoD (Walsh and Perlman 1997). In consequence, myoblasts cease to proliferate and start to differentiate (Fig. 20.4).

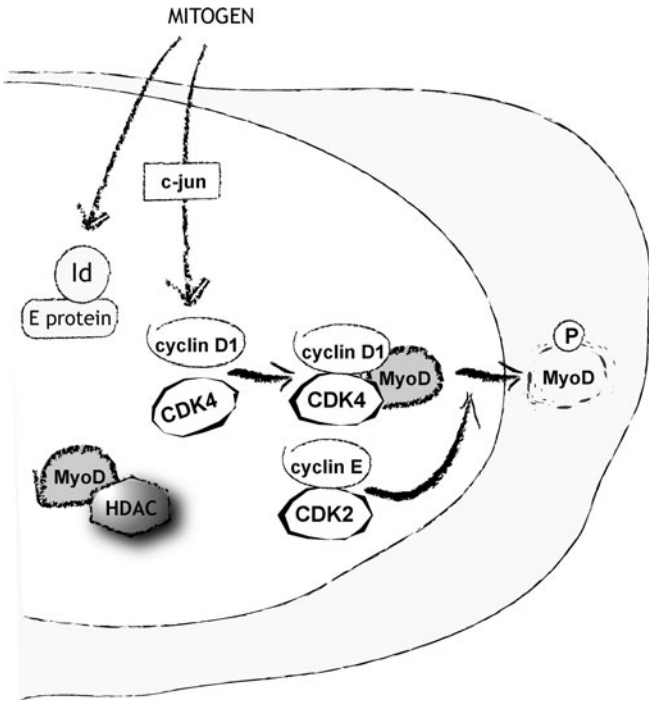

Fig. 20.3 Inhibition of MyoD in proliferating myogenic cells. In proliferating cells c-jun, cellular protooncogene activated in response to mitogens, directly binds MyoD preventing its heterodimerization with E protein and interfering with MyoD-dependent transcription. E protein is itself inhibited by Id factor. Elevated level of cyclin D1 induces CDK4 translocation to nucleus, where it forms complexes with MyoD. MyoD is also directed for degradation after phosphorylation mediated by cyclin E–CDK2 complexes. Finally, deacetylation of MyoD by HDAC prevents its binding to DNA

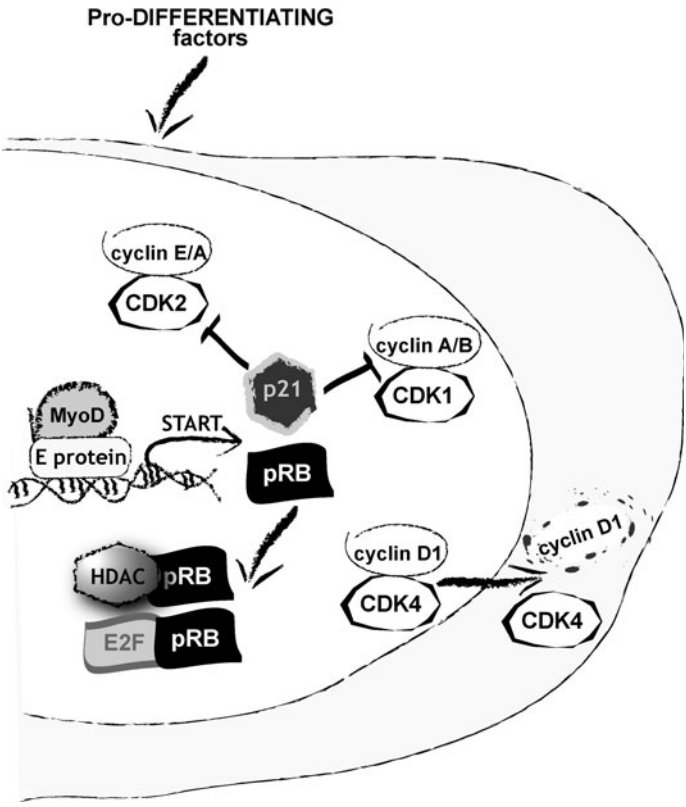

Fig. 20.4 Differentiation-associated changes in cellular machinery of myogenic cells. As a result of cyclin D1 degradation, CDK4 is released into the cytoplasm, and MyoD becomes liberated. MyoD induces expression of $p21^{CIP1}$ and pRb. $p21^{CIP1}$ inhibits CDK2 and CDK1 and thus promotes cell cycle withdrawal. pRb protein binds and inactivates E2F transcription factors preventing the transcription of cell cycle progression genes. pRb also displaces HDACs from MyoD and translocates it to the regions encoding cell cycle genes leading to their silencing. Liberated MyoD together with E protein promotes expression of muscle-specific genes and thus promotes the myogenic differentiation

Cyclin D3 was the other cyclin postulated to be involved in the regulation of myoblast proliferation and differentiation (Bartkova et al. 1998, see Sect. 20.3.2). Significantly, overexpression of cyclin D3 increases expression of negative cell cycle regulators, e.g., $p21^{CIP1}$, and muscle-specific genes such as myogenin or MyHCs (Fig. 20.5). On the other hand lack of cyclin D3 leads to the decrease in $p21^{CIP1}$, MyHCs, and α-actin (De Santa et al. 2007). Ectopic expression of cyclin D3 was shown to correct the defects in myogenic differentiation associated with myotonic dystrophy type 1 (Salisbury et al. 2008). As far as other cyclins are concerned, their roles are proproliferative, since increasing the CDK activity by overexpression of cyclins A, D, or E prevents myogenic differentiation by means of

inhibiting MyoD (Skapek et al. 1995; Guo and Walsh 1997). Moreover, cyclin E–CDK2 complexes phosphorylate MyoD at Ser^{200} directing it to proteolytic degradation, since hyperphosphorylated MyoD becomes ubiquitinated (Song et al. 1998; Kitzmann et al. 1999; Fig. 20.3). Besides MyoD, other MRF family members are also regulated by changes in their phosphorylation status. For example, phosphorylation of myogenin catalyzed by protein kinase C inhibits its interaction with DNA (Li et al. 1992b), and protein kinase A represses activity of both Myf-5 and MyoD (Winter et al. 1993).

Id proteins were shown to be other important factors regulating both proliferation and differentiation acting via the cell cycle regulators and MRFs (see Sect. 20.3.2, Fig. 20.3). Id1 was detected in activated satellite cells and then in rapidly proliferating myoblasts (Ono et al. 2009), in which it prevents expression of $p21^{CIP1}$, and thus allows cell cycle progression (Prabhu et al. 1997). Besides Id1, Id2 and Id4 are also constitutively synthesized in proliferating myoblasts. Dramatic increase in Id2 was also noticed at the initial stages of skeletal muscle regeneration, i.e., during the period of satellite cell activation and myoblasts proliferation (Zhao and Hoffman 2004). Interestingly, Id3 was postulated to be controlled by MyoD transcription factor, suggesting that the members of Id family perform independent function during myoblasts differentiation (Wyzykowski et al. 2002). Several other lines of evidence strongly supported the notion that Id3, similarly to Id1 or Id2, does not play any unique role, but also interferes with MyoD function (Loveys et al. 1996; Melnikova et al. 1999; Wu and Lim 2005). In differentiating myoblasts, i.e., exiting the cell cycle, Id gene promoters were shown to be repressed (Biggs et al. 1995), and resulting loss of these proteins correlated with the formation of MyoD–E protein complexes, induction of myogenin expression, and terminal differentiation (Jen et al. 1992; Ono et al. 2009). Id2 was also shown to be involved in the regulation of apoptosis-associated atrophy of skeletal muscles (Alway et al. 2003). Its ablation in proliferating myoblasts results in the decrease of proliferation and increase of apoptosis (Butler et al. 2009).

20.4.5 Molecular Signature of Satellite Cells and MPCs

Molecular and cytological in situ studies of quiescent satellite cells, activated or differentiated MPCs, and also in vitro experiments were supplemented with the elegant molecular analyses involving microarray and CHIP-on-CHIP techniques (Blais et al. 2005; Fukada et al. 2007; Pallafacchina et al. 2010). Obtained data confirmed previous observations documenting that negative regulators of cell cycle are highly upregulated in quiescent satellite cells. $p57^{KIP2}$ was expressed at a very high level in quiescent cells and downregulated in proliferating MPCs. However, $p21^{CIP1}$, $p27^{KIP1}$, and also p130, which were previously described as factors involved in the maintenance of quiescence, were not significantly upregulated in quiescent cells. Quiescence was also accompanied with the high expression of specific

myogenic inhibitors, e.g., Bmp4, Bmp6, Musculin/MyoR, and also some of the positive myogenic regulators, e.g., Gli2, Pax3, and Pax7 regulator Meox2 (Fukada et al. 2007). Genes encoding cell–cell adhesion molecules, the key elements in the regulation of quiescent celli niche, were also highly expressed. Among them were VE-cadherin, VCAM1, ICAM1, and Pcdhb9 (protocadherin beta 9). Interestingly, Esam, which is characteristic for HSC and mammary gland SPs, and claudin 5, which along with Esam is expressed in blood vessels, were also upregulated in quiescent satellite cells (Fukada et al. 2007; Pallafacchina et al. 2010). Satellite cell activation and cell cycle reentry were accompanied by the upregulation of other gene sets, including gene encoding factors involved in cell cycle progression, DNA, RNA, and protein synthesis, e.g., Cyclin E, CDK1, and many others (Fukada et al. 2007; Pallafacchina et al. 2010). Surprisingly, CHIP-on-CHIP assays revealed relative lack of canonical cell cycle genes that would be controlled by MRFs; however, they documented that E2F4 transcription factor, similar to E2F3, is involved in cell cycle gene expression in MPCs (Blais et al. 2005; Asp et al. 2009).

20.5 Last But Not Least – The Impact of Extracellular Factors on the MPCs Cell Cycles

Extracellular signals such as mitogens, cell–cell, and cell–ECM (extracellular matrix) interactions are crucial factors regulating cell cycle reentry of quiescent cells and their proliferation and differentiation (Charge and Rudnicki 2004). The levels of mitogens stimulating proliferation of MPCs increase drastically when the skeletal muscle becomes injured and inflammatory cells begin to infiltrate damaged tissue. These mitogens, e.g., growth factors, are mainly secreted by neutrophils, macrophages, and to a lesser extent by T-cells and platelets. Vasculature, motor neurons, and MPCs themselves are also responsible for the production and secretion of several growth factors (Cannon and St Pierre 1998). Importantly, some of the factors impacting on satellite cells and MPCs persist within ECM bound by proteoglycans (Taipale and Keski-Oja 1997) and can be easily released as a result of ECM remodeling by metalloproteases occurring after muscle injury (Levi et al. 1996; Kurisaki et al. 2003).

The first described growth factor that was shown to trigger the activation of quiescent MPCs was HGF/SF (hepatocyte growth factor/scatter factor; Nakamura et al. 1986). It binds the c-met receptor expressed by MPCs and activates multiple intracellular signaling pathways, such as MAPK pathway, eventually leading to MPCs divisions (Leshem et al. 2002). The function of other growth factors, such as insulin-like growth factors I and II (IGF-I, IGF-II), platelet-derived growth factor (PDGF), fibroblast growth factors 1, 2, 4, 6, and 9 (FGF-1, -2, -4, -6, and -9), is to promote the proliferation of already activated MPCs and also to stimulate their differentiation (Johnson and Allen 1995; Sheehan and Allen 1999; Czifra et al. 2006). Among other growth factors influencing the cell cycle of myogenic cells are

EGF and PDGF-BB (platelet growth factor BB), which in combination with other factors, such as IGF-I or FGF-2, were shown to stimulate myoblasts proliferation (Doumit et al. 1993). Other factors that impact on MPCs are cytokines, such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and leukemia inhibitory factor (LIF) (Li 2003; Cantini et al. 1995; Spangenburg and Booth 2002). Besides the induction of the cell cycle reentry and progression, extracellular factors also regulate cell cycle withdrawal and myoblast terminal differentiation. Some of them, e.g., IGFs and HGF, play a dual role, i.e., stimulate proliferation and also are able to induce differentiation. As a result, growth factors can either up- or downregulate the expression of cell cycle associated or myogenic genes (Hawke and Garry 2001). Therefore, the sequence of growth factors expression and their crosstalk is of vital importance for the proper progression of skeletal muscle regeneration and myoblasts differentiation (Fig. 20.5).

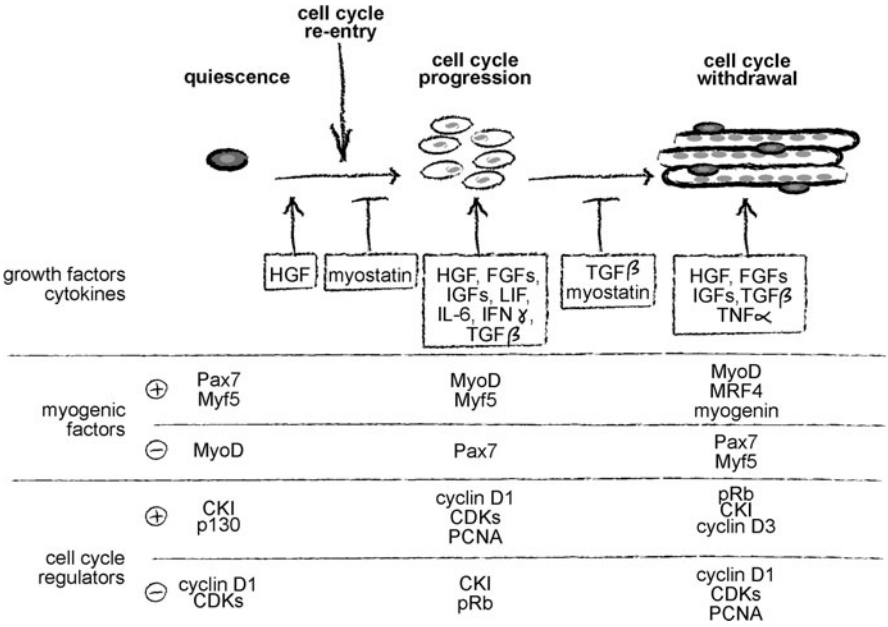

Fig. 20.5 General overview of the extracellular factors acting at the myogenic cells, and changes in the expression of crucial cell cycle regulators and myogenic factors. Cell cycle reentry of satellite cells, proliferation of MPCs, and cell cycle withdrawal associated with either terminal differentiation or quiescence remain under control of various growth factors and cytokines, and result in changes of the expression/activity of myogenic factors and cell cycle regulators. Among the myogenic factors are Pax proteins and MRFs. Cell cycle regulators include such factors as pocket proteins, cyclins, CDKs, CDK inhibitors (CKI), CIP/KIP, and PCNA. The scheme illustrates only gross changes; it does not include the subtle ones. Upregulation of the expression or increase in the activity is marked by plus; downregulation or decrease is marked by minus. *Arrows* indicate cell cycle reentry, stimulating impact of the mitogens at myogenic cells. *Blocking marks* indicate the inhibitory actions of mitogens

20.5.1 Signaling Pathways Activated in Myogenic Cells

Among the pathways activated by growth factors that regulate satellite cells or myoblasts behavior are MAP kinases, i.e., ERK1/ERK2, ERK5 or p38, phosphatidylinositol 3-kinase (PI3K), and protein kinase B (PKB or Akt). Activation of ERK1/ERK2 MAPK results in the cell cycle reentry, while other MAP kinases, PKB, and PI3K influence both proliferation and differentiation of myoblasts (Coolican et al. 1997; Gredinger et al. 1998; Jones et al. 2001, 2005; Perdiguero et al. 2007). Among the receptors that are common for various growth factors or cytokines are receptor tyrosine kinases (RTKs). RTKs interaction with the ligand leads to their dimerization and autophosphorylation enabling binding of effector proteins containing SH2 (Src homology 2) domains. Next steps include interaction with the adaptor proteins, such as Gab-1, which is the adaptor of Met kinase, and Grb2 – the adaptor of Sos-GEF (Guanine nucleotide Exchange Factor), and then downstream factors such as monomeric GTPase Ras. Induction of Ras leads to activation of Raf kinase that phosphorylates and activates MAP kinase kinase – MEK1, which in turn phosphorylates and activates MAPK ERK1/ERK2. Subsequently, active ERK1/ERK2 enters the cell nucleus and mediates the activation of factors involved in chromatin remodeling, such as histone H3 or high mobility group proteins (HMGs), or transcription factors (Sassone-Corsi et al. 1999). Among the first genes that are activated via MAPK pathway are genes encoding crucial cell cycle regulators such as cyclin D1, which allows the cell cycle reentry (Albanese et al. 1995; Lavoie et al. 1996). Interestingly, besides RTKs, MAPK pathway and other pathways, such as PI3K and Akt, can also be activated by ligand binding to G-protein-coupled receptors (Luttrell et al. 1995; Murga et al. 1998). Other growth factors, such as TGFβ, bind to serine/threonine receptors and activate the effector proteins such as Smads, which also translocate to the nucleus and induce expression of their target genes. Activation of c-Jun N-terminal kinase (JNK/SAPK1, Stress Activated Protein Kinase 1), which is also a member of MAPK family, is induced by TNF-α, a cytokine that was shown to impact on cell cycle of murine C2 myoblasts (Alter et al. 2008). Other pathways that were shown to participate in the regulation of proliferation and differentiation of MPCs are, for example, those that involve nuclear factor kappa-light-chain-enhancer (NFκB), also impacting on the expression of cell cycle regulators, such as cyclin D1 (Guttridge et al. 1999).

20.5.2 Growth Factors Impacting on MPCs

Up-to-date multiple extracellular factors were shown to affect the proliferation and differentiation of myogenic cells in vitro and in vivo. The impact of those factors on satellite cells or MPCs depends on their concentration, presence of their receptors, and functionality of signaling pathways that are activated. Presence of the other growth factors within the satellite cells or myoblasts environment is also crucial for

the final cellular reaction. As far as satellite cells and myoblasts are concerned, the role of HGF, IGFs, FGFs, TGFβs, and cytokines, such as LIF and IL-1, was extensively studied.

20.5.2.1 Hepatocyte Growth Factor

HGF/SF was first purified from rette hepatocytes (Nakamura et al. 1986). It is known, however, that its synthesis occurs also in other cells including MPCs. Moreover, it is one of the very few mitogens that was confirmed to activate quiescent satellite cells (Ten Broek et al. 2010). Thus, its action on satellite cells or myoblasts can be achieved not only by endocrine but also by paracrine/autocrine mechanisms (Anastasi et al. 1997). Importantly, HGF can be stored within ECM as a complex with heparan sulfate proteoglycans (Suzuki et al. 2002). During embryonic development, HGF is involved in the migration of muscle precursor cells, but not in their proliferation, differentiation, or survival (Dietrich et al. 1999). As far as satellite cells are concerned, HGF was shown to be able to activate them via its binding to c-met receptor, and trigger cell cycle reentry, both in vitro and in vivo. Depending on the pathway activated, e.g., MAPK and PI3K, c-met binding may sustain myoblast proliferation, or result in their differentiation (Allen et al. 1995; Anastasi et al. 1997; Tatsumi et al. 1998; Leshem et al. 2000; Miller et al. 2000; Halevy and Cantley 2004). Upregulation of HGF expression accompanies the phase of intensive MPCs proliferation and, thus, improves the regeneration of injured muscle (Tatsumi et al. 1998; Miller et al. 2000). As it was shown in murine C2C12 cells, HGF induces cyclin D1 expression and CDK4 translocation into the nucleus, pRb hyperphosphorylation, and release of E2F transcription factors (Ponzetto et al. 2000; Leshem and Halevy 2002). Simultaneously, expression of $p27^{KIP1}$ decreases, and via this mechanisms G1/S transition is secured. Yamada et al. revealed that the function of HGF in MPCs might be more complex and dependable on the concentration of this growth factor. High levels of HGF, accompanied by the expression of myostatin and $p21^{CIP1}$, was shown to inhibit proliferation of rette MPCs and induce their quiescence. On the other hand, low concentrations of HGF allowed cell proliferation (Yamada et al. 2010). Moreover, ectopic expression of HGF in chicken MPCs increases the expression of myogenic inhibitory bHLH factor Twist and decreases the expression of cell cycle inhibitor $p27^{KIP1}$ (Leshem et al. 2000, 2002). Activation of PI3K pathway by HGF is accompanied by the upregulation of myogenin and inhibition of the ERK1/ERK2 MAPK pathway. As a consequence, MPCs exit the cell cycle and differentiate (Leshem et al. 2002). Moreover, PI3K phosphorylates and activates Akt, one of the major regulators of apoptosis, indicating that, apart from sustaining quiescence of MPCs, HGF may be involved in myogenic cell survival (Halevy and Cantley 2004). Interestingly, activity of PI3K was also shown to be involved in ERK1/ERK2 MAPK activation, opposing the thesis that PI3K signaling participated only in the control of myogenic cell differentiation (Halevy and Cantley 2004).

20.5.2.2 IGF-I and IGF-II

Extensive studies devoted to the role of insulin-like growth factors in myogenesis clarified that, similarly to HGF, IGF-I and IGF-II are also able to promote both proliferation and differentiation of MPCs. IGFs are able to induce both effects in a biphasic manner. First, they stimulate proliferation and expression of genes, such as cyclin D1, next they promote differentiation and activation of myogenic genes (Coolican et al. 1997). Moreover, these factors induce both processes by binding the same receptors, but the final result depends on the signaling pathway utilized (Coolican et al. 1997). IGF-I stimulates the proliferation of MPCs via binding to RTKs, and stimulating various signaling pathways, such as ERK1/ERK2 MAPK (Coolican et al. 1997), calcineurin/NFAT (Musaro et al. 1999), p70 S6K1 (Haddad and Adams 2004), and PI3K (Chakravarthy et al. 2000; Machida and Booth 2004). Muscle injury induces increase in IGF-I levels which stimulates MPCs' proliferation resulting in muscle fiber hypertrophy (Hayashi et al. 2004). Moreover, infusion of IGF-I into rette tibialis anterior muscle leads to the increased expression of cyclin D1, higher proportion of cells in S-phase, and enhanced MPCs proliferation (Haddad and Adams 2004). However, this effect apparently did not depend on ERK1/ERK2 MAPK pathway, since simultaneous infusion of skeletal muscle with IGF-I and MEK1 inhibitor PD-098059 did not result in the significant decrease in the proliferation of analyzed MPCs (Haddad and Adams 2004). Thus, it was suggested that MAPK pathway is not essential for the IGF-I induced proliferation of MPCs. On the other hand, ERK1/ERK2 MAPK pathway was shown to transduce IGF-I-mediated mitogenic signal in L6A1 myoblasts, whereas the PI3K/p70 S6K was involved in differentiation of those cells (Coolican et al. 1997). Other studies documented that in MPCs IGF-I might "utilize" other than ERK1/ERK2 MAPK signaling pathway. Czifra et al. postulated that IGF-I action on human MPCs is exclusively mediated by PKCδ, but in C2C12 myoblasts also by ERK1/ERK2 MAPK (Czifra et al. 2006). However, other lines of evidence argued against IGF-I involvement in the regulation of human MPCs proliferation, suggesting that it causes muscle hypertrophy by increasing the cell recruitment rather then by stimulating cellular divisions (Jacquemin et al. 2004).

Besides ERK1/ERK2 MAPK, PI3K/Akt pathway is also considered as the one crucial for the regulation of MPCs proliferation mediated by IGFs. MPCs isolated from transgenic mice overexpressing IGF-I were characterized by the presence of activated PI3K and Akt, and increased proliferation potential (Chakravarthy et al. 2000). Activation of PI3K/Akt is associated with the increase in CDK2 activity, hyperphosphorylation of pRb and decrease in the level of $p27^{KIP1}$, securing the proper S-phase progression. Interestingly, ectopic expression of $p27^{KIP1}$ in murine MPCs inhibited proliferation of those cells, even if they were stimulated with IGF-I (Chakravarthy et al. 2000). IGF-I-mediated activation of PI3K/Akt pathway regulates the activity of forkhead transcription factor FOXO1 which controls cell proliferation and survival. Activation of Akt leads the phosphorylation of FOXO1 on Ser^{256} which inhibits its translocation to the nucleus. This in turn leads to decrease of the $p27^{KIP1}$ promoter activity which is regulated by FOXO1, and

downregulation of $p27^{KIP1}$ expression (Machida et al. 2003). Thus, in MPCs FOXO1 has been postulated to "mediate" between phosphorylation of Akt and regulation of activity of $p27^{KIP1}$ promoter (Machida and Booth 2004).

Another mode of IGF-I action includes the increase of MPCs survival. Results obtained by Barton et al. revealed that IGF-I ameliorates the dystrophic muscle phenotype of mdx mice, i.e., reduces necrosis and prevents apoptosis of MPCs (Barton et al. 2002). Generation of the transgenic mdx mice, characterized by IGF-I synthesis directed by myosin light chain promoter (mdx:$mIGF^{+/+}$ mice), allowed to achieve muscle-specific overexpression of this growth factor. Such mice were characterized by muscle hypertrophy and improved regeneration of their dystrophic muscles resulting from increased MPCs survival (Barton et al. 2002). The phenotype of mdx:$mIGF^{+/+}$ mice was explained by the higher expression and persistent activation of Akt kinase which is crucial for survival of MPCs. In addition, muscles of mdx:$mIGF^{+/+}$ mice were characterized with reduced fibrosis and increased strength in comparison to mdx dystrophic muscles (Barton et al. 2002).

Interestingly, IGFs regulate not only the proliferation, but can also impact on the MPCs differentiation. Their mode of action greatly depends on the duration of the stimulation. Brief exposition (1–8 h) of L6E9 myoblasts to IGF-I stimulates their proliferation by inducing cyclin D1 expression. However, 30 and 48 h long treatment leads to myogenin and MRF4 expression, and promotes the differentiation of those cells (Engert et al. 1996). Both IGFs were shown to promote terminal differentiation of C2 and C2C12 myoblasts via activation of PI3K that leads, to the induction of MyHC expression (Shanely et al. 2009). As it was described terminal differentiation of murine MPCs is correlated with the expression of the cell cycle inhibitors $p21^{CIP1}$ or $p57^{KIP2}$ and cell cycle exit (Parker et al. 1995; Zhang et al. 1999b). Similar mechanisms operate also in human myotubes that upon IGF-I treatment upregulate $p57^{KIP2}$, and increase the synthesis of myogenin and MyoD (Jacquemin et al. 2007). Interestingly, IGF-I is not able to induce differentiation when p38 MAPK is blocked with a specific inhibitor, implicating that this kinase mediates IGF-I "differentiating" action (Wu et al. 2000). Besides IGF-I, IGF-II is also able to induce the cell cycle withdrawal and myoblasts differentiation acting via ERK5 signaling pathway. Activated ERK5, similarly to ERK1/ERK2 MAPK translocates into the cell nucleus and increases MyHCs and MEF2 expression (Carter et al. 2009). Introduction of antisense IGF-II constructs into C2 myoblasts reduces both ERK5 activity and MyHC expression (Carter et al. 2009). Thus, the role of IGF-I and IGF-II in myoblast proliferation depends on the origin of analyzed myogenic cells, and their concentration present in the cellular environment.

20.5.2.3 Fibroblast Growth Factors

Among known FGFs, FGF-1 (also termed as acidic FGF, or aFGF), FGF-2 (also termed as basic FGF, or bFGF), FGF-4, -6, and -9, were shown to have a significant impact on the myogenic cell proliferation (Doumit et al. 1993; Johnson and Allen 1995; Sheehan and Allen 1999). The notion that FGFs play a crucial

function as regulators of myogenesis is also supported by the observation that their receptors, such as FGFR1, are involved in the regulation of growth and differentiation, not only of embryonic, but also of adult myoblasts (Itoh et al. 1996; Flanagan-Steet et al. 2000). Thus, it is not surprising that FGFs up-regulation is also observed during skeletal muscle regeneration.

In regenerating rette plantaris muscle expression of FGF-1, FGF-5, and -7 is associated with the expression of "early" MRF - MyoD and of PCNA protein that is involved in DNA replication and serves as a marker of actively dividing cells (Tanaka et al. 2008). Inhibition of FGF2 by specific antibodies impairs not only the number, but also the diameter of newly formed myofibers (Lefaucheur and Sebille 1995). Moreover, injection of FGF2 into tibialis anterior of mdx mice improves proliferation capacity of MPCs, and leads to the increase in number of newly regenerated myofibers (Lefaucheur and Sebille 1995). The impact of FGFs on muscle regeneration was confirmed by the analyses of the phenotype of mice lacking FGF-6. Their skeletal muscles were characterized by impaired ability to regenerate, reduced number of myoblasts expressing MyoD and myogenin, and decreased proliferative capacity of MPCs (Floss et al. 1997). However, these results were questioned in other study documenting that during skeletal muscle regeneration of FGF6-deficient mice formation of new fibers is accelerated, due to stimulation of differentiation, accompanied by increase in $p16^{INK4a}$ and $p21^{CIP1}$ (Armand et al. 2005). Importantly, Armand et al. revealed that during muscle regeneration the influence of FGF-6 is dose-dependent. Injection of high amounts of human recombinant FGF-6 into muscles of FGF-6-deficient mice results in accumulation of cyclin D1 transcripts, and stimulation of proliferation. Lower doses of FGF-6 stimulate their differentiation (Armand et al. 2005). FGF-2, -4, -6 and -9 were shown to act synergistically with HGF increasing its mitogenic effect on MPCs (Sheehan and Allen 1999). However, the detailed mechanisms of FGFs impact on the cell cycle machinery are still not well characterized. Moreover, the interpretation of experiments in that the levels of certain FGF were manipulated is difficult due to the possible functional redundancy between other existing isoforms.

The effect of FGFs on myogenic cell proliferation depends on signaling pathway activated. This was confirmed by the overexpression of FGFR1 in L6 myoblasts, which resulted in significantly higher activation of Raf-1 kinase and ERK1/ERK2 MAPK, than in the case of the overexpression of FGFR4 (Vainikka et al. 1994). Moreover, overexpression of a truncated form of FGFR1 resulted in decreased proliferation and enhanced differentiation of murine Sol 8 myoblasts (Scata et al. 1999). It was also shown that in embryonic and adult turkey MPCs FGF-2 activates ERK1/ERK2 MAPK and in murine MPCs also p38 MAPK (McFarland and Pesall 2008; Shi et al. 2010). Involvement of ERK1/ERK2 MAPK pathway in repression of MPCs differentiation was questioned by the results of experiments in that inhibition of this pathway did not enhance the myogenic differentiation of MM14 myoblasts (Jones et al. 2001). In conclusion, the influence of FGFs on MPCs' cell cycle may be regulated by acting through different receptors and activation of distinct signaling pathways. As it was shown for other growth factors their action depends on their concentration, receptor specificity, and activated pathways.

20.5.2.4 TGFβ Family

TGFβ is a family of growth factors that include TGFβs, myostatin and bone morphogenic proteins (BMPs). Depending on the cell type and conditions these factors can either promote or suppress cellular proliferation. In general, members of this family acting on their target cells bind to TGFβR-I and -II serine/threonine kinase receptors, trigger their phosphorylation, and activate the cascade of kinases leading to the phosphorylation of Smad transcription factors (Whitman 1998). Among the signaling pathways which were shown to be involved in TGFβs action are PI3K, ERK1/ERK2 MAPK and JNK pathways.

In 1980s, TGFβ was determined as a factor that negatively regulates myoblasts differentiation (Massague et al. 1986). In vitro experiments underscored the proproliferative function of TGFβ1, TGF2, and TGF3, which stimulated C2C12 murine myoblasts proliferation via inhibition of the expression of the $p21^{CIP1}$ and induction of PCNA translocation to the cell nucleus (Schabort et al. 2009). Interestingly, TGFβ1, TGFβ2, and TGFβ3 isoforms delayed myogenic commitment by increasing MyoD degradation and by decreasing myogenin and MyHCs expression (Martin et al. 1992; Schabort et al. 2009). Increase in the expression of TGFβ accompanies skeletal muscle regeneration (Sakuma et al. 2000; Zimowska et al. 2009). However, it also results in the development of fibrosis and inhibition of TGFβ with specific antibodies leads to the improved muscle repair (Zimowska et al. 2009).

A member of TGFβ family, myostatin (Mstn), was documented to be specifically expressed in the developing myotome and in the different types of adult muscles. Contrary to TGFβ1, TGFβ2, and TGFβ3, Mstn arrests muscle growth by decreasing myoblast proliferation and inhibiting G1/S progression. This is achieved via activation of GSK-3β that phosphorylates and induces degradation of cyclin D1 and leads to the drop in CDK4 activity (Yang et al. 2007). In addition, $p21^{CIP1}$ expression becomes upregulated leading to CDK2 inhibition and as a result pRb becomes dephosphorylated, i.e., able to bind and inactivate E2F (Thomas et al. 2000; Rios et al. 2001; McCroskery et al. 2003). Overexpression of Mstn in C2C12 cells was shown to prevent myoblast differentiation via reversible repression of MyoD and myogenin expression (Rios et al. 2001). Analysis of mutant mice lacking Mstn documented that the absence of Mstn leads to enhanced proliferation and delayed differentiation, resulting in the increased muscle mass and higher number of larger myofibers (McPherron et al. 1997; McCroskery et al. 2003). Such phenotype was confirmed in the analyses of other mouse and bovine models, such as Belgian Blue or Piedmontese (Grobet et al. 1997; Kambadur et al. 1997; McPherron and Lee 1997; Szabo et al. 1998).

The other members of TGFβ family, i.e., BMPs also impact on the myogenesis (Wang et al. 2010). During somite development BMP2, together with the FGF4 and Shh, inhibits the expansion of cells within the limb buds and induces chondro- and osteogenesis (Wall and Hogan 1995). Modulating the BMP-dependent signaling pathways was shown to have a significant impact on the proliferation of mesodermal precursor cells. In mice null mutation of BMP receptor fully inhibits the mesoderm development and causes early embryonic lethality by 9.5 dpc

(Mishina et al. 1995). Activation of BMP signaling pathway induces Smad phosphorylation and MPCs proliferation (Wang et al. 2010). The presence of the phosphorylated form of Smad was also observed in dividing satellite cells localized at the isolated muscle fibers, indicating that BMP signaling is active in those cells. The inhibition of BMP signaling by the Noggin overexpression represses Smad phosphorylation and leads to the decrease in the number of muscle precursor cells (Wang et al. 2010).

20.5.2.5 Cytokines Impacting on MPCs

Cytokines, such as TNF-α or IFN-γ (interferon γ), are produced by inflammatory cells, such as macrophages, natural killer cells, and T-cells migrating to the site of muscle injury, and also by endothelial cells and MPCs. TNF-α binds to TNF-α receptors p55 and p75, and IFN-γ binds and induces phosphorylation of the IFN-γ receptor, which results in the activation of such signaling pathways as p38 MAPK pathway. In injured skeletal muscle, their action concerns MPCs recruitment and their stimulation to reentry or to withdraw the cell cycle and also to differentiate (Lafreniere et al. 2006). To make the story even more complicated, the expression of cytokines and chemokines and their receptors is regulated by other cytokines and growth factors, such as IGF-I (e.g., Reem and Yeh 1984; Sironi et al. 1989). The significance of these complicated relations for proper myogenic differentiation during development or muscle regeneration is not fully understood yet. However, it is well known that various cytokines, such as TNF-α, IFN-γ, LIF, and interleukins, such as IL-1β, IL-4, or IL-13, participate in the recruitment of MPCs and their differentiation (Horsley et al. 2003; Broussard et al. 2004; Charge and Rudnicki 2004; Li et al. 2005; Jacquemin et al. 2007; Cheng et al. 2008). Moreover, LIF, IL-6, and IFN-γ were shown to have an impact on cell divisions of MPCs and also various cell lines such as C2C12 myoblasts (Charge and Rudnicki 2004; Cheng et al. 2008).

The two best studied cytokines in terms of their involvement in muscle regeneration and also in vitro differentiation of myoblasts are IFN-γ and TNF-α. IFN-γ improves murine muscle regeneration, and blocking of its action reduces proliferation of MPCs and decreases the number of MyoD-positive cells, which in turn leads to the drop in the number of reconstructed myofibers (Cheng et al. 2008). Interfering with IFN-γ receptor with specific antibody represses proliferation and fusion of in vitro cultured C2C12 myoblasts (Cheng et al. 2008). On the other hand, the other proinflammatory cytokine TNF-α was proved to regulate differentiation of C2C12 myoblasts and murine MPCs, acting via p38 MAPK pathway (Chen et al. 2005, 2007). Importantly TNF-α, both in vitro and in vivo, stimulates cell cycle withdrawal, by inducing the expression of $p21^{CIP1}$, and myogenic differentiation via expression of MEF2C and myogenin (Chen et al. 2005, 2007). Moreover, regeneration of Soleus muscle in mice lacking TNF-α receptors, i.e., p55 and p75, was accompanied by increased expression of cyclin D1 (Chen et al. 2005), proving that TNF-α is involved in cell proliferation.

Among other cytokines that regulate cycling of MPCs are LIF and IL-6 (Barnard et al. 1994; De Rossi et al. 2000). Both factors utilize the same receptor subunit gp130 and thus probably are able to activate similar signaling pathways, such as JAK/STAT pathway (Lord et al. 1991; Hibi et al. 1996; Heinrich et al. 1998). Results obtained by Cantini and Cararro showed that IL-6 stimulates proliferation of in vitro cultured human MPCs (Cantini and Carraro 1995). However, Kami and coworkers suggested that this interleukin promotes rather degeneration of damaged fibers than proliferation of myogenic cells (Kami and Senba 1998). Moreover, it was shown that muscle regeneration of LIF-deficient mice is repressed, and infusion of LIF can rescue this phenotype (Kurek et al. 1996). LIF administration into muscles of mdx mice ameliorates their regeneration, probably by stimulating myoblast proliferation (Kurek et al. 1996; Austin et al. 2000). LIF was also shown to activate JAK2/STAT3 pathway and increase proliferation of in vitro cultured C2C12 myoblasts (Spangenburg and Booth 2002). Although it was showed that IL-1 activates the p38 MAPK, and NFκB (Li et al. 2009), the detailed mode of action of interleukins, i.e., signaling pathways that are activated in myoblasts, is not well described.

Cell cycle of MPCs is orchestrated by various extracellular factors that not only stimulate their entry but also withdrawal from the cell cycle both in vivo and in vitro. Although action of growth factors and cytokines depends on experimental models that are used, it is clear that appropriate spatiotemporal pattern of their expression secures effective MPCs differentiation and also muscle regeneration.

20.6 Concluding Remarks

Development and regeneration of skeletal muscle may serve as excellent examples of processes during which cell cycle progression and withdrawal must be perfectly controlled. Spatiotemporally regulated transitions of cells from proliferating state to differentiating and quiescent ones and conversely are crucial for proper function of both growing and regenerating muscles. The number of identified factors controlling both proliferation and differentiation of myogenic cells still increases; however, the exact mechanism of their action remains, in many cases, still uncovered. The reciprocal interactions of these factors, for example, cell cycle regulators, MRFs, other muscle-specific genes, and epigenetic machinery, make this picture even more complicated. However, sooner or later due to development of precise molecular methods such as microarrays or CHIP technology combined with "traditional" ones, and detailed analyses of knockout animals, these puzzles will be put together.

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References

Adams PD (2001) Regulation of the retinoblastoma tumor suppressor protein by cyclin/cdks. Biochim Biophys Acta 1471:M123–M133

Adiga SK, Toyoshima M, Shimura T, Takeda J, Uematsu N, Niwa O (2007a) Delayed and stage specific phosphorylation of H2ax during preimplantation development of gamma-irradiated mouse embryos. Reproduction 133:415–422

Adiga SK, Toyoshima M, Shiraishi K, Shimura T, Takeda J, Taga M, Nagai H, Kumar P, Niwa O (2007b) p21 provides stage specific DNA damage control to preimplantation embryos. Oncogene 26:6141–6149

Albanese C, Johnson J, Watanabe G, Eklund N, Vu D, Arnold A, Pestell RG (1995) Transforming p21ras mutants and c-Ets-2 activate the cyclin d1 promoter through distinguishable regions. J Biol Chem 270:23589–23597

Aleem E, Berthet C, Kaldis P (2004) Cdk2 as a master of s phase entry: fact or fake? Cell Cycle 3:35–37

Allen RE, Sheehan SM, Taylor RG, Kendall TL, Rice GM (1995) Hepatocyte growth factor activates quiescent skeletal muscle satellite cells in vitro. J Cell Physiol 165:307–312

Alter J, Rozentzweig D, Bengal E (2008) Inhibition of myoblast differentiation by tumor necrosis factor alpha is mediated by c-jun n-terminal kinase 1 and leukemia inhibitory factor. J Biol Chem 283:23224–23234

Alway SE, Martyn JK, Ouyang J, Chaudhrai A, Murlasits ZS (2003) Id2 expression during apoptosis and satellite cell activation in unloaded and loaded quail skeletal muscles. Am J Physiol Regul Integr Comp Physiol 284:R540–R549

Amthor H, Christ B, Patel K (1999) A molecular mechanism enabling continuous embryonic muscle growth – a balance between proliferation and differentiation. Development 126: 1041–1053

Anastasi S, Giordano S, Sthandier O, Gambarotta G, Maione R, Comoglio P, Amati P (1997) A natural hepatocyte growth factor/scatter factor autocrine loop in myoblast cells and the effect of the constitutive met kinase activation on myogenic differentiation. J Cell Biol 137:1057–1068

Arata Y, Fujita M, Ohtani K, Kijima S, Kato JY (2000) Cdk2-dependent and -independent pathways in E2F-mediated s phase induction. J Biol Chem 275:6337–6345

Armand AS, Pariset C, Laziz I, Launay T, Fiore F, Della Gaspera B, Birnbaum D, Charbonnier F, Chanoine C (2005) FGF6 regulates muscle differentiation through a calcineurin-dependent pathway in regenerating soleus of adult mice. J Cell Physiol 204:297–308

Artus J, Cohen-Tannoudji M (2008) Cell cycle regulation during early mouse embryogenesis. Mol Cell Endocrinol 282:78–86

Asakura A, Rudnicki MA (2002) Side population cells from diverse adult tissues are capable of in vitro hematopoietic differentiation. Exp Hematol 30:1339–1345

Asp P, Acosta-Alvear D, Tsikitis M, van Oevelen C, Dynlacht BD (2009) E2F3b plays an essential role in myogenic differentiation through isoform-specific gene regulation. Genes Dev 23: 37–53

Austin L, Bower JJ, Bennett TM, Lynch GS, Kapsa R, White JD, Barnard W, Gregorevic P, Byrne E (2000) Leukemia inhibitory factor ameliorates muscle fiber degeneration in the mdx mouse. Muscle Nerve 23:1700–1705

Bajard L, Relaix F, Lagha M, Rocancourt D, Daubas P, Buckingham ME (2006) A novel genetic hierarchy functions during hypaxial myogenesis: Pax3 directly activates Myf5 in muscle progenitor cells in the limb. Genes Dev 20:2450–2464

Balakier H, Czolowska R (1977) Cytoplasmic control of nuclear maturation in mouse oocytes. Exp Cell Res 110:466–469

Banks GB, Chamberlain JS (2008) The value of mammalian models for Duchenne muscular dystrophy in developing therapeutic strategies. Curr Top Dev Biol 84:431–453

Barnard W, Bower J, Brown MA, Murphy M, Austin L (1994) Leukemia inhibitory factor (LIF) infusion stimulates skeletal muscle regeneration after injury: injured muscle expresses LIF mRNA. J Neurol Sci 123:108–113

Barr FG (2001) Gene fusions involving Pax and Fox family members in alveolar rhabdomyosarcoma. Oncogene 20:5736–5746

Bartkova J, Lukas J, Strauss M, Bartek J (1998) Cyclin D3: requirement for G1/S transition and high abundance in quiescent tissues suggest a dual role in proliferation and differentiation. Oncogene 17:1027–1037

Barton ER, Morris L, Musaro A, Rosenthal N, Sweeney HL (2002) Muscle-specific expression of insulin-like growth factor I counters muscle decline in mdx mice. J Cell Biol 157:137–148

Beauchamp JR, Heslop L, Yu DS, Tajbakhsh S, Kelly RG, Wernig A, Buckingham ME, Partridge TA, Zammit PS (2000) Expression of CD34 and Myf5 defines the majority of quiescent adult skeletal muscle satellite cells. J Cell Biol 151:1221–1234

Bendall AJ, Ding J, Hu G, Shen MM, Abate-Shen C (1999) Msx1 antagonizes the myogenic activity of Pax3 in migrating limb muscle precursors. Development 126:4965–4976

Benezra R, Davis RL, Lassar A, Tapscott S, Thayer M, Lockshon D, Weintraub H (1990a) Id: a negative regulator of helix-loop-helix DNA binding proteins. Control of terminal myogenic differentiation. Ann N Y Acad Sci 599:1–11

Benezra R, Davis RL, Lockshon D, Turner DL, Weintraub H (1990b) The protein Id: a negative regulator of helix-loop-helix DNA binding proteins. Cell 61:49–59

Bengal E, Ransone L, Scharfmann R, Dwarki VJ, Tapscott SJ, Weintraub H, Verma IM (1992) Functional antagonism between c-jun and myod proteins: a direct physical association. Cell 68:507–519

Ben-Yair R, Kalcheim C (2005) Lineage analysis of the avian dermomyotome sheet reveals the existence of single cells with both dermal and muscle progenitor fates. Development 132: 689–701

Berkes CA, Tapscott SJ (2005) MyoD and the transcriptional control of myogenesis. Semin Cell Dev Biol 16:585–595

Bienvenu F, Gascan H, Coqueret O (2001) Cyclin D1 represses Stat3 activation through a Cdk4-independent mechanism. J Biol Chem 276:16840–16847

Bienvenu F, Jirawatnotai S, Elias JE, Meyer CA, Mizeracka K, Marson A, Frampton GM, Cole MF, Odom DT, Odajima J, Geng Y, Zagozdzon A, Jecrois M, Young RA, Liu XS, Cepko CL, Gygi SP, Sicinski P (2010) Transcriptional role of cyclin D1 in development revealed by a genetic-proteomic screen. Nature 463:374–378

Biggs JR, Zhang Y, Murphy EV (1995) Repression of the Id2 (inhibitor of differentiation) gene promoter during exit from the cell cycle. J Cell Physiol 164:249–258

Birchmeier C, Brohmann H (2000) Genes that control the development of migrating muscle precursor cells. Curr Opin Cell Biol 12:725–730

Blais A, Dynlacht BD (2004) Hitting their targets: an emerging picture of E2F and cell cycle control. Curr Opin Genet Dev 14:527–532

Blais A, Tsikitis M, Acosta-Alvear D, Sharan R, Kluger Y, Dynlacht BD (2005) An initial blueprint for myogenic differentiation. Genes Dev 19:553–569

Blais A, van Oevelen CJ, Margueron R, Acosta-Alvear D, Dynlacht BD (2007) Retinoblastoma tumor suppressor protein-dependent methylation of histone H3 lysine 27 is associated with irreversible cell cycle exit. J Cell Biol 179:1399–1412

Blau HM, Pavlath GK, Hardeman EC, Chiu CP, Silberstein L, Webster SG, Miller SC, Webster C (1985) Plasticity of the differentiated state. Science 230:758–766

Bober E, Franz T, Arnold HH, Gruss P, Tremblay P (1994) Pax-3 is required for the development of limb muscles: a possible role for the migration of dermomyotomal muscle progenitor cells. Development 120:603–612

Boonen KJ, Rosaria-Chak KY, Baaijens FP, van der Schaft DW, Post MJ (2009) Essential environmental cues from the satellite cell niche: optimizing proliferation and differentiation. Am J Physiol Cell Physiol 296:C1338–C1345

Borycki AG, Li J, Jin F, Emerson CP, Epstein JA (1999) Pax3 functions in cell survival and in Pax7 regulation. Development 126:1665–1674

Brack AS, Conboy IM, Conboy MJ, Shen J, Rando TA (2008) A temporal switch from Notch to Wnt signaling in muscle stem cells is necessary for normal adult myogenesis. Cell Stem Cell 2:50–59

Braun T, Buschhausen-Denker G, Bober E, Tannich E, Arnold HH (1989) A novel human muscle factor related to but distinct from MyoD1 induces myogenic conversion in 10T1/2 fibroblasts. EMBO J 8:701–709

Broussard SR, McCusker RH, Novakofski JE, Strle K, Shen WH, Johnson RW, Dantzer R, Kelley KW (2004) Il-1beta impairs insulin-like growth factor I-induced differentiation and downstream activation signals of the insulin-like growth factor I receptor in myoblasts. J Immunol 172:7713–7720

Bryson-Richardson RJ, Currie PD (2008) The genetics of vertebrate myogenesis. Nat Rev Genet 9:632–646

Brzoska E, Grabowska I, Wrobel E, Moraczewski J (2003) Syndecan-4 distribution during the differentiation of satellite cells isolated from soleus muscle treated by phorbol ester and calphostin C. Cell Mol Biol Lett 8:269–278

Brzoska E, Przewozniak M, Grabowska I, Janczyk-Ilach K, Moraczewski J (2009) Pax3 and Pax7 expression during myoblast differentiation in vitro and fast and slow muscle regeneration in vivo. Cell Biol Int 33:483–492

Buckingham M, Relaix F (2007) The role of Pax genes in the development of tissues and organs: Pax3 and Pax7 regulate muscle progenitor cell functions. Annu Rev Cell Dev Biol 23:645–673

Butler DC, Haramizu S, Williamson DL, Alway SE (2009) Phospho-ablated Id2 is growth suppressive and pro-apoptotic in proliferating myoblasts. PLoS One 4:e6302

Cairns J (1975) Mutation selection and the natural history of cancer. Nature 255:197–200

Cannon JG, St Pierre BA (1998) Cytokines in exertion-induced skeletal muscle injury. Mol Cell Biochem 179:159–167

Cantini M, Carraro U (1995) Macrophage-released factor stimulates selectively myogenic cells in primary muscle culture. J Neuropathol Exp Neurol 54:121–128

Cantini M, Massimino ML, Rapizzi E, Rossini K, Catani C, Dalla Libera L, Carraro U (1995) Human satellite cell proliferation in vitro is regulated by autocrine secretion of Il-6 stimulated by a soluble factor(s) released by activated monocytes. Biochem Biophys Res Commun 216:49–53

Caretti G, Di Padova M, Micales B, Lyons GE, Sartorelli V (2004) The polycomb Ezh2 methyltransferase regulates muscle gene expression and skeletal muscle differentiation. Genes Dev 18:2627–2638

Carnac G, Fajas L, L'Honore A, Sardet C, Lamb NJ, Fernandez A (2000) The retinoblastoma-like protein p130 is involved in the determination of reserve cells in differentiating myoblasts. Curr Biol 10:543–546

Carter EJ, Cosgrove RA, Gonzalez I, Eisemann JH, Lovett FA, Cobb LJ, Pell JM (2009) MEK5 and ERK5 are mediators of the pro-myogenic actions of IGF-2. J Cell Sci 122:3104–3112

Cenciarelli C, De Santa F, Puri PL, Mattei E, Ricci L, Bucci F, Felsani A, Caruso M (1999) Critical role played by cyclin D3 in the MyoD-mediated arrest of cell cycle during myoblast differentiation. Mol Cell Biol 19:5203–5217

Chakravarthy MV, Abraha TW, Schwartz RJ, Fiorotto ML, Booth FW (2000) Insulin-like growth factor-I extends in vitro replicative life span of skeletal muscle satellite cells by enhancing G1/S cell cycle progression via the activation of phosphatidylinositol 3′-kinase/Akt signaling pathway. J Biol Chem 275:35942–35952

Chamberlain JS, Metzger J, Reyes M, Townsend D, Faulkner JA (2007) Dystrophin-deficient mdx mice display a reduced life span and are susceptible to spontaneous rhabdomyosarcoma. FASEB J 21:2195–2204

Charge SB, Rudnicki MA (2004) Cellular and molecular regulation of muscle regeneration. Physiol Rev 84:209–238

Chen Z, Indjeian VB, McManus M, Wang L, Dynlacht BD (2002) Cp110, a cell cycle-dependent Cdk substrate, regulates centrosome duplication in human cells. Dev Cell 3:339–350

Chen SE, Gerken E, Zhang Y, Zhan M, Mohan RK, Li AS, Reid MB, Li YP (2005) Role of TNF-{alpha} signaling in regeneration of cardiotoxin-injured muscle. Am J Physiol Cell Physiol 289:C1179–C1187

Chen SE, Jin B, Li YP (2007) TNF-alpha regulates myogenesis and muscle regeneration by activating p38 MAPK. Am J Physiol Cell Physiol 292:C1660–C1671

Cheng M, Olivier P, Diehl JA, Fero M, Roussel MF, Roberts JM, Sherr CJ (1999) The p21cip1 and p27kip1 cdk "inhibitors" are essential activators of cyclin D-dependent kinases in murine fibroblasts. EMBO J 18:1571–1583

Cheng M, Nguyen MH, Fantuzzi G, Koh TJ (2008) Endogenous interferon-gamma is required for efficient skeletal muscle regeneration. Am J Physiol Cell Physiol 294:C1183–C1191

Cheshier SH, Morrison SJ, Liao X, Weissman IL (1999) In vivo proliferation and cell cycle kinetics of long-term self-renewing hematopoietic stem cells. Proc Natl Acad Sci USA 96:3120–3125

Chiang C, Litingtung Y, Lee E, Young KE, Corden JL, Westphal H, Beachy PA (1996) Cyclopia and defective axial patterning in mice lacking sonic hedgehog gene function. Nature 383: 407–413

Choi J, Costa ML, Mermelstein CS, Chagas C, Holtzer S, Holtzer H (1990) MyoD converts primary dermal fibroblasts, chondroblasts, smooth muscle, and retinal pigmented epithelial cells into striated mononucleated myoblasts and multinucleated myotubes. Proc Natl Acad Sci USA 87:7988–7992

Christy BA, Sanders LK, Lau LF, Copeland NG, Jenkins NA, Nathans D (1991) An Id-related helix-loop-helix protein encoded by a growth factor-inducible gene. Proc Natl Acad Sci USA 88:1815–1819

Ciemerych MA, Sicinski P (2005) Cell cycle in mouse development. Oncogene 24:2877–2898

Ciemerych MA, Maro B, Kubiak JZ (1999) Control of duration of the first two mitoses in a mouse embryo. Zygote 7:293–300

Ciemerych MA, Yu Q, Szczepanska K, Sicinski P (2008) Cdk4 activity in mouse embryos expressing a single D-type cyclin. Int J Dev Biol 52:299–305

Clarke AR, Maandag ER, van Roon M, van der Lugt NM, van der Valk M, Hooper ML, Berns A, te Riele H (1992) Requirement for a functional Rb-1 gene in murine development. Nature 359:328–330

Classon M, Dyson N (2001) p107 and p130: versatile proteins with interesting pockets. Exp Cell Res 264:135–147

Cobrinik D (2005) Pocket proteins and cell cycle control. Oncogene 24:2796–2809

Coller HA, Sang L, Roberts JM (2006) A new description of cellular quiescence. PLoS Biol 4:e83

Collins CA, Gnocchi VF, White RB, Boldrin L, Perez-Ruiz A, Relaix F, Morgan JE, Zammit PS (2009) Integrated functions of Pax3 and Pax7 in the regulation of proliferation, cell size and myogenic differentiation. PLoS One 4:e4475

Conboy IM, Rando TA (2002) The regulation of notch signaling controls satellite cell activation and cell fate determination in postnatal myogenesis. Dev Cell 3:397–409

Conboy MJ, Karasov AO, Rando TA (2007) High incidence of non-random template strand segregation and asymmetric fate determination in dividing stem cells and their progeny. PLoS Biol 5:e102

Conklin JF, Sage J (2009) Keeping an eye on retinoblastoma control of human embryonic stem cells. J Cell Biochem 108:1023–1030

Coolican SA, Samuel DS, Ewton DZ, McWade FJ, Florini JR (1997) The mitogenic and myogenic actions of insulin-like growth factors utilize distinct signaling pathways. J Biol Chem 272:6653–6662

Cornelison DD, Wold BJ (1997) Single-cell analysis of regulatory gene expression in quiescent and activated mouse skeletal muscle satellite cells. Dev Biol 191:270–283

Cornelison DD, Filla MS, Stanley HM, Rapraeger AC, Olwin BB (2001) Syndecan-3 and syndecan-4 specifically mark skeletal muscle satellite cells and are implicated in satellite cell maintenance and muscle regeneration. Dev Biol 239:79–94

Cossins J, Vernon AE, Zhang Y, Philpott A, Jones PH (2002) Hes6 regulates myogenic differentiation. Development 129:2195–2207

Cotsarelis G, Sun TT, Lavker RM (1990) Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis. Cell 61:1329–1337

Coverley D, Pelizon C, Trewick S, Laskey RA (2000) Chromatin-bound cdc6 persists in S and G2 phases in human cells, while soluble cdc6 is destroyed in a cyclin A-Cdk2 dependent process. J Cell Sci 113(Pt 11):1929–1938

Czifra G, Toth IB, Marincsak R, Juhasz I, Kovacs I, Acs P, Kovacs L, Blumberg PM, Biro T (2006) Insulin-like growth factor-I-coupled mitogenic signaling in primary cultured human skeletal muscle cells and in C2C12 myoblasts. A central role of protein kinase cdelta. Cell Signal 18:1461–1472

Dahlqvist C, Blokzijl A, Chapman G, Falk A, Dannaeus K, Ibanez CF, Lendahl U (2003) Functional notch signaling is required for Bmp4-induced inhibition of myogenic differentiation. Development 130:6089–6099

Dannenberg JH, van Rossum A, Schuijff L, te Riele H (2000) Ablation of the retinoblastoma gene family deregulates G(1) control causing immortalization and increased cell turnover under growth-restricting conditions. Genes Dev 14:3051–3064

Day K, Shefer G, Shearer A, Yablonka-Reuveni Z (2010) The depletion of skeletal muscle satellite cells with age is concomitant with reduced capacity of single progenitors to produce reserve progeny. Dev Biol 340:330–343

de Bruin A, Wu L, Saavedra HI, Wilson P, Yang Y, Rosol TJ, Weinstein M, Robinson ML, Leone G (2003) Rb function in extraembryonic lineages suppresses apoptosis in the CNS of Rb-deficient mice. Proc Natl Acad Sci USA 100:6546–6551

De Falco G, Comes F, Simone C (2006) pRb: master of differentiation. Coupling irreversible cell cycle withdrawal with induction of muscle-specific transcription. Oncogene 25:5244–5249

de la Serna IL, Roy K, Carlson KA, Imbalzano AN (2001) MyoD can induce cell cycle arrest but not muscle differentiation in the presence of dominant negative Swi/Snf chromatin remodeling enzymes. J Biol Chem 276:41486–41491

de Medina Redondo M, Meraldi P (2011) The spindle assembly checkpoint: clock or domino? In: Kubiak JZ (ed) Cell cycle and development. Results and problems in cell differentiation. Springer, Heidelberg

De Rossi M, Bernasconi P, Baggi F, de Waal MR, Mantegazza R (2000) Cytokines and chemokines are both expressed by human myoblasts: possible relevance for the immune pathogenesis of muscle inflammation. Int Immunol 12:1329–1335

De Santa F, Albini S, Mezzaroma E, Baron L, Felsani A, Caruso M (2007) pRb-dependent cyclin D3 protein stabilization is required for myogenic differentiation. Mol Cell Biol 27:7248–7265

Decary S, Hamida CB, Mouly V, Barbet JP, Hentati F, Butler-Browne GS (2000) Shorter telomeres in dystrophic muscle consistent with extensive regeneration in young children. Neuromuscul Disord 10:113–120

den Elzen N, Pines J (2001) Cyclin A is destroyed in prometaphase and can delay chromosome alignment and anaphase. J Cell Biol 153:121–136

Dienstman SR, Holtzer H (1977) Skeletal myogenesis. Control of proliferation in a normal cell lineage. Exp Cell Res 107:355–364

Dietrich S, Abou-Rebyeh F, Brohmann H, Bladt F, Sonnenberg-Riethmacher E, Yamaai T, Lumsden A, Brand-Saberi B, Birchmeier C (1999) The role of SF/HGF and c-met in the development of skeletal muscle. Development 126:1621–1629

Dimova DK, Dyson NJ (2005) The E2F transcriptional network: old acquaintances with new faces. Oncogene 24:2810–2826

Doonan JH, Kitsios G (2009) Functional evolution of cyclin-dependent kinases. Mol Biotechnol 42:14–29

Doumit ME, Cook DR, Merkel RA (1993) Fibroblast growth factor, epidermal growth factor, insulin-like growth factors, and platelet-derived growth factor-bb stimulate proliferation of clonally derived porcine myogenic satellite cells. J Cell Physiol 157:326–332

Dressel U, Bailey PJ, Wang SC, Downes M, Evans RM, Muscat GE (2001) A dynamic role for HDAC7 in Mef2-mediated muscle differentiation. J Biol Chem 276:17007–17013

Dunaief JL, Strober BE, Guha S, Khavari PA, Alin K, Luban J, Begemann M, Crabtree GR, Goff SP (1994) The retinoblastoma protein and Brg1 form a complex and cooperate to induce cell cycle arrest. Cell 79:119–130

Duprez D, Fournier-Thibault C, Le Douarin N (1998) Sonic hedgehog induces proliferation of committed skeletal muscle cells in the chick limb. Development 125:495–505

Eckner R, Yao TP, Oldread E, Livingston DM (1996) Interaction and functional collaboration of p300/CBP and bHLH proteins in muscle and B-cell differentiation. Genes Dev 10: 2478–2490

Edmondson DG, Olson EN (1989) A gene with homology to the myc similarity region of myoD1 is expressed during myogenesis and is sufficient to activate the muscle differentiation program. Genes Dev 3:628–640

Elia D, Madhala D, Ardon E, Reshef R, Halevy O (2007) Sonic hedgehog promotes proliferation and differentiation of adult muscle cells: involvement of MAPK/ERK and PI3K/AKT pathways. Biochim Biophys Acta 1773:1438–1446

Emery AE (2002) The muscular dystrophies. Lancet 359:687–695

Engert JC, Berglund EB, Rosenthal N (1996) Proliferation precedes differentiation in IGF-I-stimulated myogenesis. J Cell Biol 135:431–440

Evans T, Rosenthal ET, Youngblom J, Distel D, Hunt T (1983) Cyclin: a protein specified by maternal mRNA in sea urchin eggs that is destroyed at each cleavage division. Cell 33:389–396

Faast R, White J, Cartwright P, Crocker L, Sarcevic B, Dalton S (2004) Cdk6-cyclin D3 activity in murine ES cells is resistant to inhibition by p16(Ink4a). Oncogene 23:491–502

Fisher D (2011) Control of DNA replication by cyclin-dependent kinases in development. In: Kubiak JZ (ed) Cell cycle in development. Results and problems in cell differentiation. Springer, Heidelberg

Flach G, Johnson MH, Braude PR, Taylor RA, Bolton VN (1982) The transition from maternal to embryonic control in the 2-cell mouse embryo. EMBO J 1:681–686

Flanagan-Steet H, Hannon K, McAvoy MJ, Hullinger R, Olwin BB (2000) Loss of FGF receptor 1 signaling reduces skeletal muscle mass and disrupts myofiber organization in the developing limb. Dev Biol 218:21–37

Floss T, Arnold HH, Braun T (1997) A role for FGF-6 in skeletal muscle regeneration. Genes Dev 11:2040–2051

Forcales SV, Puri PL (2005) Signaling to the chromatin during skeletal myogenesis: novel targets for pharmacological modulation of gene expression. Semin Cell Dev Biol 16:596–611

Foucrier J, Grand MC, De Conto F, Bassaglia Y, Geraud G, Scherrer K, Martelly I (1999) Dynamic distribution and formation of a para-sarcomeric banding pattern of prosomes during myogenic differentiation of satellite cells in vitro. J Cell Sci 112(Pt 7):989–1001

Foudi A, Hochedlinger K, Van Buren D, Schindler JW, Jaenisch R, Carey V, Hock H (2009) Analysis of histone 2b-GFP retention reveals slowly cycling hematopoietic stem cells. Nat Biotechnol 27:84–90

Franz T, Kothary R (1993) Characterization of the neural crest defect in splotch (sp1h) mutant mice using a lacZ transgene. Brain Res Dev Brain Res 72:99–105

Fuchs E (2009) The tortoise and the hair: slow-cycling cells in the stem cell race. Cell 137: 811–819

Fukada S, Uezumi A, Ikemoto M, Masuda S, Segawa M, Tanimura N, Yamamoto H, Miyagoe-Suzuki Y, Takeda S (2007) Molecular signature of quiescent satellite cells in adult skeletal muscle. Stem Cells 25:2448–2459

Furstenthal L, Kaiser BK, Swanson C, Jackson PK (2001a) Cyclin E uses cdc6 as a chromatin-associated receptor required for DNA replication. J Cell Biol 152:1267–1278

Furstenthal L, Swanson C, Kaiser BK, Eldridge AG, Jackson PK (2001b) Triggering ubiquitination of a Cdk inhibitor at origins of DNA replication. Nat Cell Biol 3:715–722

Furuno N, den Elzen N, Pines J (1999) Human cyclin A is required for mitosis until mid prophase. J Cell Biol 147:295–306

Gabrielli BG, Lee MS, Walker DH, Piwnica-Worms H, Maller JL (1992) Cdc25 regulates the phosphorylation and activity of the xenopus Cdk2 protein kinase complex. J Biol Chem 267:18040–18046

Gao X, Chandra T, Gratton MO, Quelo I, Prud'homme J, Stifani S, St-Arnaud R (2001) Hes6 acts as a transcriptional repressor in myoblasts and can induce the myogenic differentiation program. J Cell Biol 154:1161–1171

Geng Y, Yu Q, Sicinska E, Das M, Bronson RT, Sicinski P (2001) Deletion of the p27kip1 gene restores normal development in cyclin D1-deficient mice. Proc Natl Acad Sci USA 98:194–199

Geng Y, Yu Q, Sicinska E, Das M, Schneider JE, Bhattacharya S, Rideout WM, Bronson RT, Gardner H, Sicinski P (2003) Cyclin E ablation in the mouse. Cell 114:431–443

Geng Y, Lee YM, Welcker M, Swanger J, Zagozdzon A, Winer JD, Roberts JM, Kaldis P, Clurman BE, Sicinski P (2007) Kinase-independent function of cyclin E. Mol Cell 25:127–139

Gibson MC, Schultz E (1982) The distribution of satellite cells and their relationship to specific fiber types in soleus and extensor digitorum longus muscles. Anat Rec 202:329–337

Girard F, Strausfeld U, Fernandez A, Lamb NJ (1991) Cyclin A is required for the onset of DNA replication in mammalian fibroblasts. Cell 67:1169–1179

Gnocchi VF, White RB, Ono Y, Ellis JA, Zammit PS (2009) Further characterisation of the molecular signature of quiescent and activated mouse muscle satellite cells. PLoS One 4:e5205

Goodell MA, Brose K, Paradis G, Conner AS, Mulligan RC (1996) Isolation and functional properties of murine hematopoietic stem cells that are replicating in vivo. J Exp Med 183: 1797–1806

Gossett LA, Kelvin DJ, Sternberg EA, Olson EN (1989) A new myocyte-specific enhancer-binding factor that recognizes a conserved element associated with multiple muscle-specific genes. Mol Cell Biol 9:5022–5033

Gotoh T, Villa LM, Capelluto DGSF, C.V. (2011) Regulatory pathways coordinating cell cycle progression in early xenopus development. In: Kubiak JZ (ed) Cell cycle in development. Results and problems in cell differentiation. Springer, Heidelberg

Goulding M, Lumsden A, Paquette AJ (1994) Regulation of Pax-3 expression in the dermomyotome and its role in muscle development. Development 120:957–971

Grana X, Garriga J, Mayol X (1998) Role of the retinoblastoma protein family, pRb, p107 and p130 in the negative control of cell growth. Oncogene 17:3365–3383

Gredinger E, Gerber AN, Tamir Y, Tapscott SJ, Bengal E (1998) Mitogen-activated protein kinase pathway is involved in the differentiation of muscle cells. J Biol Chem 273:10436–10444

Grobet L, Martin LJ, Poncelet D, Pirottin D, Brouwers B, Riquet J, Schoeberlein A, Dunner S, Menissier F, Massabanda J, Fries R, Hanset R, Georges M (1997) A deletion in the bovine myostatin gene causes the double-muscled phenotype in cattle. Nat Genet 17:71–74

Grounds MD, Garrett KL, Lai MC, Wright WE, Beilharz MW (1992) Identification of skeletal muscle precursor cells in vivo by use of MyoD1 and myogenin probes. Cell Tissue Res 267:99–104

Gu W, Schneider JW, Condorelli G, Kaushal S, Mahdavi V, Nadal-Ginard B (1993) Interaction of myogenic factors and the retinoblastoma protein mediates muscle cell commitment and differentiation. Cell 72:309–324

Guan KL, Jenkins CW, Li Y, O'Keefe CL, Noh S, Wu X, Zariwala M, Matera AG, Xiong Y (1996) Isolation and characterization of p19Ink4d, a p16-related inhibitor specific to Cdk6 and Cdk4. Mol Biol Cell 7:57–70

Gubbels MJ, White M, Szatanek T (2008) The cell cycle and toxoplasma gondii cell division: tightly knit or loosely stitched? Int J Parasitol 38:1343–1358

Guo K, Walsh K (1997) Inhibition of myogenesis by multiple cyclin-Cdk complexes. Coordinate regulation of myogenesis and cell cycle activity at the level of E2F. J Biol Chem 272:791–797

Guttridge DC, Albanese C, Reuther JY, Pestell RG, Baldwin AS Jr (1999) NF-kappa b controls cell growth and differentiation through transcriptional regulation of cyclin D1. Mol Cell Biol 19:5785–5799

Haddad F, Adams GR (2004) Inhibition of MAP/ERK kinase prevents IGF-I-induced hypertrophy in rat muscles. J Appl Physiol 96:203–210

Halevy O, Cantley LC (2004) Differential regulation of the phosphoinositide 3-kinase and MAP kinase pathways by hepatocyte growth factor vs Insulin-like growth factor-I in myogenic cells. Exp Cell Res 297:224–234

Halevy O, Novitch BG, Spicer DB, Skapek SX, Rhee J, Hannon GJ, Beach D, Lassar AB (1995) Correlation of terminal cell cycle arrest of skeletal muscle with induction of p21 by MyoD. Science 267:1018–1021

Hannon GJ, Beach D (1994) P15ink4b is a potential effector of TGF-beta-induced cell cycle arrest. Nature 371:257–261

Harbour JW, Luo RX, Dei Santi A, Postigo AA, Dean DC (1999) Cdk phosphorylation triggers sequential intramolecular interactions that progressively block Rb functions as cells move through G1. Cell 98:859–869

Harper JW, Adami GR, Wei N, Keyomarsi K, Elledge SJ (1993) The p21 Cdk-interacting protein Cip1 is a potent inhibitor of G1 cyclin-dependent kinases. Cell 75:805–816

Hartwell LH (1991) Twenty-five years of cell cycle genetics. Genetics 129:975–980

Hartwell LH, Culotti J, Pringle JR, Reid BJ (1974) Genetic control of the cell division cycle in yeast. Science 183:46–51

Hawke TJ, Garry DJ (2001) Myogenic satellite cells: physiology to molecular biology. J Appl Physiol 91:534–551

Hayashi S, Aso H, Watanabe K, Nara H, Rose MT, Ohwada S, Yamaguchi T (2004) Sequence of IGF-I, IGF-II, and HGF expression in regenerating skeletal muscle. Histochem Cell Biol 122:427–434

Heinrich PC, Behrmann I, Muller-Newen G, Schaper F, Graeve L (1998) Interleukin-6-type cytokine signalling through the gp130/Jak/Stat pathway. Biochem J 334(Pt 2):297–314

Herreros B, Giannelli F (1967) Spatial distribution of old and new chromatid sub-units and frequency of chromatid exchanges in induced human lymphocyte endoreduplications. Nature 216:286–288

Hibi M, Nakajima K, Hirano T (1996) Il-6 cytokine family and signal transduction: a model of the cytokine system. J Mol Med 74:1–12

Hindley J, Phear GA (1984) Sequence of the cell division gene Cdc2 from schizosaccharomyces pombe; patterns of splicing and homology to protein kinases. Gene 31:129–134

Hoffmann I, Draetta G, Karsenti E (1994) Activation of the phosphatase activity of human Cdc25a by a Cdk2-cyclin E dependent phosphorylation at the G1/S transition. EMBO J 13: p4302–p4310

Horsley V, Jansen KM, Mills ST, Pavlath GK (2003) Il-4 acts as a myoblast recruitment factor during mammalian muscle growth. Cell 113:483–494

Houlard M, Artus J, Cohen-Tannoudji M (2009) Cell cycle checkpoints and DNA damage response in early mouse embryo. In: Kubiak JZ, Ciemerych MA, Richard-Parpaillon L (eds) Cell cycle and development in vertebrates. Research Signpost, Kerala, pp 223–244

Hu P, Geles KG, Paik JH, DePinho RA, Tjian R (2008) Codependent activators direct myoblast-specific MyoD transcription. Dev Cell 15:534–546

Huh MS, Parker MH, Scime A, Parks R, Rudnicki MA (2004) Rb is required for progression through myogenic differentiation but not maintenance of terminal differentiation. J Cell Biol 166:865–876

Ieronimakis N, Balasundaram G, Rainey S, Srirangam K, Yablonka-Reuveni Z, Reyes M (2010) Absence of CD34 on murine skeletal muscle satellite cells marks a reversible state of activation during acute injury. PLoS One 5:e10920

Irintchev A, Zeschnigk M, Starzinski-Powitz A, Wernig A (1994) Expression pattern of M-cadherin in normal, denervated, and regenerating mouse muscles. Dev Dyn 199:326–337

Itoh N, Mima T, Mikawa T (1996) Loss of fibroblast growth factor receptors is necessary for terminal differentiation of embryonic limb muscle. Development 122:291–300

Iwamori N, Naito K, Sugiura K, Tojo H (2002) Preimplantation-embryo-specific cell cycle regulation is attributed to the low expression level of retinoblastoma protein. FEBS Lett 526:119–123

Jacks T, Fazeli A, Schmitt EM, Bronson RT, Goodell MA, Weinberg RA (1992) Effects of an Rb mutation in the mouse. Nature 359:295–300

Jacquemin V, Furling D, Bigot A, Butler-Browne GS, Mouly V (2004) IGF-1 induces human myotube hypertrophy by increasing cell recruitment. Exp Cell Res 299:148–158

Jacquemin V, Butler-Browne GS, Furling D, Mouly V (2007) Il-13 mediates the recruitment of reserve cells for fusion during IGF-1-induced hypertrophy of human myotubes. J Cell Sci 120:670–681

Janatpour MJ, McMaster MT, Genbacev O, Zhou Y, Dong J, Cross JC, Israel MA, Fisher SJ (2000) Id-2 regulates critical aspects of human cytotrophoblast differentiation, invasion and migration. Development 127:549–558

Jarriault S, Le Bail O, Hirsinger E, Pourquie O, Logeat F, Strong CF, Brou C, Seidah NG, Isra l A (1998) Delta-1 activation of Notch-1 signaling results in Hes-1 transactivation. Mol Cell Biol 18:7423–7431

Jen Y, Weintraub H, Benezra R (1992) Overexpression of Id protein inhibits the muscle differentiation program: in vivo association of id with E2a proteins. Genes Dev 6:1466–1479

Johnson SE, Allen RE (1995) Activation of skeletal muscle satellite cells and the role of fibroblast growth factor receptors. Exp Cell Res 219:449–453

Jones NC, Fedorov YV, Rosenthal RS, Olwin BB (2001) Erk1/2 is required for myoblast proliferation but is dispensable for muscle gene expression and cell fusion. J Cell Physiol 186:104–115

Jones NC, Tyner KJ, Nibarger L, Stanley HM, Cornelison DD, Fedorov YV, Olwin BB (2005) The p38alpha/beta MAPK functions as a molecular switch to activate the quiescent satellite cell. J Cell Biol 169:105–116

Jory A, Le Roux I, Gayraud-Morel B, Rocheteau P, Cohen-Tannoudji M, Cumano A, Tajbakhsh S (2009) Numb promotes an increase in skeletal muscle progenitor cells in the embryonic somite. Stem Cells 27:2769–2780

Jostes B, Walther C, Gruss P (1990) The murine paired box gene, pax7, is expressed specifically during the development of the nervous and muscular system. Mech Dev 33:27–37

Kablar B, Krastel K, Ying C, Tapscott SJ, Goldhamer DJ, Rudnicki MA (1999) Myogenic determination occurs independently in somites and limb buds. Dev Biol 206:219–231

Kaldis P (1999) The Cdk-activating kinase (CAK): from yeast to mammals. Cell Mol Life Sci 55:284–296

Kambadur R, Sharma M, Smith TP, Bass JJ (1997) Mutations in myostatin (Gdf8) in double-muscled belgian blue and piedmontese cattle. Genome Res 7:910–916

Kami K, Senba E (1998) Localization of leukemia inhibitory factor and interleukin-6 messenger ribonucleic acids in regenerating rat skeletal muscle. Muscle Nerve 21:819–822

Kardon G, Campbell JK, Tabin CJ (2002) Local extrinsic signals determine muscle and endothelial cell fate and patterning in the vertebrate limb. Dev Cell 3:533–545

Kassar-Duchossoy L, Giacone E, Gayraud-Morel B, Jory A, Gomes D, Tajbakhsh S (2005) Pax3/Pax7 mark a novel population of primitive myogenic cells during development. Genes Dev 19:1426–1431

Katagiri T, Imada M, Yanai T, Suda T, Takahashi N, Kamijo R (2002) Identification of a Bmp-responsive element in Id1, the gene for inhibition of myogenesis. Genes Cells 7:949–960

Katz B (1961) The terminations of the afferent nerve fibre in the muscle spindle of the frog. Philos Trans R Soc Lond B Biol Sci 243:221–240

Khan J, Bittner ML, Saal LH, Teichmann U, Azorsa DO, Gooden GC, Pavan WJ, Trent JM, Meltzer PS (1999) cDNA microarrays detect activation of a myogenic transcription program by the Pax3-Fkhr fusion oncogene. Proc Natl Acad Sci USA 96:13264–13269

Kiel MJ, He S, Ashkenazi R, Gentry SN, Teta M, Kushner JA, Jackson TL, Morrison SJ (2007) Haematopoietic stem cells do not asymmetrically segregate chromosomes or retain BrdU. Nature 449:238–242

Kiess M, Gill RM, Hamel PA (1995) Expression of the positive regulator of cell cycle progression, cyclin D3, is induced during differentiation of myoblasts into quiescent myotubes. Oncogene 10:159–166

Kitzmann M, Carnac G, Vandromme M, Primig M, Lamb NJ, Fernandez A (1998) The muscle regulatory factors myod and Myf-5 undergo distinct cell cycle-specific expression in muscle cells. J Cell Biol 142:1447–1459

Kitzmann M, Vandromme M, Schaeffer V, Carnac G, Labbe JC, Lamb N, Fernandez A (1999) Cdk1- and Cdk2-mediated phosphorylation of myod Ser200 in growing C2 myoblasts: role in modulating myod half-life and myogenic activity. Mol Cell Biol 19:3167–3176

Koleva M, Kappler R, Vogler M, Herwig A, Fulda S, Hahn H (2005) Pleiotropic effects of sonic hedgehog on muscle satellite cells. Cell Mol Life Sci 62:1863–1870

Kong Y, Johnson SE, Taparowsky EJ, Konieczny SF (1995) Ras p21val inhibits myogenesis without altering the DNA binding or transcriptional activities of the myogenic basic helix-loop-helix factors. Mol Cell Biol 15:5205–5213

Kong LJ, Chang JT, Bild AH, Nevins JR (2007) Compensation and specificity of function within the E2F family. Oncogene 26:321–327

Korenjak M, Brehm A (2005) E2f-rb complexes regulating transcription of genes important for differentiation and development. Curr Opin Genet Dev 15:520–527

Krude T, Jackman M, Pines J, Laskey RA (1997) Cyclin/Cdk-dependent initiation of DNA replication in a human cell-free system. Cell 88:109–119

Kuang S, Kuroda K, Le Grand F, Rudnicki MA (2007) Asymmetric self-renewal and commitment of satellite stem cells in muscle. Cell 129:999–1010

Kuang S, Gillespie MA, Rudnicki MA (2008) Niche regulation of muscle satellite cell self-renewal and differentiation. Cell Stem Cell 2:22–31

Kubiak JZ, Ciemerych MA, Hupalowska A, Sikora-Polaczek M, Polanski Z (2008) On the transition from the meiotic to mitotic cell cycle during early mouse development. Int J Dev Biol 52:201–217

Kurek J, Bower J, Romanella M, Austin L (1996) Leukaemia inhibitory factor treatment stimulates muscle regeneration in the mdx mouse. Neurosci Lett 212:167–170

Kurisaki T, Masuda A, Sudo K, Sakagami J, Higashiyama S, Matsuda Y, Nagabukuro A, Tsuji A, Nabeshima Y, Asano M, Iwakura Y, Sehara-Fujisawa A (2003) Phenotypic analysis of meltrin alpha (ADAM12)-deficient mice: involvement of meltrin alpha in adipogenesis and myogenesis. Mol Cell Biol 23:55–61

Kuroda K, Tani S, Tamura K, Minoguchi S, Kurooka H, Honjo T (1999) Delta-induced notch signaling mediated by rbp-j inhibits MyoD expression and myogenesis. J Biol Chem 274:7238–7244

La Baer J, Garrett MD, Stevenson LF, Slingerland JM, Sandhu C, Chou HS, Fattaey A, Harlow E (1997) New functional activities for the p21 family of Cdk inhibitors. Genes Dev 11:847–862

LaBarge MA, Blau HM (2002) Biological progression from adult bone marrow to mononucleate muscle stem cell to multinucleate muscle fiber in response to injury. Cell 111:589–601

Lafreniere JF, Mills P, Bouchentouf M, Tremblay JP (2006) Interleukin-4 improves the migration of human myogenic precursor cells in vitro and in vivo. Exp Cell Res 312:1127–1141

Lasorella A, Noseda M, Beyna M, Yokota Y, Iavarone A (2000) Id2 is a retinoblastoma protein target and mediates signalling by myc oncoproteins. Nature 407:592–598

Latham KE (1999) Mechanisms and control of embryonic genome activation in mammalian embryos. Int Rev Cytol 193:71–124

Lattanzi L, Salvatori G, Coletta M, Sonnino C, Cusella De Angelis MG, Gioglio L, Murry CE, Kelly R, Ferrari G, Molinaro M, Crescenzi M, Mavilio F, Cossu G (1998) High efficiency myogenic conversion of human fibroblasts by adenoviral vector-mediated myod gene transfer. An alternative strategy for ex vivo gene therapy of primary myopathies. J Clin Invest 101:2119–2128

Lavoie JN, L'Allemain G, Brunet A, Muller R, Pouyssegur J (1996) Cyclin D1 expression is regulated positively by the p42/p44MAPK and negatively by the p38/hogMAPK pathway. J Biol Chem 271:20608–20616

Le Grand F, Jones AE, Seale V, Scime A, Rudnicki MA (2009) Wnt7a activates the planar cell polarity pathway to drive the symmetric expansion of satellite stem cells. Cell Stem Cell 4:535–547

LeCouter JE, Kablar B, Whyte PF, Ying C, Rudnicki MA (1998) Strain-dependent embryonic lethality in mice lacking the retinoblastoma-related p130 gene. Development 125:4669–4679

Lee MG, Nurse P (1987) Complementation used to clone a human homologue of the fission yeast cell cycle control gene cdc2. Nature 327:31–35

Lee EY, Chang CY, Hu N, Wang YC, Lai CC, Herrup K, Lee WH, Bradley A (1992) Mice deficient for Rb are nonviable and show defects in neurogenesis and haematopoiesis. Nature 359:288–294

Lee MH, Reynisdottir I, Massague J (1995) Cloning of p57kip2, a cyclin-dependent kinase inhibitor with unique domain structure and tissue distribution. Genes Dev 9:639–649

Lee MH, Williams BO, Mulligan G, Mukai S, Bronson RT, Dyson N, Harlow E, Jacks T (1996) Targeted disruption of p107: functional overlap between p107 and Rb. Genes Dev 10:1621–1632

Lee KY, Ladha MH, McMahon C, Ewen ME (1999) The retinoblastoma protein is linked to the activation of ras. Mol Cell Biol 19:7724–7732

Lees JA, Saito M, Vidal M, Valentine M, Look T, Harlow E, Dyson N, Helin K (1993) The retinoblastoma protein binds to a family of E2F transcription factors. Mol Cell Biol 13:7813–7825

Lefaucheur JP, Sebille A (1995) Muscle regeneration following injury can be modified in vivo by immune neutralization of basic fibroblast growth factor, transforming growth factor beta 1 or insulin-like growth factor I. J Neuroimmunol 57:85–91

Leone G, Nuckolls F, Ishida S, Adams M, Sears R, Jakoi L, Miron A, Nevins JR (2000) Identification of a novel E2F3 product suggests a mechanism for determining specificity of repression by Rb proteins. Mol Cell Biol 20:3626–3632

Leshem Y, Halevy O (2002) Phosphorylation of prb is required for HGF-induced muscle cell proliferation and is p27kip1-dependent. J Cell Physiol 191:173–182

Leshem Y, Spicer DB, Gal-Levi R, Halevy O (2000) Hepatocyte growth factor (HGF) inhibits skeletal muscle cell differentiation: a role for the bHLH protein twist and the Cdk inhibitor p27. J Cell Physiol 184:101–109

Leshem Y, Gitelman I, Ponzetto C, Halevy O (2002) Preferential binding of grb2 or phosphatidylinositol 3-kinase to the met receptor has opposite effects on HGF-induced myoblast proliferation. Exp Cell Res 274:288–298

Levi E, Fridman R, Miao HQ, Ma YS, Yayon A, Vlodavsky I (1996) Matrix metalloproteinase 2 releases active soluble ectodomain of fibroblast growth factor receptor 1. Proc Natl Acad Sci USA 93:7069–7074

Li YP (2003) TNF-alpha is a mitogen in skeletal muscle. Am J Physiol Cell Physiol 285: C370–C376

Li L, Clevers H (2010) Coexistence of quiescent and active adult stem cells in mammals. Science 327:542–545

Li L, Chambard JC, Karin M, Olson EN (1992a) Fos and jun repress transcriptional activation by myogenin and MyoD: the amino terminus of jun can mediate repression. Genes Dev 6: 676–689

Li L, Zhou J, James G, Heller-Harrison R, Czech MP, Olson EN (1992b) FGF inactivates myogenic helix-loop-helix proteins through phosphorylation of a conserved protein kinase C site in their DNA-binding domains. Cell 71:1181–1194

Li YP, Chen Y, John J, Moylan J, Jin B, Mann DL, Reid MB (2005) TNF-alpha acts via p38 MAPK to stimulate expression of the ubiquitin ligase atrogin1/mafbx in skeletal muscle. FASEB J 19:362–370

Li W, Moylan JS, Chambers MA, Smith J, Reid MB (2009) Interleukin-1 stimulates catabolism in C2C12 myotubes. Am J Physiol Cell Physiol 297:C706–C714

Liu S, Spinner DS, Schmidt MM, Danielsson JA, Wang S, Schmidt J (2000) Interaction of MyoD family proteins with enhancers of acetylcholine receptor subunit genes in vivo. J Biol Chem 275:41364–41368

Lord KA, Abdollahi A, Thomas SM, DeMarco M, Brugge JS, Hoffman-Liebermann B, Liebermann DA (1991) Leukemia inhibitory factor and interleukin-6 trigger the same immediate early response, including tyrosine phosphorylation, upon induction of myeloid leukemia differentiation. Mol Cell Biol 11:4371–4379

Loveys DA, Streiff MB, Kato GJ (1996) E2a basic-helix-loop-helix transcription factors are negatively regulated by serum growth factors and by the Id3 protein. Nucleic Acids Res 24:2813–2820

Lundberg AS, Weinberg RA (1998) Functional inactivation of the retinoblastoma protein requires sequential modification by at least two distinct cyclin-Cdk complexes. Mol Cell Biol 18:753–761

Luttrell LM, van Biesen T, Hawes BE, Koch WJ, Touhara K, Lefkowitz RJ (1995) G beta gamma subunits mediate mitogen-activated protein kinase activation by the tyrosine kinase insulin-like growth factor 1 receptor. J Biol Chem 270:16495–16498

Ma T, Van Tine BA, Wei Y, Garrett MD, Nelson D, Adams PD, Wang J, Qin J, Chow LT, Harper JW (2000) Cell cycle-regulated phosphorylation of p220(Npat) by cyclin E/Cdk2 in Cajal bodies promotes histone gene transcription. Genes Dev 14:2298–2313

Macaluso M, Montanari M, Giordano A (2006) Rb family proteins as modulators of gene expression and new aspects regarding the interaction with chromatin remodeling enzymes. Oncogene 25:5263–5267

Machida S, Booth FW (2004) Insulin-like growth factor 1 and muscle growth: implication for satellite cell proliferation. Proc Nutr Soc 63:337–340

Machida S, Spangenburg EE, Booth FW (2003) Forkhead transcription factor Foxo1 transduces insulin-like growth factor's signal to p27kip1 in primary skeletal muscle satellite cells. J Cell Physiol 196:523–531

Magenta A, Cenciarelli C, De Santa F, Fuschi P, Martelli F, Caruso M, Felsani A (2003) MyoD stimulates Rb promoter activity via the Creb/p300 nuclear transduction pathway. Mol Cell Biol 23:2893–2906

Mal A, Harter ML (2003) MyoD is functionally linked to the silencing of a muscle-specific regulatory gene prior to skeletal myogenesis. Proc Natl Acad Sci USA 100:1735–1739

Mal A, Sturniolo M, Schiltz RL, Ghosh MK, Harter ML (2001) A role for histone deacetylase HDAC1 in modulating the transcriptional activity of myod: inhibition of the myogenic program. EMBO J 20:1739–1753

Malumbres M, Barbacid M (2005) Mammalian cyclin-dependent kinases. Trends Biochem Sci 30:630–641

Mariappan I, Parnaik VK (2005) Sequestration of pRb by cyclin D3 causes intranuclear reorganization of lamin A/C during muscle cell differentiation. Mol Biol Cell 16:1948–1960

Maroto M, Reshef R, Munsterberg AE, Koester S, Goulding M, Lassar AB (1997) Ectopic Pax-3 activates MyoD and Myf-5 expression in embryonic mesoderm and neural tissue. Cell 89:139–148

Martelli F, Cenciarelli C, Santarelli G, Polikar B, Felsani A, Caruso M (1994) MyoD induces retinoblastoma gene expression during myogenic differentiation. Oncogene 9:3579–3590

Martin JF, Li L, Olson EN (1992) Repression of myogenin function by TGF-beta 1 is targeted at the basic helix-loop-helix motif and is independent of E2a products. J Biol Chem 267:10956–10960

Massague J, Cheifetz S, Endo T, Nadal-Ginard B (1986) Type beta transforming growth factor is an inhibitor of myogenic differentiation. Proc Natl Acad Sci USA 83:8206–8210
Masui Y (2001) From oocyte maturation to the in vitro cell cycle: the history of discoveries of maturation-promoting factor (MPF) and cytostatic factor (CSF). Differentiation 69:1–17
Masui Y, Markert CL (1971) Cytoplasmic control of nuclear behavior during meiotic maturation of frog oocytes. J Exp Zool 177:129–145
Mauro A (1961) Satellite cell of skeletal muscle fibers. J Biophys Biochem Cytol 9:493–495
Mayanil CS, George D, Freilich L, Miljan EJ, Mania-Farnell B, McLone DG, Bremer EG (2001) Microarray analysis detects novel Pax3 downstream target genes. J Biol Chem 276:49299–49309
McCroskery S, Thomas M, Maxwell L, Sharma M, Kambadur R (2003) Myostatin negatively regulates satellite cell activation and self-renewal. J Cell Biol 162:1135–1147
McFarland DC, Pesall JE (2008) Phospho-MAPK as a marker of myogenic satellite cell responsiveness to growth factors. Comp Biochem Physiol B Biochem Mol Biol 149:463–467
McGeachie JK, Grounds MD (1987) Initiation and duration of muscle precursor replication after mild and severe injury to skeletal muscle of mice. An autoradiographic study. Cell Tissue Res 248:125–130
McKinnell IW, Ishibashi J, Le Grand F, Punch VG, Addicks GC, Greenblatt JF, Dilworth FJ, Rudnicki MA (2008) Pax7 activates myogenic genes by recruitment of a histone methyltransferase complex. Nat Cell Biol 10:77–84
McKinsey TA, Zhang CL, Olson EN (2001) Control of muscle development by dueling HATs and HDACs. Curr Opin Genet Dev 11:497–504
McPherron AC, Lee SJ (1997) Double muscling in cattle due to mutations in the myostatin gene. Proc Natl Acad Sci USA 94:12457–12461
McPherron AC, Lawler AM, Lee SJ (1997) Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature 387:83–90
Melnikova IN, Christy BA (1996) Muscle cell differentiation is inhibited by the helix-loop-helix protein Id3. Cell Growth Differ 7:1067–1079
Melnikova IN, Bounpheng M, Schatteman GC, Gilliam D, Christy BA (1999) Differential biological activities of mammalian id proteins in muscle cells. Exp Cell Res 247:94–104
Miller KJ, Thaloor D, Matteson S, Pavlath GK (2000) Hepatocyte growth factor affects satellite cell activation and differentiation in regenerating skeletal muscle. Am J Physiol Cell Physiol 278:C174–C181
Miner JH, Wold B (1990) Herculin, a fourth member of the myod family of myogenic regulatory genes. Proc Natl Acad Sci USA 87:1089–1093
Minshull J, Golsteyn R, Hill CS, Hunt T (1990) The A- and B-type cyclin associated Cdc2 kinases in xenopus turn on and off at different times in the cell cycle. EMBO J 9:2865–2875
Mishina Y, Suzuki A, Ueno N, Behringer RR (1995) Bmpr encodes a type I bone morphogenetic protein receptor that is essential for gastrulation during mouse embryogenesis. Genes Dev 9:3027–3037
Molkentin JD, Black BL, Martin JF, Olson EN (1995) Cooperative activation of muscle gene expression by Mef2 and myogenic bHLH proteins. Cell 83:1125–1136
Momčilović O, Navara C, Schatten G (2011) Cell cycle adaptations and maintenance of genomic integrity in embryonic stem cells and induced pluripotent stem cells. In: Kubiak JZ (ed) Cell cycle in development. Results and problems in cell differentiation. Springer, Heidelberg
Moon NS, Dyson N (2008) E2f7 and E2F8 keep the E2F family in balance. Dev Cell 14:1–3
Moraczewski J, Archacka K, Brzoska E, Ciemerych MA, Grabowska I, Janczyk-Ilach K, Streminska W, Zimowska M (2008) From planarians to mammals – the many faces of regeneration. Int J Dev Biol 52:219–227
Morgenbesser SD, Williams BO, Jacks T, De Pinho RA (1994) p53-dependent apoptosis produced by Rb-deficiency in the developing mouse lens. Nature 371:72–74
Murga C, Laguinge L, Wetzker R, Cuadrado A, Gutkind JS (1998) Activation of AKT/protein kinase B by G protein-coupled receptors. A role for alpha and beta gamma subunits of heterotrimeric G proteins acting through phosphatidylinositol-3-OH kinase gamma. J Biol Chem 273:19080–19085

Musaro A, McCullagh KJ, Naya FJ, Olson EN, Rosenthal N (1999) IGF-1 induces skeletal myocyte hypertrophy through calcineurin in association with GATA-2 and NF-ATC1. Nature 400:581–585

Nakamura T, Teramoto H, Ichihara A (1986) Purification and characterization of a growth factor from rat platelets for mature parenchymal hepatocytes in primary cultures. Proc Natl Acad Sci USA 83:6489–6493

Nameroff M, Holtzer H (1969) Contact-mediated reversible suppression of myogenesis. Dev Biol 19:380–396

Novitch BG, Mulligan GJ, Jacks T, Lassar AB (1996) Skeletal muscle cells lacking the retinoblastoma protein display defects in muscle gene expression and accumulate in S and G2 phases of the cell cycle. J Cell Biol 135:441–456

Novitch BG, Spicer DB, Kim PS, Cheung WL, Lassar AB (1999) pRb is required for Mef2-dependent gene expression as well as cell-cycle arrest during skeletal muscle differentiation. Curr Biol 9:449–459

Okuda M, Horn HF, Tarapore P, Tokuyama Y, Smulian AG, Chan PK, Knudsen ES, Hofmann IA, Snyder JD, Bove KE, Fukasawa K (2000) Nucleophosmin/b23 is a target of Cdk2/cyclin E in centrosome duplication. Cell 103:127–140

Olson E (1992) Activation of muscle-specific transcription by myogenic helix-loop-helix proteins. Symp Soc Exp Biol 46:331–341

Olson EN, Klein WH (1994) bHLH factors in muscle development: dead lines and commitments, what to leave in and what to leave out. Genes Dev 8:1–8

Ono Y, Gnocchi VF, Zammit PS, Nagatomi R (2009) Presenilin-1 acts via Id1 to regulate the function of muscle satellite cells in a gamma-secretase-independent manner. J Cell Sci 122: 4427–4438

Ott MO, Bober E, Lyons G, Arnold H, Buckingham M (1991) Early expression of the myogenic regulatory gene, myf-5, in precursor cells of skeletal muscle in the mouse embryo. Development 111:1097–1107

Pagano M, Pepperkok R, Verde F, Ansorge W, Draetta G (1992) Cyclin A is required at two points in the human cell cycle. EMBO J 11:961–971

Pallafacchina G, Francois S, Regnault B, Czarny B, Dive V, Cumano A, Montarras D, Buckingham M (2010) An adult tissue-specific stem cell in its niche: a gene profiling analysis of in vivo quiescent and activated muscle satellite cells. Stem Cell Res 4:77–91

Park GH, Kariya S, Monani UR (2010) Spinal muscular atrophy: new and emerging insights from model mice. Curr Neurol Neurosci Rep 10:108–117

Parker SB, Eichele G, Zhang P, Rawls A, Sands AT, Bradley A, Olson EN, Harper JW, Elledge SJ (1995) p53-independent expression of p21cip1 in muscle and other terminally differentiating cells. Science 267:1024–1027

Parker MH, Seale P, Rudnicki MA (2003) Looking back to the embryo: defining transcriptional networks in adult myogenesis. Nat Rev Genet 4:497–507

Perdiguero E, Ruiz-Bonilla V, Gresh L, Hui L, Ballestar E, Sousa-Victor P, Baeza-Raja B, Jardi M, Bosch-Comas A, Esteller M, Caelles C, Serrano AL, Wagner EF, Munoz-Canoves P (2007) Genetic analysis of p38 MAP kinases in myogenesis: fundamental role of p38alpha in abrogating myoblast proliferation. EMBO J 26:1245–1256

Petersen BO, Lukas J, Sorensen CS, Bartek J, Helin K (1999) Phosphorylation of mammalian cdc6 by cyclin A/Cdk2 regulates its subcellular localization. EMBO J 18:396–410

Polyak K, Kato JY, Solomon MJ, Sherr CJ, Massague J, Roberts JM, Koff A (1994) p27kip1, a cyclin-Cdk inhibitor, links transforming growth factor-beta and contact inhibition to cell cycle arrest. Genes Dev 8:9–22

Ponzetto C, Pante G, Prunotto C, Ieraci A, Maina F (2000) Met signaling mutants as tools for developmental studies. Int J Dev Biol 44:645–653

Potten CS, Booth C, Pritchard DM (1997) The intestinal epithelial stem cell: the mucosal governor. Int J Exp Pathol 78:219–243

Prabhu S, Ignatova A, Park ST, Sun XH (1997) Regulation of the expression of cyclin-dependent kinase inhibitor p21 by E2a and Id proteins. Mol Cell Biol 17:5888–5896

Puri PL, Avantaggiati ML, Balsano C, Sang N, Graessmann A, Giordano A, Levrero M (1997a) p300 is required for MyoD-dependent cell cycle arrest and muscle-specific gene transcription. EMBO J 16:369–383

Puri PL, Sartorelli V, Yang XJ, Hamamori Y, Ogryzko VV, Howard BH, Kedes L, Wang JY, Graessmann A, Nakatani Y, Levrero M (1997b) Differential roles of p300 and pCAF acetyltransferases in muscle differentiation. Mol Cell 1:35–45

Puri PL, Iezzi S, Stiegler P, Chen TT, Schiltz RL, Muscat GE, Giordano A, Kedes L, Wang JY, Sartorelli V (2001) Class I histone deacetylases sequentially interact with MyoD and pRb during skeletal myogenesis. Mol Cell 8:885–897

Quelle DE, Ashmun RA, Hannon GJ, Rehberger PA, Trono D, Richter KH, Walker C, Beach D, Sherr CJ, Serrano M (1995) Cloning and characterization of murine p16ink4a and p15ink4b genes. Oncogene 11:635–645

Ramocki MB, Johnson SE, White MA, Ashendel CL, Konieczny SF, Taparowsky EJ (1997) Signaling through mitogen-activated protein kinase and Rac/Rho does not duplicate the effects of activated ras on skeletal myogenesis. Mol Cell Biol 17:3547–3555

Ramocki MB, White MA, Konieczny SF, Taparowsky EJ (1998) A role for ralGDS and a novel ras effector in the ras-mediated inhibition of skeletal myogenesis. J Biol Chem 273:17696–17701

Rao SS, Kohtz DS (1995) Positive and negative regulation of D-type cyclin expression in skeletal myoblasts by basic fibroblast growth factor and transforming growth factor beta. A role for cyclin D1 in control of myoblast differentiation. J Biol Chem 270:4093–4100

Rao PN, Wilson B, Puck TT (1977) Premature chromosome condensation and cell cycle analysis. J Cell Physiol 91:131–141

Rao SS, Chu C, Kohtz DS (1994) Ectopic expression of cyclin D1 prevents activation of gene transcription by myogenic basic helix-loop-helix regulators. Mol Cell Biol 14:5259–5267

Reed SA, Ouellette SE, Liu X, Allen RE, Johnson SE (2007) E2F5 and Lek1 translocation to the nucleus is an early event demarcating myoblast quiescence. J Cell Biochem 101:1394–1408

Reem GH, Yeh NH (1984) Interleukin 2 regulates expression of its receptor and synthesis of gamma interferon by human T lymphocytes. Science 225:429–430

Reimann J, Irintchev A, Wernig A (2000) Regenerative capacity and the number of satellite cells in soleus muscles of normal and mdx mice. Neuromuscul Disord 10:276–282

Relaix F, Rocancourt D, Mansouri A, Buckingham M (2004) Divergent functions of murine Pax3 and Pax7 in limb muscle development. Genes Dev 18:1088–1105

Relaix F, Rocancourt D, Mansouri A, Buckingham M (2005) A Pax3/Pax7-dependent population of skeletal muscle progenitor cells. Nature 435:948–953

Renault V, Thornell LE, Eriksson PO, Butler-Browne G, Mouly V (2002) Regenerative potential of human skeletal muscle during aging. Aging Cell 1:132–139

Ridgeway AG, Skerjanc IS (2001) Pax3 is essential for skeletal myogenesis and the expression of Six1 and Eya2. J Biol Chem 276:19033–19039

Rios R, Carneiro I, Arce VM, Devesa J (2001) Myostatin regulates cell survival during C2C12 myogenesis. Biochem Biophys Res Commun 280:561–566

Rosenblatt JD, Lunt AI, Parry DJ, Partridge TA (1995) Culturing satellite cells from living single muscle fiber explants. In Vitro Cell Dev Biol Anim 31:773–779

Rossi CA, Pozzobon M, Ditadi A, Archacka K, Gastaldello A, Sanna M, Franzin C, Malerba A, Milan G, Cananzi M, Schiaffino S, Campanella M, Vettor R, De Coppi P (2010) Clonal characterization of rat muscle satellite cells: proliferation, metabolism and differentiation define an intrinsic heterogeneity. PLoS One 5:e8523

Rudnicki MA, Braun T, Hinuma S, Jaenisch R (1992) Inactivation of MyoD in mice leads to up-regulation of the myogenic HLH gene Myf-5 and results in apparently normal muscle development. Cell 71:383–390

Russell P, Nurse P (1987) The mitotic inducer Nim1+ functions in a regulatory network of protein kinase homologs controlling the initiation of mitosis. Cell 49:569–576

Russo S, Tomatis D, Collo G, Tarone G, Tato F (1998) Myogenic conversion of NIH3T3 cells by exogenous MyoD family members: dissociation of terminal differentiation from myotube formation. J Cell Sci 111(Pt 6):691–700

Ryder-Cook AS, Sicinski P, Thomas K, Davies KE, Worton RG, Barnard EA, Darlison MG, Barnard PJ (1988) Localization of the mdx mutation within the mouse dystrophin gene. EMBO J 7:3017–3021

Sabourin LA, Girgis-Gabardo A, Seale P, Asakura A, Rudnicki MA (1999) Reduced differentiation potential of primary myod−/− myogenic cells derived from adult skeletal muscle. J Cell Biol 144:631–643

Sage J, Mulligan GJ, Attardi LD, Miller A, Chen S, Williams B, Theodorou E, Jacks T (2000) Targeted disruption of the three Rb-related genes leads to loss of G(1) control and immortalization. Genes Dev 14:3037–3050

Sakuma K, Watanabe K, Sano M, Uramoto I, Totsuka T (2000) Differential adaptation of growth and differentiation factor 8/myostatin, fibroblast growth factor 6 and leukemia inhibitory factor in overloaded, regenerating and denervated rat muscles. Biochim Biophys Acta 1497:77–88

Salisbury E, Sakai K, Schoser B, Huichalaf C, Schneider-Gold C, Nguyen H, Wang GL, Albrecht JH, Timchenko LT (2008) Ectopic expression of cyclin D3 corrects differentiation of DM1 myoblasts through activation of RNA CUG-binding protein, CUGBP1. Exp Cell Res 314:2266–2278

Sartorelli V, Caretti G (2005) Mechanisms underlying the transcriptional regulation of skeletal myogenesis. Curr Opin Genet Dev 15:528–535

Sartorelli V, Puri PL, Hamamori Y, Ogryzko V, Chung G, Nakatani Y, Wang JY, Kedes L (1999) Acetylation of myod directed by pCAF is necessary for the execution of the muscle program. Mol Cell 4:725–734

Sassone-Corsi P, Mizzen CA, Cheung P, Crosio C, Monaco L, Jacquot S, Hanauer A, Allis CD (1999) Requirement of Rsk-2 for epidermal growth factor-activated phosphorylation of histone H3. Science 285:886–891

Sassoon D, Lyons G, Wright WE, Lin V, Lassar A, Weintraub H, Buckingham M (1989) Expression of two myogenic regulatory factors myogenin and myod1 during mouse embryogenesis. Nature 341:303–307

Sato T, Rocancourt D, Marques L, Thorsteinsdottir S, Buckingham M (2010) A Pax3/Dmrt2/Myf5 regulatory cascade functions at the onset of myogenesis. PLoS Genet 6:e1000897

Savatier P, Huang S, Szekely L, Wiman KG, Samarut J (1994) Contrasting patterns of retinoblastoma protein expression in mouse embryonic stem cells and embryonic fibroblasts. Oncogene 9:809–818

Savatier P, Lapillonne H, van Grunsven LA, Rudkin BB, Samarut J (1996) Withdrawal of differentiation inhibitory activity/leukemia inhibitory factor up-regulates D-type cyclins and cyclin-dependent kinase inhibitors in mouse embryonic stem cells. Oncogene 12:p309–p322

Scata KA, Bernard DW, Fox J, Swain JL (1999) FGF receptor availability regulates skeletal myogenesis. Exp Cell Res 250:10–21

Schabort EJ, van der Merwe M, Loos B, Moore FP, Niesler CU (2009) TGF-beta's delay skeletal muscle progenitor cell differentiation in an isoform-independent manner. Exp Cell Res 315:373–384

Schmalbruch H, Hellhammer U (1976) The number of satellite cells in normal human muscle. Anat Rec 185:279–287

Schmalbruch H, Hellhammer U (1977) The number of nuclei in adult rat muscles with special reference to satellite cells. Anat Rec 189:169–175

Schneider JW, Gu W, Zhu L, Mahdavi V, Nadal-Ginard B (1994) Reversal of terminal differentiation mediated by p107 in Rb−/− muscle cells. Science 264:1467–1471

Schultz E, Gibson MC, Champion T (1978) Satellite cells are mitotically quiescent in mature mouse muscle: an EM and radioautographic study. J Exp Zool 206:451–456

Schuster-Gossler K, Cordes R, Gossler A (2007) Premature myogenic differentiation and depletion of progenitor cells cause severe muscle hypotrophy in delta1 mutants. Proc Natl Acad Sci USA 104:537–542

Seale P, Sabourin LA, Girgis-Gabardo A, Mansouri A, Gruss P, Rudnicki MA (2000) Pax7 is required for the specification of myogenic satellite cells. Cell 102:777–786

Serrano M, Hannon GJ, Beach D (1993) A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/Cdk4. Nature 366:704–707

Shanely RA, Zwetsloot KA, Childs TE, Lees SJ, Tsika RW, Booth FW (2009) IGF-I activates the mouse type IIb myosin heavy chain gene. Am J Physiol Cell Physiol 297:C1019–C1027

Sharpless NE, DePinho RA (2002) p53: good cop/bad cop. Cell 110:9–12

Sheaff RJ, Groudine M, Gordon M, Roberts JM, Clurman BE (1997) Cyclin E-Cdk2 is a regulator of p27kip1. Genes Dev 11:1464–1478

Sheehan SM, Allen RE (1999) Skeletal muscle satellite cell proliferation in response to members of the fibroblast growth factor family and hepatocyte growth factor. J Cell Physiol 181:499–506

Shefer G, Van de Mark DP, Richardson JB, Yablonka-Reuveni Z (2006) Satellite-cell pool size does matter: defining the myogenic potency of aging skeletal muscle. Dev Biol 294:50–66

Sherr CJ, Roberts JM (1999) Cdk inhibitors: positive and negative regulators of G1-phase progression. Genes Dev 13:1501–1512

Sherr CJ, Roberts JM (2004) Living with or without cyclins and cyclin-dependent kinases. Genes Dev 18:2699–2711

Sherr CJ, Matsushime H, Roussel MF (1992) Regulation of cyl/cyclin D genes by colony-stimulating factor 1. Ciba Found Symp 170:209–219

Shi H, Boadu E, Mercan F, Le AM, Roth Flach RJ, Zhang L, Tyner KJ, Olwin BB, Bennett AM (2010) MAP kinase phosphatase-1 deficiency impairs skeletal muscle regeneration and exacerbates muscular dystrophy. FASEB J 24:2985–2997

Shin EK, Shin A, Paulding C, Schaffhausen B, Yee AS (1995) Multiple change in E2F function and regulation occur upon muscle differentiation. Mol Cell Biol 15:2252–2262

Shinin V, Gayraud-Morel B, Gomes D, Tajbakhsh S (2006) Asymmetric division and cosegregation of template DNA strands in adult muscle satellite cells. Nat Cell Biol 8:677–687

Shinin V, Gayraud-Morel B, Tajbakhsh S (2009) Template DNA-strand co-segregation and asymmetric cell division in skeletal muscle stem cells. Methods Mol Biol 482:295–317

Sicinski P, Geng Y, Ryder-Cook AS, Barnard EA, Darlison MG, Barnard PJ (1989) The molecular basis of muscular dystrophy in the mdx mouse: a point mutation. Science 244:1578–1580

Sikora-Polaczek M, Hupalowska A, Polanski Z, Kubiak JZ, Ciemerych MA (2006) The first mitosis of the mouse embryo is prolonged by transitional metaphase arrest. Biol Reprod 74:734–743

Simanis V, Nurse P (1986) The cell cycle control gene cdc2+ of fission yeast encodes a protein kinase potentially regulated by phosphorylation. Cell 45:261–268

Simone C, Forcales SV, Hill DA, Imbalzano AN, Latella L, Puri PL (2004) p38 pathway targets Swi-Snf chromatin-remodeling complex to muscle-specific loci. Nat Genet 36:738–743

Sironi M, Breviario F, Proserpio P, Biondi A, Vecchi A, Van Damme J, Dejana E, Mantovani A (1989) Il-1 stimulates Il-6 production in endothelial cells. J Immunol 142:549–553

Skapek SX, Rhee J, Spicer DB, Lassar AB (1995) Inhibition of myogenic differentiation in proliferating myoblasts by cyclin D1-dependent kinase. Science 267:1022–1024

Smith LD, Ecker RE (1971) The interaction of steroids with Rana pipiens oocytes in the induction of maturation. Dev Biol 25:232–247

Song A, Wang Q, Goebl MG, Harrington MA (1998) Phosphorylation of nuclear MyoD is required for its rapid degradation. Mol Cell Biol 18:4994–4999

Spangenburg EE, Booth FW (2002) Multiple signaling pathways mediate LIF-induced skeletal muscle satellite cell proliferation. Am J Physiol Cell Physiol 283:C204–C211

Stead E, White J, Faast R, Conn S, Goldstone S, Rathjen J, Dhingra U, Rathjen P, Walker D, Dalton S (2002) Pluripotent cell division cycles are driven by ectopic Cdk2, cyclin A/E and E2F activities. Oncogene 21:8320–8333

Straface G, Aprahamian T, Flex A, Gaetani E, Biscetti F, Smith RC, Pecorini G, Pola E, Angelini F, Stigliano E, Castellot JJ Jr, Losordo DW, Pola R (2009) Sonic hedgehog regulates angiogenesis and myogenesis during post-natal skeletal muscle regeneration. J Cell Mol Med 13:2424–2435

Strahl BD, Allis CD (2000) The language of covalent histone modifications. Nature 403:41–45
Strober BE, Dunaief JL, Guha GSP (1996) Functional interactions between the hBRM/hBRG1 transcriptional activators and the pRb family of proteins. Mol Cell Biol 16:1576–1583
Sun XH, Copeland NG, Jenkins NA, Baltimore D (1991) Id proteins Id1 and Id2 selectively inhibit DNA binding by one class of helix-loop-helix proteins. Mol Cell Biol 11:5603–5611
Sun D, Li H, Zolkiewska A (2008) The role of delta-like 1 shedding in muscle cell self-renewal and differentiation. J Cell Sci 121:3815–3823
Sunkara PS, Al-Bader AA, Riker MA, Rao PN (1980) Induction of prematurely condensed chromosomes by mitoplasts. Cell Biol Int Rep 4:1025–1029
Suzuki S, Yamanouchi K, Soeta C, Katakai Y, Harada R, Naito K, Tojo H (2002) Skeletal muscle injury induces hepatocyte growth factor expression in spleen. Biochem Biophys Res Commun 292:709–714
Szabo G, Dallmann G, Muller G, Patthy L, Soller M, Varga L (1998) A deletion in the myostatin gene causes the compact (cmpt) hypermuscular mutation in mice. Mamm Genome 9:671–672
Taipale J, Keski-Oja J (1997) Growth factors in the extracellular matrix. FASEB J 11:51–59
Tajbakhsh S, Rocancourt D, Cossu G, Buckingham M (1997) Redefining the genetic hierarchies controlling skeletal myogenesis: Pax-3 and Myf-5 act upstream of MyoD. Cell 89:127–138
Takahashi C, Bronson RT, Socolovsky M, Contreras B, Lee KY, Jacks T, Noda M, Kucherlapati R, Ewen ME (2003) Rb and N-ras function together to control differentiation in the mouse. Mol Cell Biol 23:5256–5268
Tanaka Y, Yamaguchi A, Fujikawa T, Sakuma K, Morita I, Ishii K (2008) Expression of mRNA for specific fibroblast growth factors associates with that of the myogenic markers myod and proliferating cell nuclear antigen in regenerating and overloaded rat plantaris muscle. Acta Physiol (Oxf) 194:149–159
Tanaka KK, Hall JK, Troy AA, Cornelison DD, Majka SM, Olwin BB (2009) Syndecan-4-expressing muscle progenitor cells in the SP engraft as satellite cells during muscle regeneration. Cell Stem Cell 4:217–225
Tarapore P, Okuda M, Fukasawa K (2002) A mammalian in vitro centriole duplication system: evidence for involvement of Cdk2/cyclin E and nucleophosmin/B23 in centrosome duplication. Cell Cycle 1:75–81
Tatsumi R, Anderson JE, Nevoret CJ, Halevy O, Allen RE (1998) HGF/SF is present in normal adult skeletal muscle and is capable of activating satellite cells. Dev Biol 194:114–128
Ten Broek RW, Grefte S, Von den Hoff JW (2010) Regulatory factors and cell populations involved in skeletal muscle regeneration. J Cell Physiol 224:7–16
Thomas M, Langley B, Berry C, Sharma M, Kirk S, Bass J, Kambadur R (2000) Myostatin, a negative regulator of muscle growth, functions by inhibiting myoblast proliferation. J Biol Chem 275:40235–40243
Tong W, Pollard JW (2001) Genetic evidence for the interactions of cyclin D1 and p27(kip1) in mice. Mol Cell Biol 21:1319–1328
Tsai KY, Hu Y, Macleod KF, Crowley D, Yamasaki L, Jacks T (1998) Mutation of E2F-1 suppresses apoptosis and inappropriate S phase entry and extends survival of Rb-deficient mouse embryos. Mol Cell 2:293–304
Umeda M, Shimotohno A, Yamaguchi M (2005) Control of cell division and transcription by cyclin-dependent kinase-activating kinases in plants. Plant Cell Physiol 46:1437–1442
Vainikka S, Joukov V, Wennstrom S, Bergman M, Pelicci PG, Alitalo K (1994) Signal transduction by fibroblast growth factor receptor-4 (FGFR-4). Comparison with FGFR-1. J Biol Chem 269:18320–18326
Venuti JM, Morris JH, Vivian JL, Olson EN, Klein WH (1995) Myogenin is required for late but not early aspects of myogenesis during mouse development. J Cell Biol 128:563–576
Wall NA, Hogan BL (1995) Expression of bone morphogenetic protein-4 (BMP-4), bone morphogenetic protein-7 (BMP-7), fibroblast growth factor-8 (FGF-8) and sonic hedgehog (SHH) during branchial arch development in the chick. Mech Dev 53:383–392

Walsh K, Perlman H (1997) Cell cycle exit upon myogenic differentiation. Curr Opin Genet Dev 7:597–602

Wang Y, Blelloch R (2011) Cell cycle regulation by micrornas in stem cells. In: Kubiak JZ (ed) Cell cycle in development. Results and problems in cell differentiation. Springer, Heidelberg

Wang J, Helin K, Jin P, Nadal-Ginard B (1995) Inhibition of in vitro myogenic differentiation by cellular transcription factor E2F1. Cell Growth Differ 6:1299–1306

Wang H, Noulet F, Edom-Vovard F, Le Grand F, Duprez D (2010) BMP signaling at the tips of skeletal muscles regulates the number of fetal muscle progenitors and satellite cells during development. Dev Cell 18:643–654

Weintraub H, Tapscott SJ, Davis RL, Thayer MJ, Adam MA, Lassar AB, Miller AD (1989) Activation of muscle-specific genes in pigment, nerve, fat, liver, and fibroblast cell lines by forced expression of MyoD. Proc Natl Acad Sci USA 86:5434–5438

Weintraub H, Davis R, Tapscott S, Thayer M, Krause M, Benezra R, Blackwell TK, Turner D, Rupp R, Hollenberg S et al (1991) The MyoD gene family: nodal point during specification of the muscle cell lineage. Science 251:761–766

White J, Dalton S (2005) Cell cycle control of embryonic stem cells. Stem Cell Rev 1:131–138

White RB, Ziman MR (2008) Genome-wide discovery of Pax7 target genes during development. Physiol Genomics 33:41–49

White J, Stead E, Faast R, Conn S, Cartwright P, Dalton S (2005) Developmental activation of the Rb-E2F pathway and establishment of cell cycle-regulated cyclin-dependent kinase activity during embryonic stem cell differentiation. Mol Biol Cell 16:2018–2027

Whitman M (1998) Smads and early developmental signaling by the TGFbeta superfamily. Genes Dev 12:2445–2462

Williams BA, Ordahl CP (1994) Pax-3 expression in segmental mesoderm marks early stages in myogenic cell specification. Development 120:785–796

Wilson A, Laurenti E, Oser G, van der Wath RC, Blanco-Bose W, Jaworski M, Offner S, Dunant CF, Eshkind L, Bockamp E, Lio P, Macdonald HR, Trumpp A (2008) Hematopoietic stem cells reversibly switch from dormancy to self-renewal during homeostasis and repair. Cell 135:1118–1129

Winter B, Braun T, Arnold HH (1993) Camp-dependent protein kinase represses myogenic differentiation and the activity of the muscle-specific helix-loop-helix transcription factors Myf-5 and MyoD. J Biol Chem 268:9869–9878

Wong JT (1996) Protozoan cell cycle control. Biol Signals 5:301–308

Wozniak AC, Anderson JE (2005) Single-fiber isolation and maintenance of satellite cell quiescence. Biochem Cell Biol 83:674–676

Wrobel E, Brzoska E, Moraczewski J (2007) M-cadherin and beta-catenin participate in differentiation of rat satellite cells. Eur J Cell Biol 86:99–109

Wu J, Lim RW (2005) Regulation of inhibitor of differentiation gene 3 (Id3) expression by Sp2-motif binding factor in myogenic C2C12 cells: downregulation of DNA binding activity following skeletal muscle differentiation. Biochim Biophys Acta 1731:13–22

Wu Z, Woodring PJ, Bhakta KS, Tamura K, Wen F, Feramisco JR, Karin M, Wang JY, Puri PL (2000) p38 and extracellular signal-regulated kinases regulate the myogenic program at multiple steps. Mol Cell Biol 20:3951–3964

Wu L, de Bruin A, Saavedra HI, Starovic M, Trimboli A, Yang Y, Opavska J, Wilson P, Thompson JC, Ostrowski MC, Rosol TJ, Woollett LA, Weinstein M, Cross JC, Robinson ML, Leone G (2003) Extra-embryonic function of Rb is essential for embryonic development and viability. Nature 421:942–947

Wyzykowski JC, Winata TI, Mitin N, Taparowsky EJ, Konieczny SF (2002) Identification of novel myod gene targets in proliferating myogenic stem cells. Mol Cell Biol 22:6199–6208

Xiao J, Jethanandani P, Ziober BL, Kramer RH (2003) Regulation of alpha7 integrin expression during muscle differentiation. J Biol Chem 278:49780–49788

Xiong Y, Menninger J, Beach D, Ward DC (1992) Molecular cloning and chromosomal mapping of ccnd genes encoding human D-type cyclins. Genomics 13:575–584

Yablonka-Reuveni Z, Rudnicki MA, Rivera AJ, Primig M, Anderson JE, Natanson P (1999) The transition from proliferation to differentiation is delayed in satellite cells from mice lacking MyoD. Dev Biol 210:440–455

Yaffe D, Saxel O (1977a) A myogenic cell line with altered serum requirements for differentiation. Differentiation 7:159–166

Yaffe D, Saxel O (1977b) Serial passaging and differentiation of myogenic cells isolated from dystrophic mouse muscle. Nature 270:725–727

Yamada M, Tatsumi R, Yamanouchi K, Hosoyama T, Shiratsuchi S, Sato A, Mizunoya W, Ikeuchi Y, Furuse M, Allen RE (2010) High concentrations of HGF inhibit skeletal muscle satellite cell proliferation in vitro by inducing expression of myostatin: a possible mechanism for reestablishing satellite cell quiescence in vivo. Am J Physiol Cell Physiol 298: C465–C476

Yan Z, Choi S, Liu X, Zhang M, Schageman JJ, Lee SY, Hart R, Lin L, Thurmond FA, Williams RS (2003) Highly coordinated gene regulation in mouse skeletal muscle regeneration. J Biol Chem 278:8826–8836

Yang W, Zhang Y, Li Y, Wu Z, Zhu D (2007) Myostatin induces cyclin d1 degradation to cause cell cycle arrest through a phosphatidylinositol 3-kinase/Akt/Gsk-3 beta pathway and is antagonized by insulin-like growth factor 1. J Biol Chem 282:3799–3808

Yeoh GC, Holtzer H (1977) The effect of cell density, conditioned medium and cytosine arabinoside on myogenesis in primary and secondary cultures. Exp Cell Res 104:63–78

Zabludoff SD, Csete M, Wagner R, Yu X, Wold BJ (1998) p27kip1 is expressed transiently in developing myotomes and enhances myogenesis. Cell Growth Differ 9:1–11

Zacksenhaus E, Jiang Z, Chung D, Marth JD, Phillips RA, Gallie BL (1996) Prb controls proliferation, differentiation, and death of skeletal muscle cells and other lineages during embryogenesis. Genes Dev 10:3051–3064

Zammit PS, Golding JP, Nagata Y, Hudon V, Partridge TA, Beauchamp JR (2004) Muscle satellite cells adopt divergent fates: a mechanism for self-renewal? J Cell Biol 166:347–357

Zammit PS, Partridge TA, Yablonka-Reuveni Z (2006) The skeletal muscle satellite cell: the stem cell that came in from the cold. J Histochem Cytochem 54:1177–1191

Zarkowska T, Mittnacht S (1997) Differential phosphorylation of the retinoblastoma protein by G1/S cyclin-dependent kinases. J Biol Chem 272:12738–12746

Zhang JM, Wei Q, Zhao X, Paterson BM (1999a) Coupling of the cell cycle and myogenesis through the cyclin D1-dependent interaction of myod with cdk4. EMBO J 18:926–933

Zhang P, Wong C, Liu D, Finegold M, Harper JW, Elledge SJ (1999b) p21(cip1) and p57(kip2) control muscle differentiation at the myogenin step. Genes Dev 13:213–224

Zhang CL, McKinsey TA, Olson EN (2002) Association of class II histone deacetylases with heterochromatin protein 1: potential role for histone methylation in control of muscle differentiation. Mol Cell Biol 22:7302–7312

Zhao P, Hoffman EP (2004) Embryonic myogenesis pathways in muscle regeneration. Dev Dyn 229:380–392

Ziebold U, Reza T, Caron A, Lees JA (2001) E2f3 contributes both to the inappropriate proliferation and to the apoptosis arising in Rb mutant embryos. Genes Dev 15:386–391

Zimowska M, Szczepankowska D, Streminska W, Papy D, Tournaire MC, Gautron J, Barritault D, Moraczewski J, Martelly I (2001) Heparan sulfate mimetics modulate calpain activity during rat soleus muscle regeneration. J Cell Physiol 188:178–187

Zimowska M, Duchesnay A, Dragun P, Oberbek A, Moraczewski J, Martelly I (2009) Immunoneutralization of TGFbeta1 improves skeletal muscle regeneration: effects on myoblast differentiation and glycosaminoglycan content. Int J Cell Biol 2009:659372

Zou L, Stillman B (2000) Assembly of a complex containing cdc45p, replication protein A, and MCM2p at replication origins controlled by S-phase cyclin-dependent kinases and cdc7p-DBF4p kinase. Mol Cell Biol 20:3086–3096