Stem Cell-Based and Tissue Engineering Approaches for Skeletal Muscle Repair

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Contents

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Abstract

Skeletal muscle tissue exhibits significant regeneration capacity upon injury or disease. This intrinsic regeneration potential is orchestrated by stem cells termed satellite cells, which undergo activation and differentiation in response to muscle insult, giving rise to fusion-competent myogenic progenitors responsible for tissue rejuvenation. Skeletal muscle diseases such as Duchenne muscular dystrophy are characterized by progressive loss of muscle mass which precipitates reduced motility, paralysis, and in some occurrences untimely death. A manifold of muscle pathologies involve a failure to efficiently regenerate the muscle tissue, rendering stem cell-based approaches an attractive therapeutic strategy. Here we will present past and contemporary methods to treat skeletal muscle degeneration by stem cell therapy, covering prominent challenges facing this technology and potential means to overcome current hurdles. A primary focus of this chapter is directed toward illustrating innovative ways to utilize stem cells alone or in conjunction with biomaterials and tissue engineering techniques to remedy Duchenne muscular dystrophy or volumetric muscle loss.

1 Introduction

Human locomotion is carried out by skeletal muscle, a soft tissue composed of postmitotic multinucleated myofibers that contract to generate movement. In addition, skeletal muscle tissue contains mononucleated muscle resident cells in the form of fibroadipogenic progenitors, satellite, and endothelial and hematopoietic cells which play pivotal roles in skeletal muscle tissue homeostasis and repair (Fig. 1) (Giordani et al. 2019; Dell'Orso et al. 2019; Wosczyna and Rando 2018; Rubenstein et al. 2020).

Adult skeletal muscle harbors a high propensity for regeneration, which is dependent on resident stem cells within the skeletal muscle tissue known as satellite cells (Mauro 1961). These unique cells are located between the sarcolemma and basal lamina and are typically quiescent under homeostatic conditions, undergoing activation and proliferation during injury or disease to repair the tissue (Snow 1978; Schultz et al. 1978). Skeletal muscle regeneration follows a well-defined process via a myogenic differentiation program. In adult skeletal muscle, this process initiates when quiescent satellite cells (QSCs) undergo activation to form transient-amplifying activated satellite cells (ASCs) also known as myoblasts. These progenitors can further differentiate into myocytes, which are fusion-competent cells that can merge with muscle fibers to regenerate the tissue (Comai and Tajbakhsh 2014; Yin et al. 2013). This unique process is governed by key transcription factors specific to the myogenic program. QSCs express high levels of the transcription factor Paired Box Protein 7 (Pax7) as well as other unique genes such as Sprouty1 and Notch receptors (Seale et al. 2000; Shea et al. 2010; Mourikis and Tajbakhsh 2014). Upon activation, satellite cells downregulate quiescent genes while upregulating activation genes such as myoblast determination protein 1 (MyoD) and Myf5 (Comai and Tajbakhsh
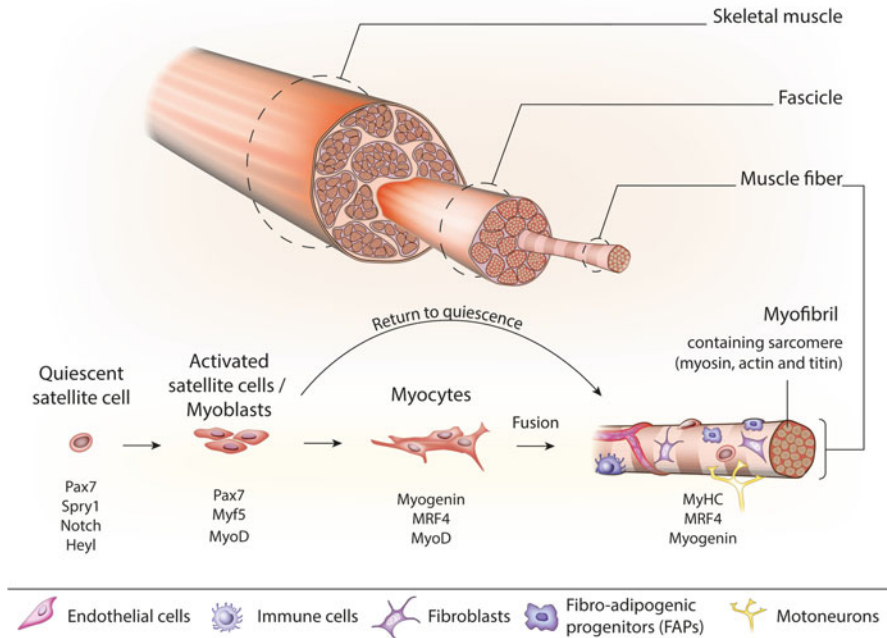
Fig. 1 Skeletal muscle tissue is composed of multinucleated aligned muscle fibers as well as other muscle resident cells. Regeneration of skeletal muscle is a step-wise process initiated by activation of quiescent satellite cells, which give rise to highly proliferative myoblasts and fusion-competent myocytes that merge with each other or with damaged myofibers to regenerate the tissue. In addition to muscle cells, a milieu of resident cells in the form of fibroadipogenic progenitors, endothelial, white blood cells, and other cell types reside in skeletal muscle tissue, playing key roles in its homeostasis and regeneration

2014; Yin et al. 2013). Myocytes further upregulate myogenin and MRF4, whereas differentiated multinucleated myofibers express various myosin heavy chain (MyHC) isoforms and a plethora of other differentiation-associated genes (Fig. 1) (Yin et al. 2013; Comai and Tajbakhsh 2014). The capacity to regenerate skeletal muscle is dependent on satellite cells, as their ablation completely abrogates skeletal muscle regeneration following injury (Murphy et al. 2011; Lepper et al. 2011; Sambasivan et al. 2011). In addition, mice lacking Pax7 exhibit growth retardation and small muscle mass size and typically die several weeks to months post birth (Seale et al. 2000; Oustanina et al. 2004). Recent research utilizing single cell sequencing methods have demonstrated that satellite cells display a large heterogeneity during homeostasis or regeneration, which is mirrored in their transcriptional expression profile (Yartseva et al. 2020; De Micheli et al. 2020).

Muscle regeneration is impaired in a wide array of pathological conditions such as traumatic muscle injury in the form of volumetric muscle loss (VML)(Corona et al. 2016), cancer-associated cachexia (Baracos et al. 2018), age-associated sarcopenia (Dennison et al. 2017), or muscular dystrophies (Motohashi et al.

2019). The latter group comprise a cluster of diseases characterized by progressive muscle wasting attributed to genetic mutations in genes that are critical for muscle function (Motohashi et al. 2019). Duchenne muscular dystrophy (DMD) is the most prevalent form of muscular dystrophy. It is an X-linked disorder that affects approximately 1 in 5000 boys worldwide, inflicting progressive muscle atrophy during early childhood, which eventually leads to complete muscle wasting and dysfunction (Yiu and Kornberg 2015). Patients with DMD experience death during the second or third decade of life as a result of cardiac or respiratory failure (Yiu and Kornberg 2015). The rapid muscle loss in DMD patients is attributed to a genetic mutation in dystrophin, an essential protein for healthy muscle function (Hoffman et al. 1987; Koenig et al. 1987). Dystrophin is expressed in differentiated myofibers, where it connects the sarcolemma to the extra cellular matrix (ECM) (Nowak and Davies 2004). More recently, it was reported to be expressed also in satellite cells, where it plays an essential role in asymmetric cell division during regeneration, and its absence significantly impairs satellite cell self-renewal (Dumont et al. 2015). As of today, there is a paucity of treatment for patients suffering from DMD and other muscle diseases such as VML, cachexia, and sarcopenia, rendering novel approaches in regenerative medicine and stem cell therapy attractive to treat these ailments as was shown for other somatic tissues (Mao and Mooney 2015; Blau and Daley 2019). For example, stem cell therapy via bone marrow engraftment is routinely used to treat blood disorders and more recently has been successfully used to treat skin and ocular diseases, raising hope for future stem cell therapies for skeletal muscle diseases (Blau and Daley 2019).

In this book chapter, we will present various stem cell-based and tissue engineering approaches to treat muscle diseases, with emphasis on treating patients who suffer from DMD or VML. We will further present past and contemporary challenges in utilizing stem cells or tissue engineering to treat muscle diseases and discuss innovative ways to resolve them. Lastly, we will highlight future research directions spearheaded by these technologies for skeletal muscle reparative therapy.

2   Cell Replacement Therapy for the Treatment of Muscle Disorders

Cell replacement therapy is an attractive approach to treat muscle-associated diseases characterized by cell death such as muscular dystrophies. The ultimate goal of this approach is to repair muscle damage via engraftment of healthy donor-derived cells into a disease-afflicted muscle tissue (Blau and Daley 2019). Candidate cell types proposed for this therapeutic approach include muscle stem or progenitor cells in the form of myoblasts (Partridge et al. 1989) or satellite cells (Montarras et al. 2005; Collins et al. 2005). Alternatively, other cell types can also be utilized via systemic delivery (Cossu et al. 2015; Sampaolesi et al. 2003; Torrente et al. 2004). The candidate cells can be healthy donor-derived allogeneic cells or autologous cells which are derived from the patient and therefore may require an ex vivo gene correction procedure (Fig. 2). To date, a majority of completed clinical trials have
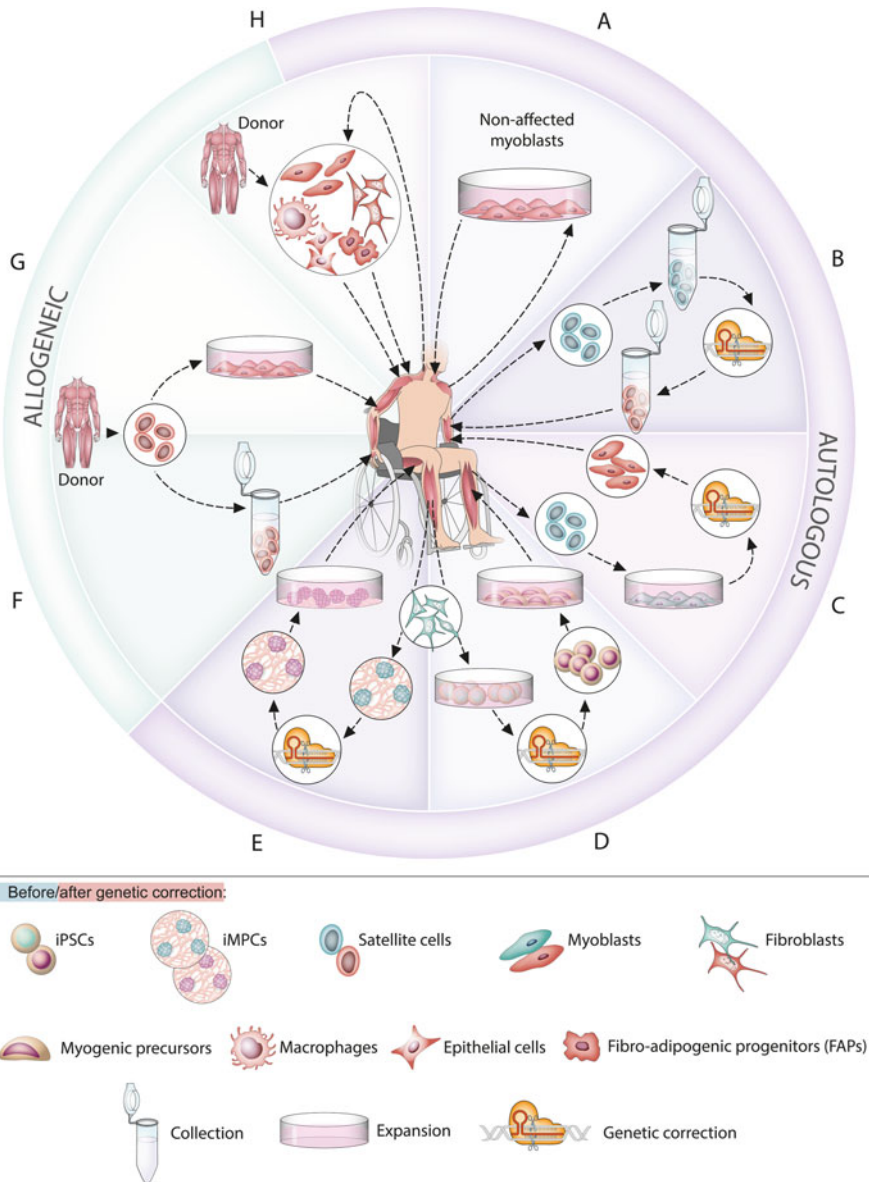
Fig. 2 Allogeneic and autologous cell replacement therapy approaches to treat muscular dystrophies. (**a**) Autologous myoblasts derived from healthy muscles are engrafted into dystrophic muscles. (**b**) Autologous satellite cells are genetically corrected during a transient ex vivo phase followed by engraftment. (**c**) Autologous myoblasts are transplanted back into muscles after expansion and ex vivo genetic correction phase. (**d**) Patient-derived induced pluripotent stem cells (iPSCs) are genetically corrected and differentiated into disease-free muscle precursors, which are engrafted back into the patient. (**e**) Patient-derived induced myogenic progenitor cells (iMPCs) are genetically corrected and engrafted back into the patient. (**f**) Engraftment of allogeneic

investigated the potential of myoblasts to treat skeletal muscle disorders, as these cells are relatively easy to isolate and expand in vitro, whereas very few studies have investigated the potential of other cell types to assist in muscle repair (Cossu et al. 2015; Torrente et al. 2007). In this section, we will briefly summarize historical and recent clinical trials conducted to treat muscle diseases by myoblast transplantation, focusing primarily on Duchenne muscular dystrophy (DMD) as a model. We will strive to introduce the main challenges and recent advancements in the field.

2.1   Myoblast Transplantation for the Treatment of Duchenne Muscular Dystrophy

Cell-based therapy as an approach to treat muscle diseases was first conceptualized in a 1978 seminal study by Partridge and colleagues (Partridge et al. 1978). Highlights of this pivotal study demonstrated that mouse donor-derived myoblasts could fuse with host cells upon intramuscular injection, leading to formation of hybrid myofibers composed of both recipient and donor cells (Partridge et al. 1978). Follow-up studies utilizing this approach established that injection of wild-type mouse myoblasts could form dystrophin-positive hybrid myofibers in dystrophic muscles of a mouse model for DMD (Partridge et al. 1989; Karpati et al. 1989), providing the conceptual framework to attempt myoblast transplantation trials in DMD patients during the 1990s (Law et al. 1991; Gussoni et al. 1992; Huard et al. 1992; Karpati et al. 1993; Tremblay et al. 1993a, b; Morandi et al. 1995; Mendell et al. 1995; Miller et al. 1997). Between 1990 and 1997, several clinical trials were conducted to assess myoblast transplantation as a potential therapy to treat DMD patients. Law and colleagues conducted the first clinical trial for myoblast transplantation in three DMD patients and detected dystrophin-positive myofibers in all of the patients' *extensor digitorum brevis* muscles 3 months post cell delivery (Law et al. 1990, 1991). In the notable 1992 Gussoni and colleagues clinical trial, donor-derived cultured myoblasts from a father or sibling were injected into the *tibialis anterior* muscles of eight DMD patients, who were treated concomitantly with cyclosporine to counteract immune rejection of donor-derived cells (Gussoni et al. 1992). One month post transplantation, dystrophin mRNA from donor-derived cells was detected via PCR analysis in muscle samples from three patients; however it was deemed inconclusive whether dystrophin protein was successfully restored (Gussoni et al. 1992). Strikingly, re-analyses of muscle biopsies using fluorescence in situ hybridization (FISH) of six patients after intramuscular myoblast injection revealed fused and unfused donor nuclei in all examined muscles of the patients

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Fig. 2 (continued) satellite cells derived from a healthy donor into dystrophic muscles. (**g**) Engraftment of allogeneic myoblasts derived from a healthy donor into dystrophic muscles. (**h**) Co-engraftment of muscle cells with other cell types involved in muscle repair could enhance muscle regeneration and remedy dystrophic symptoms

(Gussoni et al. 1997). In parallel and following the Gussoni study, additional clinical trials utilizing similar experimental designs were completed, however differed in the use of immunosuppressive drugs, injection strategies, and interpretation of outcome (Karpati et al. 1993; Huard et al. 1992; Tremblay et al. 1993a, b; Morandi et al. 1995; Mendell et al. 1995; Miller et al. 1997). An extensive comparison of these studies has been previously reported (Skuk 2004). Collectively, these studies confirmed that myoblast transplantation in humans is feasible and safe; however the clinical outcome was deemed deficient (Karpati et al. 1993; Gussoni et al. 1992; Huard et al. 1992; Tremblay et al. 1993a, b; Morandi et al. 1995; Mendell et al. 1995; Miller et al. 1997). Of note, a few studies reported slight beneficial effects on muscle strength following myoblast transplantation (Huard et al. 1992; Karpati et al. 1993; Tremblay et al. 1993a; Law et al. 1991), however the majority of studies did not asses or report on functional improvement and failed to detect dystrophin-positive myofibers in patients (Morandi et al. 1995; Tremblay et al. 1993b; Mendell et al. 1995; Miller et al. 1997). Possible explanations for the unfavorable clinical outcome have been extensively discussed (Negroni et al. 2016; Skuk and Tremblay 2014), with attributing factors deemed to be (i) poor myoblast survival in host muscles; (ii) immune rejection against donor-derived myoblasts; (iii) failure of myoblasts to efficiently migrate from the injection site; and (iv) inability of cultured myoblasts to restore the muscle stem cell reservoir and elicit robust regeneration (Karpati et al. 1993; Wilschut et al. 2012; Maffioletti et al. 2014; Fan et al. 1996; Guerette et al. 1995; Qu et al. 1998). The rather disappointing human clinical trials conducted during the 1990s impeded subsequent clinical trials and their ramifications linger to some extent to this day.

2.2 Addressing Translational Roadblocks for Myoblast Transplantation

Despite the results of the unsuccessful clinical trials conducted during the 1990s, more recent studies performed on non-human primates have addressed a portion of the aforementioned challenges with the objective of improving myoblast transplantation (Table 1) (Skuk and Tremblay 2014).

One such approach is to modulate the type of immunosuppressive drugs administered to counteract immunological responses in patients. Administration of immunosuppressive drugs for successful allogeneic myoblast transplantation has been rigorously demonstrated in both rodent and non-human primate studies (Kinoshita et al. 1994; Pavlath et al. 1994; Kinoshita et al. 1996). Historically, cyclosporine was the preferred immunosuppressant used in the majority of early human trials (Gussoni et al. 1992; Morandi et al. 1995; Mendell et al. 1995; Miller et al. 1997). However, more recent studies have shown that cyclosporine impedes myoblast fusion and differentiation (Hong et al. 2002). Alternative treatment of non-human primates with the immunosuppressant tacrolimus have led to long-term engraftment of allogeneic myoblasts (Kinoshita et al. 1996), resulting in tacrolimus replacing cyclosporine as the immunosuppressant of choice.

Table 1 Select studies that have investigated myoblast transplantation in non-human primates

Study/topic	Primary experiments	Results/findings
Kinoshita et al. (1996) **Immune system**	Intramuscular injection of allogeneic myoblasts (*LacZ*) into NHPs treated with tacrolimus or without immunosuppressant	Lymphocyte infiltration and increase in cytokines 7 days post MT in the absence of tacrolimus. ß-Gal-positive fibers were not detected 4 weeks post MT Detection of ß-Gal-positive fibers 1, 4, and 12 weeks post MT with significant reduced lymphocyte infiltration and cytokines with tacrolimus compared to no tacrolimus administration
Skuk et al. (1999) **Notexin**	Allogeneic myoblasts (*LacZ*) were injected with or without notexin and varying cell number (4×10^6, 8×10^6, 24×10^6) with 35–40 injections (separated by 1 mm)	8×10^6 led to most ß-Gal-positive fibers 4 weeks post MT Injection of 8×10^6 myoblasts suspended in notexin led to a 50% increase of ß-Gal fibers 4 weeks post MT
Skuk et al. (2002) **Injection, immune system**	Injection of allogeneic myoblasts (*LacZ*) with varying inter-injection distances (1 mm, 1–1.5 mm, 2 mm) and different concentrations of tacrolimus alone or combined with mycophenolate mofetil	Detection of 25–67% ß-Gal-positive fibers 1 month post MT (injection distance 1 mm) Combination of tacrolimus with mycophenolate mofetil enabled a decreased dosage of tacrolimus
Lafreniere et al. (2009) **Growth factors**	Intramuscular injection of allogeneic myoblasts (*LacZ*) combined either with bFGF or IGF-1	Growth factors increased myoblast migration 60 h post MT No significant differences detected in ß-Gal-positive fiber formation 4 weeks post MT
Skuk et al. (2011) **Migration**	Allogeneic myoblasts (*LacZ*) were subcutaneously injected above a needle-damaged muscle	Detection of migrated myoblasts that formed ß-Gal-positive myofibers within a damaged muscle along the needle trajectories 1 cm apart from injected site, 1 month post subcutaneous MT
Skuk et al. (2013) **Electroporation**	A 1 mm^2 muscle area was electroporated with 3 pulses of 400 V/cm before allogeneic myoblasts (*LacZ*) were injected either in a matrix consisting of 25 injections or radial injection	Myofiber necrosis 1 day and maximal tissue distortion 7 days post electroporation Complete muscle regeneration 2–3 months post electroporation Increased ß-Gal-positive fibers after electroporation compared to injection alone (1.6–6.3-fold for matrices and 2.5–9 for radial injections)
Skuk et al. (2014) **Injection**	Intramuscular injection of allogeneic myoblasts (*LacZ*) with varying needle sizes (27 G, 22 G, 18 G), amount of cells (10^2, 10^3, 10^4, 10^5, 10^6/cm injection trajectory), and injected volume (1 ul, 5 ul, 25 ul/cm injection trajectory)	Muscle sections revealed that an injection of at least 100,000 cells/cm in 1 µl/cm trajectory with a 27 G generated highest amounts of ß-Gal-positive fibers 1 or 2 months post MT

Table 1 (continued)

Study/topic	Primary experiments	Results/findings
Skuk and Tremblay (2017a) **Cell death**	Injection of radiolabeled autologous or allogeneic myoblasts (with or without *LacZ*) into NHPs (with or without immunosuppressant)	Majority of cells (80–92%) died within the first 7 days regardless of whether 1), they were autologous or allogeneic or 2) if the recipient NHP received an immunosuppressant drug. No further cell death 3 weeks post injection
Skuk and Tremblay (2017b) **Engraftment**	Intramuscular injection of myoblasts (*LacZ*) and subsequent assessment of cell engraftment (after 1 h, 1 day, 3 days, 7 days and 3 weeks)	Detection of majority of myoblasts in between the muscle bundle and the perimysium 1 h and 1 day post MT. Detection of ß-Gal-positive myofibers along the injection trajectories 3 weeks post MT

NHPs non-human primates, *MT* myoblast transplantation, *ß-Gal* ß-galactosidase

Inflicting localized muscle damage by irradiation, mechanical pressure, freezing, or chemicals is a commonly used method to enhance muscle stem and progenitor cell-engraftment in rodent transplantation models (Mueller and Bloch 2019; Hardy et al. 2016). Moreover, studies performed in non-human primates reported partial increase in engrafted myofibers when myoblasts were transplanted into injured muscle tissue by notexin or electroporation (Skuk et al. 1999, 2000, 2013). However, inflicting muscle damage prior to transplantation is both ethically and technically challenging to translate to human patients due to potential adverse side effects (Skuk et al. 2002). Therefore, myoblast engraftment has been investigated without inducing muscle damage with the exception of localized insult caused by the injection needle (Skuk et al. 2002). Of note, the non-human primate studies demonstrated migration of myoblasts toward damaged myofibers and engraftment at the injection site (Skuk et al. 2002, 2011). Based on these observations, it was suggested that in the absence of extensive muscle damage, multiple close proximity injections will be required to achieve substantial engraftment of transplanted myoblasts (Skuk et al. 2002, 2006b, 2011). This hypothesis has led to two clinical trials involving human patients that utilized several novel strategies (Table 2) (Skuk et al. 2004, 2006a, 2007, 2010; Skuk and Tremblay 2016). In the first study, nine DMD patients were injected with high-density allogeneic myoblasts in the *tibialis anterior* muscle while being treated in parallel with the immunosuppressant tacrolimus (Skuk et al. 2006a). In contrast to previous trials, between 3.5% and 26% dystrophin-positive myofibers were detected in sampled muscles, while patients did not develop a major immune reaction (Skuk et al. 2006a). In a separate study, an entire *thenar eminence* muscle was injected with myoblasts to assess the safety of high-density injections (Skuk et al. 2007). The procedure was well tolerated by the patient without severe adverse effects or complications. The patient further showed an increase in force generation in comparison to pre-transplantation (Skuk et al. 2007). Remarkably, donor-derived muscle cells

Table 2 Myoblast transplantation trials in DMD and oculopharyngeal muscular dystrophy (OPMD) patients between 2004 and 2014

Study	Patient cohort (Number/age demographic)	Donor	Study protocol: (a) Quantity of injected myoblasts/muscle type (b) Injection method (c) Immunosuppressive drug (d) Blinded vs. non-blinded	Results: (a) Molecular findings (b) Functional findings
Skuk et al. (2004, 2006a, 2010), Skuk and Tremblay (2016)	9 patients/age: 8–17 years	Father or mother	(a) 18.5–30×10^6 into TA (b) 0.25 cm^3 with 25 injections 1–2 mm apart with 25- or 22-gauge needle; or 1 cm^3 with 25 or 100 injections 1–2 mm apart with 27-, 26- or 25-gauge needle (c) Tacrolimus (d) Non-blinded	(a) Dystrophin-positive myofibers detected in TA of 8 patients (3.5–26%), specific antibody staining showed that dystrophin-positive myofibers were donor-derived in 7 patients. Detection of two groups of dystrophin-positive myofibers: Large fibers derived from fusion with existing fibers and small fibers derived from fusion of donor cells alone, donor mRNA was detected in 9 patients, detection of mononuclear donor-derived myoblasts in the satellite cell niche 4 weeks post MT, detection of antibodies against donor cells in two patients (already detected pre-transplantation) (b) Not assessed
Skuk et al. (2007)	1 patient/age: 26 years	Father	(a) 275×10^6 into TE (whole muscle), 538×10^6 into BB (whole muscle), 135×10^6 into G (b) High-density injections (separated by 1 mm) with 27- or 26-gauge needle (c) Tacrolimus (d) Non-blinded	(a) Dystrophin-positive myofibers detected in G (27.5% 1 month, 34.5% 18 months post MT), massive fibrosis and adipose tissue in BB and only 2 dystrophin-positive myofibers detected, detection of donor-derived mRNA in BB and G (b) Increased strength of first metacarpal flexion post MT (70% 1 month, 100% 2 months, 50% 15 months post MT compared to pre-transplantation)
Perie et al. (2014)	12 patients/age: 18–75 years	Cells derived from patient's unaffected Q or SCM	(a) 178×10^6 (median) into pharyngeal muscles (b) Myotomy before injection, 12 injections, 10 cm^2 (c) Not administered (d) Non-blinded	(a) Myoblast engraftment was not assessed (b) Upper esophageal sphincter function improved in 8 patients 2 years post MT, increased quality of life score in 12 patients, no degradation in swallowing function in 10 patients

MT myoblast transplantation, *TA* tibialis anterior, *BB* biceps brachii, *TE* thenar eminence, *G* gastrocnemius, *Q* quadriceps, *SCM* sternocleidomastoid

remained at the engraftment site 18 months post transplantation, suggesting a long-term engraftment potential (Skuk et al. 2007). Currently, safety and functional outcome of myoblast transplantation throughout extensor *carpi radialis* muscles of DMD patients are being tested in a clinical phase I/II trial (NCT02196467).

Inflicting confined muscle damage to provide a niche for cell engraftment carries potential significant health risks for human DMD patients. However in the context of blood diseases, bone marrow ablation by irradiation prior to blood stem cell infusion is a well-established treatment procedure (Blau and Daley 2019). Therefore, it may be of interest to assess if localized ablation of muscle cells by irradiation followed by high-proximity injection of myoblasts into dystrophic muscles could elicit migration beyond the injection site, achieving robust regeneration. Given evident experimental success in animal models, there is potential to adapt this approach in human patients during future trials.

2.3   Clinical Procedures Involving Autologous Myoblast Transplantation

To date, only allogeneic myoblasts with or without immunosuppressive drug administration have been used to treat human DMD patients (Gussoni et al. 1992; Huard et al. 1992; Karpati et al. 1993; Tremblay et al. 1993a, b; Morandi et al. 1995; Mendell et al. 1995; Miller et al. 1997; Skuk et al. 2006a, 2007; Law et al. 1991). In contrast, autologous myoblast transplantation has been successfully employed in animal models and several clinical trials for urinary incontinence (Mitterberger et al. 2008; Sebe et al. 2011; Blaganje and Lukanovic 2012; Stangel-Wojcikiewicz et al. 2014; Jankowski et al. 2018; Eberli et al. 2012), fecal incontinence (Frudinger et al. 2015; Romaniszyn et al. 2015; Boyer et al. 2018; Bisson et al. 2015), as well as oculopharyngeal muscular dystrophy (OPMD)(Perie et al. 2014). For further reading on these procedures, we refer the readers to recently published reviews (Hillary et al. 2020; Simillis et al. 2019; Trebol et al. 2018). During these trials, immunosuppressive drugs were not administered, thereby simplifying the procedure and reducing the risk of adverse health complications. Notably, a recent success in utilizing autologous myoblasts to treat OPMD has been reported (Perie et al. 2014) (Fig. 2a). This type of muscular dystrophy is characterized by progressive degradation and weakening of the ocular and pharyngeal muscles, leading to ptosis and dysphagia (Brais et al. 1998). OPMD is caused by an autosomal gene mutation that results in amplification of GCG nucleotides in the PABPN1 gene (Brais et al. 1998). Currently, symptoms are treated by a cricopharyngeal myotomy; however, the long-term benefits of this procedure remain controversial (Duranceau et al. 1980; Perie et al. 2014). In rare disparity to other muscular dystrophies, not all muscles of OPMD patients are affected (Perie et al. 2006). Comparisons of myoblasts derived from affected and non-affected muscles of OPMD patients have shown that the latter exhibited higher proliferation and myogenic regeneration capacity (Perie et al. 2006). This observation was followed by a non-placebo controlled clinical trial that tested myoblast transplantation in OPMD patients (Perie et al. 2014).

Autologous myoblasts derived from unaffected *quadriceps* or *sternocleidomastoid* muscles were injected into pharyngeal muscles of 12 OPMD patients after myotomy (Perie et al. 2014). Remarkably, this procedure successfully ceased further degradation of pharyngeal muscles in patients 2 years post-surgery in addition to improving quality of life criteria factors in all patients (Perie et al. 2014). To date, this study is one of a handful to demonstrate a beneficial therapeutic outcome of myoblast transplantation. In the future, it will be central to corroborate these promising results with additional experiments that include placebo-controlled groups and patients subjected to myoblast engraftment with or without prior myotomy. Autologous myoblast transplantation from non-afflicted muscles may be applicable to other muscular dystrophies such as facioscapulohumeral muscular dystrophy and could provide a beneficial method to treat muscle diseases (Fig. 2a) (Vilquin et al. 2005).

Autologous myoblasts expressing a shorter but functional micro-dystrophin have been successfully transplanted into non-human primates (Quenneville et al. 2007). However, autologous myoblast transplantation in human cell engraftment patients has not been reported, although rapid advances in genome engineering techniques may pave way for investigating such an approach in the future (Doudna and Charpentier 2014; Briggs and Morgan 2013; Min et al. 2019) (Fig. 2c). Harnessing the CRISPR-Cas9 genome editing system to correct the dystrophin mutation in the Dmd^{mdx} mouse model was recently reported by several seminal studies, demonstrating functional restoration of the dystrophin protein in myofibers (Long et al. 2016; Tabebordbar et al. 2016; Nelson et al. 2016) and potentially muscle stem cells (Tabebordbar et al. 2016; Nance et al. 2019). Dmd^{mdx} myoblasts were also genetically corrected in vitro using CRISPR-Cas9 and reported to give rise to dystrophin-positive fibers upon transplantation (Zhu et al. 2017; Matre et al. 2019; Ousterout et al. 2015). With respect to correction of human dystrophin mutations, Young and colleagues recently developed a strategy to fix a mutational hot spot by a CRISPR-Cas9 exon skipping-based approach, which encompasses approximately 60% of all DMD patient mutations (Young et al. 2016). In this elegant study, DMD patient-derived fibroblasts were first reprogrammed into induced pluripotent stem cells (iPSCs) (Young et al. 2016). Correction of the dystrophin mutation was performed at the pluripotent state, followed by directed differentiation of the iPSCs into dystrophin-positive muscle cells (Young et al. 2016). By taking a similar experimental approach, myoblasts could be expanded from patients, corrected by genome engineering, and then transplanted back into patients (Fig. 2c). Similarly, it might be feasible to correct satellite cells during a short-lived ex vivo phase followed by engraftment (Fig. 2b). However, it is important to note that restoration of dystrophin expression by transplantation of autologous myoblasts carries the risk of eliciting an immune reaction against a "foreign" protein, necessitating potential use of immunosuppressants (Selvaraj et al. 2019).

2.4 Further Considerations for Improvement of Myoblast Transplantation

The overarching goal of cell replacement therapy for muscle diseases is to establish the long-term regeneration potential of transplanted cells, which requires

contribution to the muscle stem cell reservoir. However, it remains unclear whether myoblasts carry an efficient propensity to induce such long-term regeneration capacity, albeit some studies indicate feasibility (Yao and Kurachi 1993; Heslop et al. 2001; Skuk et al. 2010). Notably, a clinical trial in DMD human patients detected a presence of donor-derived mononuclear cells in muscles, suggestive of contribution to the satellite cell niche (Skuk et al. 2006a, 2010). In support of this observation, dystrophin-positive myofibers have been detected in DMD patients 18 months post myoblast transplantatio n (Skuk et al. 2007). Similar observations have been documented in myoblast transplantation trials for the treatment of fecal or urinary incontinences (Jankowski et al. 2018; Frudinger et al. 2015; Romaniszyn et al. 2015), although cell engraftment was not thoroughly assessed (Jankowski et al. 2018; Frudinger et al. 2015).

Whereas the contribution of transplanted myoblasts to long-term muscle regeneration has yet to be fully elucidated, satellite cells exhibit a high regeneration capacity and can efficiently contribute to the muscle stem cell reservoir (Montarras et al. 2005; Collins et al. 2005; Cerletti et al. 2008). In the next sections, we will discuss advances in direct isolation and transplantation of satellite cells or engraftment after an ex vivo propagation phase. We will further discuss new techniques that could allow partial retainment of satellite-cell characteristics in vitro. These novel approaches could pave the way for utilizing satellite cells instead of myoblasts as the preferred cells for engraftment in clinical settings.

3 Engraftment of Freshly Isolated Satellite Cells for Muscle Regeneration

Despite the immense therapeutic potential of utilizing satellite cells to treat muscle-associated diseases, unresolved challenges have limited their use in cell-based therapies. Shortly after QSCs are mechanically and enzymatically dissociated from muscle fibers they undergo activation, a process characterized by rapid upregulation of myoblast-associated genes and commitment to a myogenic differentiation program (Machado et al. 2017; Pietrosemoli et al. 2017; van Velthoven et al. 2017). This renders the therapeutic use of satellite cells for muscle transplantation challenging, as their engraftment potential decreases once expanded in vitro (Montarras et al. 2005; Collins et al. 2005; Quarta et al. 2016; Xu et al. 2015b; Sacco et al. 2008). To overcome this challenge, satellite cells can be isolated by a fluorescence-activated cell sorting (FACS) machine and injected directly into muscles. A manifold of reports have shown that by utilizing this approach, injected mouse or human satellite cells could significantly contribute to muscle regeneration (Montarras et al. 2005; Quarta et al. 2016; Xu et al. 2015b; Sherwood et al. 2004; Kuang et al. 2007). Moreover, engrafted satellite cells can enter their respective niche under the basal lamina (Xu et al. 2015b; Kuang et al. 2007), sustain multiple rounds of injury-induced regeneration (Collins et al. 2005; Rocheteau et al. 2012), and in addition be subjected to serial transplantation for up to seven rounds in mice (Rocheteau et al. 2012). Furthermore, engrafted myofiber fragments containing adjoined satellite cells can promote robust muscle regeneration and repair (Collins et al. 2005; Hall et al.

2010; Marg et al. 2014). Strikingly, a seminal study reported that a single satellite cell can regenerate a significant segment of skeletal muscle tissue in mice (Sacco et al. 2008).

Satellite cells comprise a subset of the mononucleated cell fraction in skeletal muscle tissue (Dell'Orso et al. 2019; Giordani et al. 2019; Rubenstein et al. 2020). This necessitates usage of genetic reporters or identification of surface markers for prospective isolation and transplantation of homogenous cell populations. Genetic reporters for Pax3 and Pax7 have been successfully employed to isolate murine satellite cells (Fig. 3) (Bosnakovski et al. 2008; Sambasivan et al. 2009; Montarras et al. 2005); however isolation of humans satellite cells using this approach is not feasible. Alternatively, surface markers can be applied to isolate satellite cells by a FACS machine. To this end, several murine-positive surface markers have been identified including CD34, Cxcr4/ITGB1, Vcam1, and alpha-7 integrin (Sherwood et al. 2004; Liu et al. 2013; Beauchamp et al. 2000; Fukada et al. 2004; Cerletti et al. 2008; Kuang et al. 2007). Similarly, several positive surface markers have been successfully identified that allow prospective isolation of human muscle stem cells including CD56/CD29 (Xu et al. 2015b), CD56/CD29/CXCR4 (Garcia et al. 2018), CD56/ITGA7 (Castiglioni et al. 2014), CD82/CD318 (Uezumi et al. 2016), and CD82 (Alexander et al. 2016). These efforts to identify, isolate, and characterize muscle stem cells have provided a plethora of new knowledge in respect to transplantation methods and assessment of satellite cell regenerative potential. For
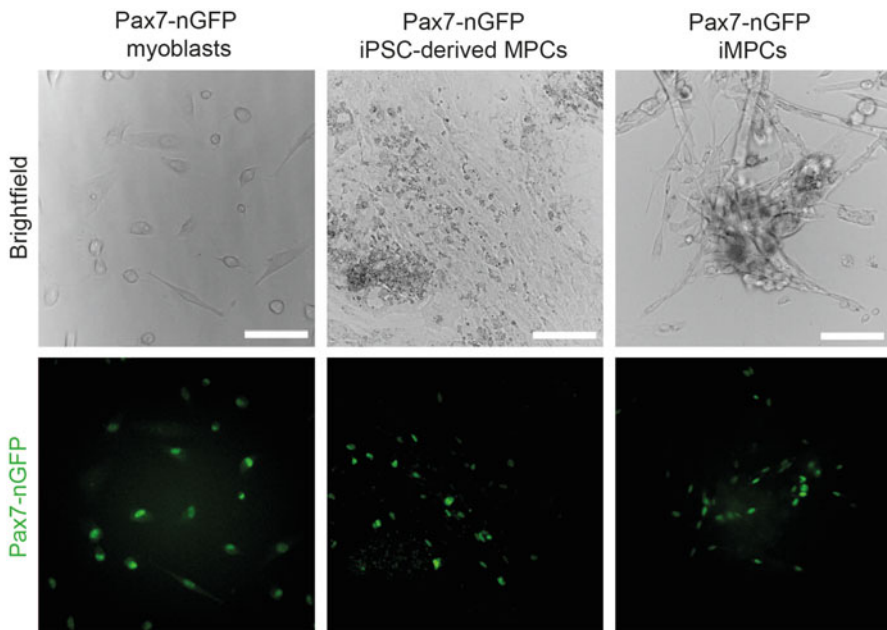

Fig. 3 Pax7 nuclear GFP reporter expression in cultured myoblasts, iPSC-derived myogenic precursors and fibroblast-derived induced myogenic progenitors (iMPCs). Scale bar, 100 μm

example, studies have reported that freshly isolated human satellite cells efficiently fuse with myofibers of immunodeficient or dystrophic mice (Alexander et al. 2016; Uezumi et al. 2016; Xu et al. 2015b). Furthermore, 5 weeks post muscle transplantation, human spectrin, and dystrophin-positive myofibers were detected in mouse muscles, and putative human satellite cells were identified under the basal lamina, suggesting contribution to the satellite cell niche (Xu et al. 2015b). Remarkably, engrafted human satellite cells were also shown to sustain two rounds of serial transplantation in mice (Garcia et al. 2018).

Akin to myoblasts, satellite cells cannot be delivered systemically and do not efficiently migrate across the muscle beyond the injection area. Due to this limitation, Garcia and colleagues opted to transplant satellite cells across multiple injection sites within the same muscle, demonstrating that as few as 2000 human satellite cells have led to the formation of approximately 155 human spectrin-positive myofibers (Garcia et al. 2018). Additionally, they detected increased quantities of human donor-derived Pax7^{+} cells around the injection sites (Garcia et al. 2018). The authors suggest that satellite cell-delivery utilizing multiple injection sites is essential and more important than the number of injected cells (Garcia et al. 2018). This observation is reminiscent of the enhanced myoblast engraftment potential seen in human patients transplanted using close-proximity injections (Skuk et al. 2006a).

An additional limiting factor of using satellite cells for regenerative medicine purposes is low extraction yield of cells from allogeneic muscle donors. An alternative source for obtaining high quantities of satellite cells could be cadavers, as quiescent satellite cells have been shown to maintain their regenerative capacity in muscles for up to 17 days post mortem (Latil et al. 2012) or following hypothermic storage (Marg et al. 2014). These intriguing observations suggest that muscles of deceased individuals could potentially be used for satellite cell extraction, similar to donor-derived human organs purposed for transplantation.

Although pure myogenic stem cells can be isolated from muscles via a suite of surface markers, no clinical trials to date have investigated the potential of freshly isolated human satellite cells to remedy muscle-associated diseases in humans. Taking into consideration evidence from transplantation experiments of human myoblasts and satellite cells, one can cautiously postulate that engraftment of satellite cells into dystrophic muscles of DMD patients will be superior to that of myoblasts. To test this hypothesis, it will be of interest to assess the capacity of freshly isolated human satellite cells and myoblasts to engraft into muscles of non-human primates, similar to reports that have assessed myoblast engraftment in non-human primates (Skuk et al. 2011; Skuk and Tremblay 2017a; Skuk et al. 2002). Skeletal muscle of primates may provide a more receptive host niche for engraftment of human muscle stem cells due to species similarity and size. Successes in generating human-primate hybrid muscles will provide salient insights into the propensity of freshly isolated human satellite cells to engraft, migrate, and regenerate muscles, in addition to bearing implications for adapting this technique in humans.

Notable challenges of satellite cell utilization in cell therapy include low cell extraction yield, poor cell migration, and an inability to deliver the cells systemically. In consideration of these limitations, it might be beneficial to exploit satellite cells in

clinical settings for muscles that are of small size and in conjunction with close-proximity injections. For example, localized satellite cell transplantation into finger muscles of DMD patients might curtail muscle degeneration and thus provide substantial improvement in life quality measures, despite not treating the underlying cause of mortality (Fig. 2f).

Besides allogeneic satellite cells, autologous satellite cells could be isolated from a patient's biopsy followed by correction of the dystrophin gene and subsequent engraftment into dystrophic muscles (Fig. 2b). While it was reported that quiescent satellite cells cannot be transduced by adeno-associated viral (AAV) vectors (Arnett et al. 2014), recent studies suggest that muscle stem cells can be targeted and gene corrected in vivo using AAV serotype 9 (Tabebordbar et al. 2016; Goldstein et al. 2019; Nance et al. 2019). However, in vitro correction of satellite cells remains challenging, mainly due to the conversion of satellite cells into myoblasts shortly after isolation and culture.

In summary, obtaining sufficient quantities of satellite cells for muscle injections still remains a formidable challenge. This hurdle highlights the need for generating expandable myogenic stem cells apt for regenerative medicine purposes. In the next section, we will introduce alternative methods for generating copious amounts of expandable muscle precursor cells in vitro.

4   Generation of Myogenic Precursors from Pluripotent Stem Cells

An alternative cellular source for production of myogenic precursors are pluripotent stem cells (PSCs) in the form of blastocyst-derived embryonic stem cells (ESCs) or somatic cell-derived induced pluripotent stem cells (iPSCs) (Selvaraj et al. 2019; Magli and Perlingeiro 2017). An advantage for using PSCs is their ability to expand indefinitely in vitro, thus enabling the generation of high quantities of muscle precursors (Selvaraj et al. 2019). The following section will briefly recount recent works which reported on successful differentiation of PSCs into myogenic precursors. For a comprehensive overview of this approach, we refer readers to recently published literature (Chal and Pourquie 2017; Kodaka et al. 2017; Selvaraj et al. 2019; Magli and Perlingeiro 2017).

ESCs are pluripotent cells that form the inner cell mass of blastocyst-stage embryos. These undifferentiated cells can expand indefinitely in vitro while maintaining the potential to differentiate into multiple cell types from the three embryonic germ layers (Martin 1981; Evans and Kaufman 1981; Thomson et al. 1998; Itskovitz-Eldor et al. 2000). Unlike ESCs, iPSCs are generated from adult somatic cells by overexpression of defined transcription factors (Takahashi and Yamanaka 2006; Takahashi et al. 2007). Since iPSCs can originate from an autologous cellular source, they could bypass immune rejection issues and ethical roadblocks associated with use of fetus-derived allogeneic ESCs (Takahashi and Yamanaka 2006).

Early studies revealed that both mouse and human PSCs can successfully differentiate into cells with myogenic potential (Barberi et al. 2007; Ozasa et al. 2007; Zheng et al. 2006; Mizuno et al. 2010; Dekel et al. 1992). Two major approaches

have since been successfully employed to differentiate PSCs into myogenic cells: (i) transgene-dependent overexpression of canonical myogenic transcription factors and (ii) treatment with small molecules involved in differentiation-related signaling pathways (Kodaka et al. 2017; Chal and Pourquie 2017). Typical differentiation protocols occur in a two-dimensional monolayer or three-dimensional embryoid bodies. Given the highly heterogenous nature of these differentiated cultures, cell purification by surface markers indicative of muscle stem or progenitor cells is often employed (Kodaka et al. 2017; Chal et al. 2015).

Darabi and colleagues pioneering study first demonstrated that ectopic over-expression of the early developmental myogenic transcription factor Pax3 can form myogenic cells with capacity to engraft muscle in vivo (Darabi et al. 2008). A subsequent notable work further demonstrated that conditional Pax7 expression induces differentiation of human ESCs and iPSCs into expandable myogenic pre-cursors (Darabi et al. 2012). Engrafted cells restored dystrophin expression in dystrophic murine muscles and donor-derived Pax7 cells contributed to the satellite cell pool, highlighting the immense potential of PSC-derived myogenic precursors to remedy dystrophic symptoms (Darabi et al. 2011, 2012). A follow-up study further demonstrated that ESC-derived myogenic precursors engraft and can fuse to form dystrophin-positive myofibers in a model of severe muscular dystrophy (Filareto et al. 2012). Continued research followed a similar trajectory demonstrating efficient differentiation of ESCs and iPSCs into myogenic precursors or skeletal myocytes by overexpression of MyoD (Goudenege et al. 2012; Tanaka et al. 2013; Pawlowski et al. 2017; Maffioletti et al. 2015), Pax3, or Pax7 (Rao et al. 2018; Filareto et al. 2013). Whereas this approach was shown to be successful with respect to production of engraftable myogenic cells, the use of ectopic transgenes renders it less favorable for clinical application.

An alternative and safer method to facilitate conversion of PSCs into myogenic precursors is via small molecule treatment. Several recent studies have reported on PSC-differentiation into myogenic progenitors solely by small molecules which include bFGF, Forskolin and GSK3-β inhibitor (GSK3-βi) (Xu et al. 2013), GSK3-βi and FGF2 (Shelton et al. 2014; van der Wal et al. 2018), WNT3A (Hwang et al. 2014), GSK3-βi and DAPT (Choi et al. 2016), BMP4, TGF-β and GSK3-β inhibitors (Xi et al. 2017; Wu et al. 2018). A notable study by Chal and colleagues uncovered genetic pathways upregulated during paraxial mesoderm differentiation during mouse embryonic development, assisting in development of a step-wise differentiation protocol for derivation of myogenic precursors from PSCs by BMP4 and GSK3-β inhibitor treatment (Chal et al. 2015). A follow-up study further refined this protocol by allowing for long-term capture of myogenic pre-cursors in vitro when serum was added as a media supplement (Fig. 3) (Chal et al. 2018). The myogenic precursors both express Pax7 and promote muscle regenera-tion in dystrophic murine muscles, further contributing Pax7 positive cells to the satellite cell pool (Chal et al. 2015; Chal et al. 2018). Due to the heterogeneity of PSC-derived differentiated cultures reported using this protocol, myogenic precur-sors can be further purified by cell surface markers (Kim et al. 2017). Of note, such FACS-sorting techniques have been successfully employed by multiple studies to

efficiently purify muscle precursors from PSC-differentiated cultures (Magli et al. 2017; Borchin et al. 2013; Wu et al. 2018; Kim et al. 2017; Hicks et al. 2018).

Patient-specific iPSCs from Duchenne patients carry the same mutation as their somatic parental cells (Park et al. 2008). Recent developments of the CRISPR-Cas9 genome editing system enable correction of the dystrophin mutation in iPSCs, followed by directed differentiation into dystrophin-positive muscle cells (Young et al. 2016; Li et al. 2015). Upon transplantation, corrected cells fuse to form dystrophin-positive myofibers within host murine muscles (Young et al. 2016). These findings illuminate the powerful therapeutic potential of combining genome engineering and stem cell differentiation methods to streamline new therapeutic treatments (Fig. 2d). However, the generation of gene-corrected iPSC-derived muscle stem cells in vitro remains a challenge (Ortiz-Vitali and Darabi 2019). For a comprehensive overview detailing PSC treatment methods of muscular dystrophies, we refer readers to recent reviews (Selvaraj et al. 2019; Ortiz-Vitali and Darabi 2019).

An additional approach for generating PSC-derived myogenic precursors is via in vivo developmental processes that can help further mature engrafted myogenic cells (Incitti et al. 2019). PSCs form tumors commonly known as teratomas upon in vivo engraftment, which contain differentiated cells indicative of all three embryonic germ layers (Ben-David and Benvenisty 2011). In a recent captivating study, Chan and colleagues capitalized on the PSC haphazard differentiation process during teratoma formation to detect and purify myogenic progenitors with an astounding regenerative capacity (Chan et al. 2018). FACS-sorted teratoma-derived α7-Integrin$^+$/VCAM-1$^+$ myogenic progenitors promoted robust regeneration upon engraftment into irradiated and cardiotoxin-injured dystrophic leg muscles in mice, restoring dystrophin expression in 80% of the *tibialis anterior* muscle and contributing up to 50% of the total DNA content (Chan et al. 2018). The teratoma-derived myogenic stem cells could further sustain regeneration in repeated injury and serial transplantation assays, demonstrating bona fide stem cell attributes. These cells exhibited a superior engraftment potential in comparison to previously published PSC-derived myogenic precursor cells (Chan et al. 2018). This remarkable contribution to muscle regeneration unleashes the vast potential of engrafted myogenic precursors to regenerate large muscle areas, which to date has only been achieved with partial success.

From a clinical perspective, a risk for teratoma formation by residual PSCs precludes facile adoption of this approach for therapy, and as such it will be of high interest to recapitulate this developmental process by a directed differentiation assay. To this end, single-cell sequencing could decipher the molecular trajectory PSC undergo during their differentiation into myogenic progenitors in teratomas. Such analysis may uncover candidate genes and signaling pathways that could be tested to produce teratoma-derived myogenic precursors in the culture dish, as was recently demonstrated for in vitro paraxial mesoderm and somite formation (Chal et al. 2018; Chal et al. 2015; Xi et al. 2017).

Prominent advances have been made in recent years in respect to generating PSC-derived myogenic precursors with therapeutic applicability. However additional

research is vital to translate bench lab findings to bedside treatments. Ethical limitations involving use of embryo-derived cells, risks for teratoma formation, and spurious differentiation of PSCs inhibit efforts to utilize PSC-derived myogenic cells to treat muscle-associated diseases. In respect to myogenic precursors, further investigation is certainly required to characterize the cells both molecularly and functionally, as well as devise safe and efficient protocols for their induction, purification, and in vitro maintenance. Future and ongoing human trials involving PSC-derived cells to treat diseases such as macular degeneration and Parkinson's disease hold paramount implications for assessing the therapeutic potential of PSC derived cells in clinical settings (Blau and Daley 2019). Successes are expected to expand the appetite for utilizing PSC-derived cells to treat other diseases, strengthen the nexus between scientists and clinicians, and may eventually destine PSC-based therapy to become a leading technology in regenerative medicine.

5   Direct Reprogramming of Somatic Cells into Myogenic Progenitors

Limitations of utilizing PSC-derived myogenic progenitors include both ethical and safety concerns and challenges associated with inducing PSCs to differentiate into adult mature cells. The aforementioned hurdles significantly hamper their utility in clinical settings, necessitating the search for additional approaches to produce expandable myogenic cells. An alternative method that can circumvent these challenges is direct lineage reprogramming, also known as "transdifferentiation." This approach denotes the conversion of one cell type into another by either ectopic overexpression of cell-type-specific transcription factors or small molecule treatment (Xu et al. 2015a). Historical pioneering studies spearheading this technique have shown that forced overexpression of the myogenic transcription factor MyoD in fibroblasts can convert them into skeletal myocytes via a short-lived myoblast stage (Davis et al. 1987; Weintraub et al. 1989; Tapscott et al. 1988). Since the landmark work by Davis and colleagues (Davis et al. 1987), a plethora of studies have reported on successful generation of various cell types by direct lineage reprogramming methods as reviewed (Xu et al. 2015a), including direct conversion into tissue-specific progenitors such as cardiac and neural precursors (Lalit et al. 2016; Lujan et al. 2012; Ring et al. 2012). Despite the formation of skeletal myocytes by MyoD overexpression being the first representation of direct lineage reprogramming, surprisingly only in recent years successful conversion into myogenic progenitors has been achieved (Ito et al. 2017; Bar-Nur et al. 2018; Lee et al. 2018; Sato et al. 2019; Bansal et al. 2019). We will next briefly introduce these new works, further highlighting unresolved issues and desired research directions spanning this technology.

Ito and colleagues were first to report that overexpressing various combinations of transcription factors such as Pax3, Pax7, Pitx1, Mef2b, and MyoD in mouse fibroblasts could give rise to myogenic progenitors (Ito et al. 2017). Reprogrammed myogenic progenitors upregulate satellite cell markers such as endogenous Pax3 and

Myf5, although intriguingly did not upregulate endogenous Pax7 expression (Ito et al. 2017). Additionally, the myogenic progenitors generated dystrophin-positive myofibers when injected into dystrophic murine muscles; however it is yet to be determined if these cells can contribute to the satellite cell pool in vivo (Ito et al. 2017). Another recent work reported on the conversion of fibroblasts into induced myogenic progenitor cells (iMPCs) by transient overexpression of MyoD in concert with three small molecules treatment (Bar-Nur et al. 2018). In stark contrast to overexpression of MyoD alone in fibroblasts, which generates myocytes (Davis et al. 1987), the combined treatment with Forskolin, a cyclic-AMP agonist, RepSox, a TGF-β inhibitor, and CHIR-99021, a GSK3-β inhibitor, surprisingly formed heterogenous cultures containing both undifferentiated progenitors and differentiated contractile myofibers (Bar-Nur et al. 2018). These progenitors can expand extensively in vitro, express high levels of endogenous Pax7 and Myf5, and engraft into both wild-type and dystrophic murine muscles (Fig. 3) (Bar-Nur et al. 2018). Remarkably, iMPCs efficiently contribute to the satellite cell pool and sustain multiple rounds of regeneration by repeated injury assay (Bar-Nur et al. 2018). Two additional reports have recently further demonstrated reprogramming of fibroblasts into induced myogenic precursor cells (Lee et al. 2018; Sato et al. 2019). Lee and colleagues have shown that overexpression of Six1, Eya1, Esrrb, and Pax3 can generate myogenic precursors that express endogenous Pax7 and fuse to form dystrophin-positive myofibers in dystrophic mice (Lee et al. 2018). In addition, Sato and colleagues established that overexpression of Pax3, Heyl, and KLF4 in concert with transient MyoD expression can generate myogenic precursors from both mouse and human fibroblasts (Sato et al. 2019), these precursors can expand long-term, upregulate satellite cell markers such as Pax7, Spry1, and Sdc4, and efficiently engraft into dystrophic muscles including the satellite cell niche (Sato et al. 2019). It will be of interest to assess if the induced precursors are true myogenic stem cells that can both sustain regeneration in a repeated injury assay as well as maintain engraftment by serial transplantation. Lastly, a new report demonstrated that small molecule treatment alone in fibroblasts can elicit skeletal myocyte formation via a short-lived progenitor state (Bansal et al. 2019). Of note, several of the small molecules (i.e., Forskolin, RepSox and CHIR-99021) are identical to the ones used in conjunction with transient MyoD expression to form iMPCs (Bar-Nur et al. 2018) or maintain quiescence of satellite cells in vitro (Quarta et al. 2016). However, myogenic cells produced by small molecule treatment alone did not permanently capture a myogenic progenitor state in vitro nor was the capacity of the induced cells to contribute to muscle regeneration in vivo investigated.

Generation of induced myogenic precursor/progenitor cells by direct lineage reprogramming is an attractive approach to produce expandable cells for therapy; however notable challenges and unresolved questions remain. An interesting question that still requires further interrogation is how similar to one another are the induced cells generated by the aforementioned methods. Likewise, it will be of interest to assess how akin induced myogenic precursor/progenitor cells are molecularly and functionally to both myoblasts and satellite cells, and whether they are true myogenic stem cells that can sustain muscle regeneration by a serial

transplantation assay. For translational purposes, future works will need to assess if these cells can be generated without integration of viral vectors, thus mitigating risks for insertional mutagenesis. To this end, synthetic mRNA transfection or protein transduction could be adapted to generate induced myogenic precursor/progenitor cells as was shown for iPSCs (Malik and Rao 2013). Similarly, production of these cells by small molecule treatment alone may provide a safer and more scalable approach to generate cells for translational purposes. Additional aspects of interest include disease modeling of muscular dystrophies using these cells and investigating their adoption for drug screens. In summary, this promising and nascent technique is in its infancy, and as such a litany of remaining questions will need to be thoroughly addressed prior to considering its potential use in clinical applications.

6   Maintaining Satellite Cell Potency In Vitro

Isolation of QSCs from skeletal muscle tissue is commonly performed by enzymatic digestion and mechanical breakage vital to dislodge the cells from their association with myofibers and the extracellular matrix (ECM). This harsh treatment mimics to an extent dissociation of satellite cells from their natural environment during injury or disease and likewise elicits rapid activation of myoblast-associated genes (Machado et al. 2017; Pietrosemoli et al. 2017; van Velthoven et al. 2017). Typically, freshly isolated satellite cells are separated from other mononucleated cell types by a pre-plating procedure or by FACS-sorting followed by seeding onto culture dishes coated with basement membrane substrates and in medium containing high serum levels and basic FGF (Rando and Blau 1994). Under these conditions, it was shown that nascent myoblasts rapidly proliferate and can fuse to form multinucleated myotubes in low serum conditions (Rando and Blau 1994). Upon further in vitro expansion, activated satellite cells promptly lose regenerative capacity as they form a population of proliferative myoblasts (Montarras et al. 2005). In the following section, we will outline various techniques that have been shown to ebb precocious differentiation of isolated satellite cells cultured in vitro and further augment their engraftment potential (Fig. 4a). We will focus on unique basement membrane substrates, treatment with small molecules, and induction of genes that promote an undifferentiated satellite cell state.

6.1   Basement Membrane Proteins that Support an Undifferentiated Satellite Cell State

During homeostasis native satellite cells are located between the sarcolemma and a structure of the basement membrane known as the basal lamina, providing an anatomical environment known as the "satellite cell niche." An intricate signaling crosstalk between the cells and their surrounding governs the satellite cell quiescent state (Rayagiri et al. 2018; Baghdadi et al. 2018). External stimuli such as the ones experienced during muscle injury and disease induce a signaling cascade that
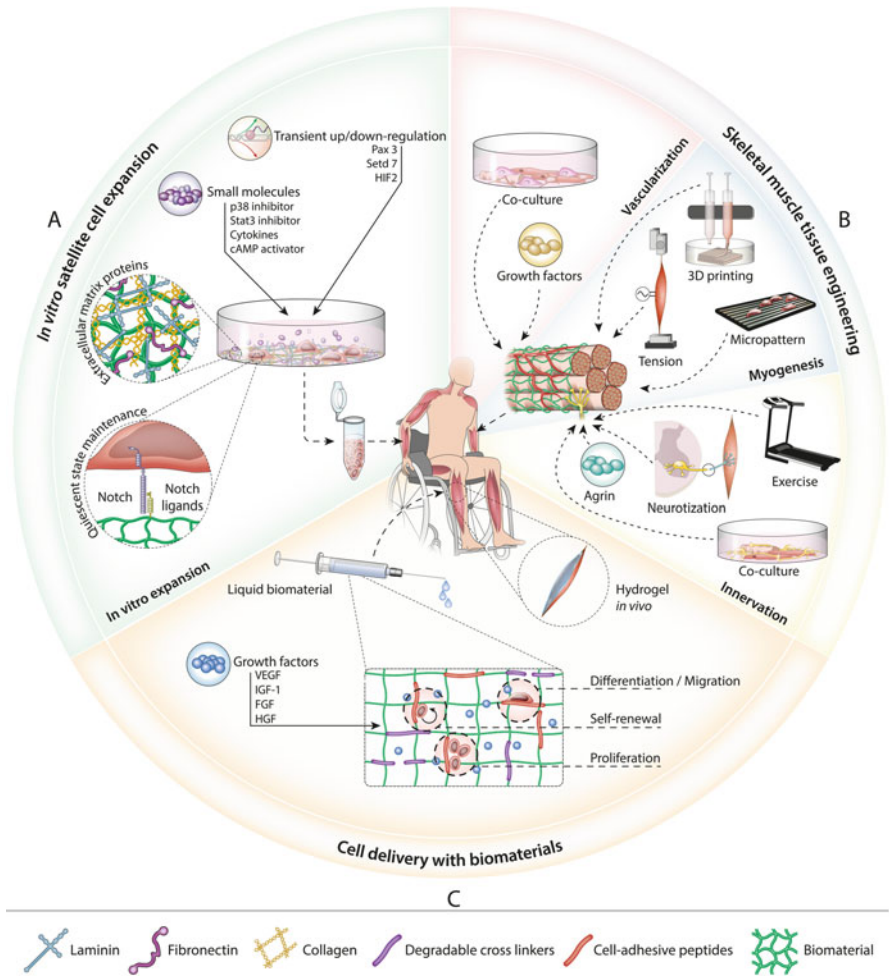
Fig. 4 Biomaterial and tissue engineering strategies to enhance satellite cell expansion, engraftment and reconstruction of skeletal muscle tissue. (**a**) Select approaches to expand satellite cells in vitro while maintaining in vivo engraftment potential. Different methods can be utilized including expansion on unique basement membrane proteins, treatment with small molecules and induction or repression of genetic pathways. (**b**) Tissue engineering approaches to treat severe muscle dystrophy or VML using in vitro generated muscle bioconstructs which consist of satellite cells, MRCs, and aligned, multinucleated myofibers. Bioconstruct can be further innervated or vascularized to facilitate engraftment and retention of grafts in muscles. (**c**) Strategies to enhance satellite cell engraftment using injectable biomaterials which extend satellite cell viability and retention at the injury site

promote satellite cell activation and proliferation, which are imperative for muscle repair (Dumont and Rudnicki 2017). In their endogenous microenvironment, satellite cells are embedded in ECM, which encapsulate myofibers and is associated with different proteins during quiescence and activation, including laminins

(Yao et al. 1996), fibronectin (Bentzinger et al. 2013), and collagen (Urciuolo et al. 2013). Conventional basement membrane proteins such as laminin-111, collagen I, Matrigel, and fibronectin are commonly used to expand satellite cells as myoblasts in vitro (Urciuolo et al. 2013; Maley et al. 1995; Grefte et al. 2012; Wilschut et al. 2010; Boonen et al. 2009; Duffy et al. 2016; Kuhl et al. 1986; Foster et al. 1987; Ocalan et al. 1988). These matrices are essential for attachment of freshly isolated satellite cells to the culture dish; however basement membrane proteins such as Matrigel are secreted by murine tumors and are composed of thousands of peptides, rendering them unsuitable for therapeutic applications in humans (Hughes et al. 2010). In addition, other basement membrane proteins confer on myoblasts reduced differentiation potential and loss of engraftment capacity during extended passaging. We will next discuss recent studies that set to uncover basement membrane proteins that could support satellite cell expansion while maintaining robust differentiation in vitro and high engraftment capacity in vivo.

Laminins (LMs) are active protein components of the ECM and belong to a glycoprotein family consisting of different chains including α, β, and γ. (Colognato and Yurchenco 2000). These proteins can support in vitro growth of myoblasts, albeit which laminin components form the satellite cell niche or are upregulated during injury was only recently thoroughly assessed (Ishii et al. 2018; Rayagiri et al. 2018). In one recent study, extensive analysis of the different laminin isoforms in skeletal muscle revealed that the satellite cell niche is composed of LM-α2, LM-α3, LM-α4, and LM-α5, which could then be mimicked in vitro by using Laminin E8 (LM-E8) fragments, which are truncated proteins composed of the α, β, and γ chains C-terminus domain (Ishii et al. 2018). Freshly isolated satellite cells cultured on LM-E8 derivative substrates remained undifferentiated in comparison to satellite cells cultured on Matrigel as indicated by higher quantities of proliferative Pax7$^+$/MyoD$^-$ cells (Ishii et al. 2018). Furthermore, mouse and human satellite cells expanded on LM-E8 could robustly contribute to muscle regeneration in vivo and restore dystrophin expression in mouse dystrophic muscles (Ishii et al. 2018). Another recent study examined conventional substrates in the form of Matrigel and LM-111 to biologically relevant laminins present in muscles such as adult LM-211, embryonic LM-521, and others (Penton et al. 2016). This meticulous analysis demonstrated that freshly isolated mouse and human satellite cells cultured as myoblasts on LM-521 demonstrate a robust differentiation potential as assessed by myotube size and fusion index in comparison to myoblasts cultured on conventional basement membrane proteins (Penton et al. 2016). However, the number of Pax7 and MyoD positive cells was similar among all tested conditions, and in vivo engraftment utilizing LM-521 cultured myoblasts was not assessed (Penton et al. 2016).

In concordance with these findings, a recent study reported that satellite cells regulate their quiescence via secretion of LM-α1, and genetic ablation of this protein impairs satellite cell self-renewal (Rayagiri et al. 2018). Similarly, another study demonstrated that collagen V (COLV) is produced by satellite cells and is key for their regeneration capacity, as blocking its production severely precludes satellite cell proliferation and leads to depletion of the satellite cell pool (Baghdadi et al. 2018). It will be of interest to assess if overexpression of LM-α1, LM-521, or COLV

could maintain satellite cell characteristics in vitro and augment muscle engraftment of cultured cells. Determining which basement membrane protein can best support satellite cell proliferation, and differentiation is expected to yield widespread implications with respect to the potential of human satellite cells cultured on these unique matrices to regenerate muscles in vivo.

6.2   Inhibition of Satellite Cell Differentiation by Small Molecules, Ligands, and Cytokines

Disruption of satellite cell quiescence by injury or disease is accompanied by activation of cellular signaling cascades that promote proliferation and regeneration. However, these pathways are altered in high-passage myoblast cultures, which is one attribute to their loss of engraftment potential. Small molecules that affect signaling pathways could mitigate this effect and promote maintenance of satellite cell characteristics in vitro. We will briefly describe recent efforts to harness small molecules to culture and propagate satellite cells.

The p38 mitogen-activated protein kinase (MAPK) pathway is upregulated during activation of mouse satellite cells (Jones et al. 2005; Simone et al. 2004). Furthermore, previous studies documented that p38 inhibitor treatment of satellite cells attenuated muscle aging while increasing functionality of muscles in aged mice (Cosgrove et al. 2014; Bernet et al. 2014). Charville and colleague recently corroborated this observation by demonstrating that human satellite cells similarly upregulate p38 pathway in vitro, and its inhibition blunted the differentiation of satellite cells into committed myoblasts (Charville et al. 2015). Treatment of human ASCs with p38 MAPK inhibitor SB03580 reportedly increased proliferation rate while mitigating precocious differentiation into myoblasts and myotubes (Charville et al. 2015). Remarkably, SB03580-treated satellite cells robustly engrafted into healthy and dystrophic muscles in comparison to non-treated cells or freshly isolated satellite cell controls and could contribute cells to the muscle stem cell reservoir (Charville et al. 2015). Another study corroborated this finding by demonstrating that p38 inhibition maintains satellite cell-like phenotype and proliferation of freshly isolated bovine satellite cells (Ding et al. 2018).

Another well-studied pathway associated with satellite cell quiescence, activation, and differentiation is the Notch pathway(Mourikis and Tajbakhsh 2014), first reported to be upregulated during activation of satellite cells (Conboy and Rando 2002). Subsequent studies have documented that Notch and its downstream targets Hey1, HeyL, and Hes1 are highly expressed in QSCs and downregulated upon differentiation (Mourikis et al. 2012; Bjornson et al. 2012; Brohl et al. 2012). Abrogation of Notch in satellite cells mitigates their proliferation rate and elicits precocious differentiation into mature muscle cells (Mourikis et al. 2012; Bjornson et al. 2012; Brohl et al. 2012). In line with these observations, overexpression of Notch-1 abolishes expression of muscle-associated differentiation genes (Conboy and Rando 2002), and overexpression of constitutively active intracellular domain of Notch1 (NICD1) can rescue precocious differentiation in satellite cells lacking Pax7 (Pasut et al. 2016). Different Notch ligands have been implicated in regulating satellite cell quiescence and

self-renewal (Baghdadi et al. 2018; Low et al. 2018; Verma et al. 2018). Of note, a recent study highlighted the role of endothelial cells in maintenance of satellite cell quiescence through the Notch ligand Dll4 (Verma et al. 2018).

These collective findings suggest that manipulating the Notch pathway could impact proliferation and differentiation potential of cultured satellite cells and myoblasts. Indeed, Parker and colleagues were first to report that culturing canine freshly isolated satellite cells in conditions that promote Notch activation blunted differentiation and facilitated muscle engraftment, strikingly in equal levels to those of freshly isolated canine satellite cells (Parker et al. 2012). Similarly, mouse and human satellite cells expanded on Notch ligands reportedly proliferated better, elevated expression level of Notch downstream targets, and reduced expression of differentiation-associated genes (Sakai et al. 2017). However, contribution of cells to engraftment in host muscles was similar between treated and control cells (Sakai et al. 2017). In another recent work, Gerli and colleagues cultured freshly isolated satellite cells and myoblasts on Dll4 ligand in concert with PDGF-BB supplementation (Gerli et al. 2019). This treatment attenuated proliferation and differentiation of cultured satellite cells, increased the proportion of $Pax7^+/MyoD^-$ cells and elevated expression of Notch and its downstream targets (Gerli et al. 2019). The authors hypothesize that the combined treatment augments perivascular and satellite cell attributes in cultured myoblasts (Gerli et al. 2019). However, the in vivo capacity of treated myoblasts to engraft into muscles in vivo is yet to be determined (Gerli et al. 2019). Collectively, conflicting reports exist with respect to the capacity of Notch ligands to enhance engraftment of cultured myoblasts in vivo; however this pathway undisputedly helps in sustaining satellite cell attributes in vitro. More work is required to resolve if alteration of this pathway can enhance engraftment of myogenic cells in vivo.

Forskolin is a small molecule that has been recently implicated in enhancement of muscle stem or progenitor cell proliferation and engraftment potential (Xu et al. 2013; Bar-Nur et al. 2018; Quarta et al. 2016). Forskolin increases cAMP intracellular levels that further activate the protein kinase A (PKA) pathway, which subsequently phosphorylates the transcription factor cAMP response element-binding protein (CREB). Activation of this pathway was previously shown to be essential for WNT-related induction of embryonic myogenesis (Chen et al. 2005). Recent works implicated Forskolin in enhancing expansion of mouse satellite cells in vitro (Xu et al. 2013). Freshly isolated satellite cells cultured in the presence of Forskolin retained satellite cell characteristics in vitro, and treated cultures could engraft robustly into dystrophic mouse muscles (Xu et al. 2013). Forskolin is also a component of a small molecule cocktail which reportedly maintains muscle stem cell quiescence in vitro in conjunction with engineered muscles fibers (Quarta et al. 2016). This artificial construct can regenerate muscle in vivo upon engraftment (Quarta et al. 2016). Lastly, forskolin is one of three small molecules that have been reported as critical for induction and proliferation of induced myogenic progenitor cells from fibroblasts in concert with MyoD (Bar-Nur et al. 2018).

Muscle damage initiates infiltration of white blood cells to the injury site, where these cells play important role in muscle repair via secretion of cytokines (Woszczyna and Rando 2018). Growing amount of evidence suggest that cytokines can directly affect satellite cells and myoblasts. Notable examples include leukemia inhibitory

factor (LIF), which reportedly increases the proliferation of cultured myoblasts (Austin and Burgess 1991; Austin et al. 1992; Alter et al. 2008). Accordingly, LIF was recently shown to effectively enhance the transplantation potential of freshly isolated myoblasts in a DMD mouse model, presumably by attenuating apoptosis (Ito et al. 2016). LIF is one of several members of the IL-6 cytokine family, which includes IL-6, IL-27, IL-11, and Oncostatin (OSM) (Stefan Rose-John 2018). It functions by binding to the LIfr/gp130 receptor which activates JAK1 signaling cascade leading to phosphorylation and activation of the transcription factor Stat3 (Nicola and Babon 2015). Similarly, IL-6 is a proinflammatory cytokine which is upregulated during the initial phase of muscle regeneration and mediates its effect through Stat3 downstream activation (Munoz-Canoves et al. 2013). Stat3 pathway is crucial for myogenic differentiation, and absence of Stat3 signaling perturbs efficient muscle regeneration (Tierney et al. 2014; Wang et al. 2008; Sun et al. 2007). Accordingly, IL-6 supplementation upregulates MyoD expression through Stat3 signaling, promoting muscle regeneration (Tierney et al. 2014). Attenuating Stat3 expression enhances myoblasts proliferation; however engraftment potential of these cells was not assessed (Tierney et al. 2014). In accordance with this observation, another cytokine of the IL-6 pathway that activate the Stat3 pathway is OSM, which reportedly blocks differentiation of myoblasts and keeps them in a progenitor-like state (Xiao et al. 2011). A recent study revealed that OSM is secreted by muscle fibers, exerting a quiescent phenotype on muscle stem cells (Sampath et al. 2018). OSM treatment of cultured myoblasts maintains their stemness in vitro as judged by Pax7-GFP reporter expression, and this treatment dramatically enhances myoblast engraftment potential and further enables serial transplantation of cells (Sampath et al. 2018). Wnt4 is another recently reported niche-specific factor secreted from myofibers that regulates satellite cell quiescence (Eliazer et al. 2019). It will be of interest to assess if akin to OSM treatment of freshly isolated satellite cells, administration of Wnt4 can help support in vitro muscle stem cell quiescence and enhance in vivo engraftment potential. Building upon the notable effects cytokines have on muscle stem cells, Fu and colleagues screened multiple proinflammatory cytokines to find combinations of cytokines that promote satellite cell expansion (Fu et al. 2015). This effort uncovered culture conditions that consist of the T-cell secreted cytokines IL-1α, IL-13, TNF-α, and IFN-γ to support extensive expansion of satellite-like cells (Fu et al. 2015). Expanded cells treated in these conditions could very efficiently engraft into muscles and further replenish the satellite cell reservoir (Fu et al. 2015).

6.3   Genetic Alteration that Support Satellite Cell Self-Renewal and Regeneration

Aside from basement membrane proteins and small molecule treatment, alteration of genes and genetic pathways is an additional method to augment satellite cell expansion potential. An elegant manifestation of this approach was recently reported by Filareto and colleagues who demonstrated that transient overexpression of the transcription factor Pax3 in freshly isolated satellite cells abates spontaneous differentiation into

myoblasts, and further enhances cell proliferation without compromising satellite cell capacity to give rise to myotubes in response to differentiation cues (Filareto et al. 2015). Moreover, treated satellite cells could robustly restore dystrophin expression in DMD mice and contribute cells to the satellite cell pool (Filareto et al. 2015). To further investigate the translation potential of this approach, freshly isolated satellite cells extracted from DMD mice were subjected to transient Pax3 overexpression and infected with a construct encoding human micro-dystrophin (Filareto et al. 2015). Following this procedure, cells were engrafted into dystrophic mouse muscles and could restore dystrophin expression and remedy symptoms of the affliction, demonstrating an elegant autologous satellite cell-based approach to treat DMD in a mouse model (Filareto et al. 2015), which can be adapted to humans (Fig. 2b).

A few additional studies have recently reported means to sustain satellite cell expansion in vitro by altering genetic pathways. One study demonstrated that deletion of the lysine methyltransferase Setd7 enables in vitro expansion of undifferentiated freshly isolated human and mouse satellite cells and could further enhance their engraftment potential in vivo (Judson et al. 2018). This phenotype is mediated via interaction of Setd7 with β-catenin and modification of its methylation state, which subsequently induces a differentiation myogenic gene commitment program that is abated in Setd7 deleted cells (Judson et al. 2018). Inhibition of Setd7 can be mimicked by pharmacological treatment, providing a facile approach to utilize this method for therapeutic interventions (Judson et al. 2018). Another study reported that inhibition of HIF2A support satellite cell proliferation (Xie et al. 2018). Quiescent satellite cells express the hypoxia-inducible factor 2A (HIF2A) and are in a hypoxic state during homeostasis (Xie et al. 2018). This state is rapidly altered in normoxic state during in vitro growth (Xie et al. 2018). Capitalizing on this unique observation, it was shown that short-lived inhibition of HIF2A by pharmacological modulation accelerates muscle stem cell proliferation, while deletion of HIF2A abrogates muscle regeneration due to depletion of the satellite cell reservoir (Xie et al. 2018). It will be of interest to assess whether satellite cells subjected to this short-lived treatment can better engraft into muscles in vivo.

Culturing satellite cells using the aforementioned treatments has been demonstrated to mitigate precocious differentiation and enhance engraftment potential of cells. Further research is required to investigate the mode of action by which these treatments work. Additionally, a manifold of these studies have been reported in mouse cells, and it is of interest to assess which method can efficiently adapt to expand human satellite cells. Lastly, it will be of interest to investigate the effects of combinatorial administration of small molecules on human satellite cells to assess if combined treatment can facilitate the expansion and engraftment of cells in comparison to individual treatment.

7 Enhancing Muscle Stem Cell Engraftment Using Biomaterials

Delivery methods of myogenic cells into recipient muscles could impact translational outcomes by increasing engraftment efficacy and decreasing the requirement for high quantities of donor-derived satellite cells (Fig. 4c) (Boldrin et al. 2007).

In early myoblast transplantation trials, engrafted cells were typically resuspended in HBSS or PBS prior to injections (Huard et al. 1992; Tremblay et al. 1993a; Mendell et al. 1995). However, aftereffects of these trials were disappointing, and low cell survival may have accounted for the unfavorable outcome (Beauchamp et al. 1999). This observation raises an interesting question whether delivery of muscle stem or progenitors cells in conjunction with unique substances such as biomaterials could manifest better therapeutic outcomes.

Biomaterials are defined as a synthetic or natural substance, or combination of substances, that can remedy or replace tissues and organs in the body (National Institutes of Health Consensus Development 1983). To date, numerous natural and synthetic biomaterials have been widely investigated for their potential to boost skeletal muscle regeneration (Cezar and Mooney 2015; Qazi et al. 2015). Biomaterials can encapsulate cells, for instance, in the form of soft hydrogels that are created by the crosslinking of hydrophilic polymers or 3D scaffolds, which are generated by various techniques including chemical crosslinking, freeze-drying, or electrospinning (Qazi et al. 2015; Wolf et al. 2015; Hu et al. 2019). An injectable or implantable biomaterial can protect the engrafted cells from apoptosis and increase cell proliferation while negating immunological responses (Han et al. 2017). Moreover, degradable biomaterials can be replaced over time by a regenerated tissue, which is important once a therapeutic objective is achieved (Han et al. 2017). Commonly used biomaterials which have been reported to sustain cell delivery into skeletal muscle tissue include natural alginate (Wang et al. 2014; Hill et al. 2006), hyaluronic acid (HA) (Rossi et al. 2011; Davoudi et al. 2018), ECM (Rao et al. 2017), or fibrin (Matthias et al. 2018; Page et al. 2011; Gerard et al. 2012), as well as synthetic scaffolds in the form of poly(ethylene glycol) (PEG) (Han et al. 2018, 2019), poly(lactic-co-glycolic acid) (PLGA) (Boldrin et al. 2007, 2008), or a combined PEG-fibrinogen constructs (Fuoco et al. 2012, 2014, 2015).

Several studies have reported on the beneficial effects of utilizing synthetic or natural biomaterials during myoblast engraftment into murine muscles (Boldrin et al. 2007, 2008; Hill et al. 2006; Wang et al. 2014; Rao et al. 2017). For example, high quantities of donor-derived myofibers were detected when myoblasts were encapsulated inside micropatterned PGA scaffolds and engrafted into pre-injured mouse muscles (Boldrin et al. 2007, 2008). A subsequent study demonstrated enhanced muscle regenerative capacity upon delivery of myoblasts embedded in alginate scaffolds compared to injection of cells alone (Hill et al. 2006). In these studies, scaffolds containing myoblasts in their native size were implanted into muscles (Boldrin et al. 2007, 2008; Hill et al. 2006). However, an injectable biomaterial could additionally enable a less invasive cell delivery method (Qazi et al. 2015). This can be achieved by using shape-memory scaffolds (Wang et al. 2014) or injectable biomaterials that can be polymerized into gels in situ due to a temperature shift (Davoudi et al. 2018), light (Rossi et al. 2011; Fuoco et al. 2015), or ions (Sleep et al. 2017). Shape-memory scaffolds can be compressed during transplantation and then expand back to their original size in situ (Lendlein and Langer 2002). An alginate-based shape-memory scaffold has been suggested as a vehicle for myoblast delivery, as it enables a minimally invasive transplantation procedure (Wang et al. 2014).

Upon engraftment into pre-injured muscles, increased myoblast viability, muscle regeneration, and reduced fibrosis were reported (Wang et al. 2014). Further, robust myoblast proliferation and engraftment efficacy were demonstrated upon assembly of myogenic cells inside an ECM hydrogel and injection into ischemic muscles in conjunction with fibroblasts (Rao et al. 2017).

Prolonged in vitro expansion of myoblasts reduces engraftment potential as compared to freshly isolated satellite cells (Montarras et al. 2005). As such, biomaterial-based delivery of satellite cells has been recently investigated with hope of increasing engraftment efficacies (Sleep et al. 2017; Davoudi et al. 2018; Han et al. 2018, 2019; Rossi et al. 2011). In a notable study, Rossi and colleagues delivered myoblasts or satellite cells embedded in a photocrosslinkable hyaluronan hydrogel into pre-injured mouse muscles, reporting both increased detection of donor-derived myofibers and improved contraction forces (Rossi et al. 2011). Recently, Sleep and colleagues reported on a method to embed satellite cells in a liquid crystalline scaffold prior to intramuscular injections (Sleep et al. 2017). The scaffold stiffness was adjusted to physiological values, in agreement with previously published works highlighting the effects of mechanical properties on myogenesis (Engler et al. 2004; Gilbert et al. 2010; Sleep et al. 2017). Utilizing a unique apparatus that forms aligned scaffolds in vivo, freshly isolated satellite cells were encapsulated in a biomimetic scaffold and engrafted into muscles, demonstrating robust regeneration in comparison to control non-encapsulated cells (Sleep et al. 2017). Of interest, the scaffold degradation pace was akin to the typical time period necessary for muscle tissue regeneration, leading the authors to suggest that this temporal concordance is key for vascularization and innervation of the regenerating tissue (Sleep et al. 2017).

In a recent study, a hydrogel-based cell delivery system promoting cell viability, proliferation, and differentiation has been reported (Han et al. 2018). The synthetic hydrogel consisted of both four-arm PEG and maleimide groups (PEG-4MAL) and was further functionalized with arginine, glycine, and aspartic acid (RGD) peptides (Han et al. 2018). RGD motifs are found in fibronectin and other extracellular matrix proteins that are essential for both satellite cell expansion and myoblast differentiation (Ruoslahti and Pierschbacher 1987; Garcia et al. 1999; Lukjanenko et al. 2016) and are frequently used to support cell adhesion (Wang et al. 2014; Hill et al. 2006; Han et al. 2018, 2019; Borselli et al. 2011). Utilizing this delivery system, RGD functionalized hydrogels increased freshly isolated satellite cell viability, proliferation, and migration, and the RGD adhesive sites were key for cell fusion in vitro (Han et al. 2018). Of interest, utilizing a protease-degradable crosslinker enabled degradation of the hydrogel and further enhanced cell viability and proliferation in vitro (Han et al. 2018). Lastly, satellite cell survival and proliferation were also improved via hydrogel delivery during "supra-muscular" injections onto the muscle surface of aged or dystrophic mice (Han et al. 2018). In another notable study, Davoudi and colleagues demonstrated that satellite cell delivery in a hyaluronan and methylcellulose (HAMC) hydrogel resulted in a 45% increase of donor-derived myofiber engraftment compared to saline control (Davoudi et al. 2018). The authors noted improved dispersion of regenerated myofibers, suggesting that cell migration was enhanced by use of the hydrogel (Davoudi et al. 2018). They further

conducted several experiments to elucidate the mechanisms governing the enhanced engraftment observed with HAMC usage (Davoudi et al. 2018). For instance, hydrogels have been shown to protect various cells from mechanical forces during the injection process (Aguado et al. 2012). To note, HAMC did not affect the viability of extruded satellite cells however led to a 6% increase in cell number (Davoudi et al. 2018). Collectively, the authors suggest that the enhanced engraftment could be attributed to elevated muscle stem cell proliferation, protection from active clearance by the immune system and detaining precocious differentiation (Davoudi et al. 2018).

An additional advantage of cell encapsulation inside biomaterials entails the potential of cell delivery with incorporation of various growth factors. Whereas growth factors mixed in a saline solution tend to diffuse rapidly inside a recipient tissue, a scaffold can support gradual release of growth factors into the tissue (Qazi et al. 2015; Han et al. 2017; Sleep et al. 2017). To this end, Borselli and colleagues encapsulated myoblasts in conjunction with the growth factors VEGF and IGF-1 inside an alginate scaffold and delivered the bioconstruct into pre-injured murine muscles (Borselli et al. 2011). This technique reportedly improved cell engraftment and further stimulated vascularization and myogenesis in the host tissue (Borselli et al. 2011). In another study, Hill and colleagues embedded myoblasts in an alginate scaffold in the presence of HGF and FGF2 prior to delivery (Hill et al. 2006). They reported increased cell viability, prevention of terminal differentiation, and improved regeneration in muscles engrafted with this construct (Hill et al. 2006). Additional studies further demonstrated that sustained release of bFGF from engineered constructs facilitated myoblast or satellite cell engraftment (Hagiwara et al. 2016; Sleep et al. 2017). Lastly, another recent report demonstrated the assembly of a PEG-4MAL hydrogel with muscle stem cells and the protein Wnt7a (Han et al. 2019), a pro-myogenic factor involved in muscle repair and stem cell migration (von Maltzahn et al. 2011; Bentzinger et al. 2014). This effort has led to an increase in muscle mass and regeneration following construct delivery into pre-injured muscles and strikingly also elevated stem cell migration (Han et al. 2019). Collectively, the aforementioned reports suggest that the delivery of biomaterials together with unique small molecules and growth factors could augment myogenic engraftment efficacy.

The various studies discussed in this section indicate that synthetic or natural materials can enhance muscle stem cell engraftment. However, the molecular mechanisms that mediate this process are not completely understood and additional research is warranted. Furthermore, it will be of interest to assess whether combining different cell types inside a biomaterial could enhance regeneration capacity. Ideal candidates include cell types that are associated with skeletal muscle repair (Woszczyna and Rando 2018), such as resident endothelial cells, fibro-adipogenic progenitors, or macrophages which reportedly promote muscle regeneration (Lukjanenko et al. 2019; Woszczyna et al. 2019; Latroche et al. 2017; Joe et al. 2010). Collectively, amassing inside a biomaterial multiple cell types native to muscle tissue and essential for its repair could boost the therapeutic competence of this tissue engineering approach.

8   Stem Cell-Based Approaches to Engineer Skeletal Muscle Tissue

Volumetric muscle loss (VML) denotes the irrecoverable structural and functional deficits of skeletal muscle tissue induced by acute injury or surgical removal (Greising et al. 2019). Due to extensive muscle loss, satellite and other muscle resident cells fail to repair the tissue damage which is often times replaced by fibrotic tissue (Greising et al. 2019; Corona et al. 2019). Harvest of healthy muscle fragments known as "muscle flaps" followed by engraftment into VML-afflicted muscle sites can partially treat this muscle loss; however this complicated surgery is often associated with donor site morbidity (Lin et al. 2007; Klinkenberg et al. 2013; Gilbert-Honick and Grayson 2019). Several late-stage muscular dystrophies such as DMD share resemblances to VML, as the muscle tissue is both severely damaged and typically replaced by adipogenic and fibrotic tissues (Klingler et al. 2012; Hooijmans et al. 2017; Skuk et al. 2007). If an entire muscle segment is acutely damaged, muscle stem cells cannot efficiently regenerate skeletal muscle, and myogenic cell engraftment is expected to fail in the absence of a supportive tissue. Notably, this has previously been shown for DMD patients following allogeneic myoblast transplantation, which was reportedly effective when cells were engrafted into an intact muscle tissue, however failed to engraft following injections into highly dystrophic muscles devoid of parenchyma (Skuk et al. 2007). An alternative therapeutic approach to cell transplantation involves reconstructing a functional skeletal muscle tissue in vitro that could incorporate into VML-afflicted muscle sites or acutely dystrophic muscles (Fig. 4b) (Juhas and Bursac 2013). In the following section, we will highlight attempts to engineer tissue-like muscle constructs in vitro utilizing myogenic stem or progenitor cells seeded on designated scaffolds prior to engraftment. For further reading into other approaches that involve tissue engineering of skeletal muscle, we refer the readers to recently published literature (Kwee and Mooney 2017).

8.1   Engineering Skeletal Muscle Tissue In Vitro Using Myogenic Precursors

Historically, early attempts to engineer bioartificial skeletal muscle tissue utilized avian myotubes or immortalized mouse myoblast cell lines such as C2C12 (Vandenburgh and Kaufman 1979; Vandenburgh et al. 1988, 1998, 1996). The latter have been oftentimes used as "biological vehicles" to deliver growth factors into muscle tissue (Vandenburgh et al. 1996, 1998). Vandenburg and colleagues reported on a method to produce a bioartificial muscle (BAM) consisting of parallel myotubes that upon muscle engraftment secreted recombinant human growth factors and attenuated muscle atrophy in mice (Vandenburgh et al. 1998). The BAM was formed by coalescing collagen and Matrigel with C2C12 myoblasts, which were genetically engineered to express a specific growth factor (Vandenburgh et al. 1988). This pre-gel solution was allowed to solidify in long casts, thus forming aligned myotubes

which were successfully subcutaneously transplanted (Vandenburgh et al. 1996, 1998). Multiple groups have since utilized C2C12 to produce muscle constructs in vitro by various tissue engineering techniques (Engler et al. 2004; Costantini et al. 2017; Zhang and Guo 2017; Kang et al. 2016). Furthermore, C2C12 has also been incorporated into engineered muscle constructs to replace muscle tissue in vivo (Levenberg et al. 2005; Koffler et al. 2011; Kaufman et al. 2019). While these studies provided the experimental framework to engineer skeletal muscle cells, C2C12 is an immortalized cell line which is physiologically distinct from normal myogenic cells, necessitating usage of physiologically relevant and therapeutically acceptable primary cells (Yaffe and Saxel 1977; Morgan et al. 1992; Wernig et al. 1991). To this end, skeletal muscle constructs have also been generated from primary myogenic cells derived from rodent (Juhas et al. 2014; Corona et al. 2014; Machingal et al. 2011) or human (Gholobova et al. 2015; Quarta et al. 2017; Madden et al. 2015; Powell et al. 1999) sources. To induce muscle construct formation, parallel alignment of differentiated myotubes is typically generated by patterned scaffolds and substrates (Neal et al. 2014; Kang et al. 2016; Takahashi et al. 2013; Bian et al. 2009; Nakayama et al. 2019), or platforms that induce unidirectional tension in muscle bundles (Powell et al. 1999; Gholobova et al. 2015; Vandenburgh et al. 1998). A uniform muscle architecture has been elegantly demonstrated using parallel multinucleated myofibers and sarcomeric striations (Juhas et al. 2014; Madden et al. 2015). Moreover, several studies reported on functional muscle contractions involving active calcium signaling in vitro and contribution to force generation in vivo (Madden et al. 2015; Quarta et al. 2017; Vandenburgh et al. 2008). Interrogating the regeneration potential of an engineered muscle construct in vitro is key for predicting therapeutic outcomes in vivo. This can be achieved by inflicting muscle damage and recording the regeneration capacity of the engineered tissue in vitro (Juhas et al. 2014). In a notable study, Juhas and colleagues generated 3D engineered muscle bundles from neonatal rat myogenic cells and intriguingly observed Pax7 satellite-like cells under the basal lamina in these constructs (Juhas et al. 2014). In concordance with this observation, the engineered construct could regenerate muscle fibers in vitro following localized cardiotoxin muscle injury (Juhas et al. 2014).

An alternative myogenic cell source for tissue engineering of skeletal muscle are iPSCs, as they can potentially differentiate into an unlimited number of myogenic precursors that can be used for muscle reconstruction (Pantelic and Larkin 2018; Del Carmen Ortuno-Costela et al. 2019). Rao and colleagues recently reported on the first generation of functional skeletal muscle tissue entirely from human iPSCs (Rao et al. 2018). Human iPSCs were exposed to the GSK3-β inhibitor CHIR-99201 in conjunction with transient Pax7 overexpression, resulting in differentiation into myogenic precursors that express endogenous Pax7 (Rao et al. 2018). These cells were further cultured in 2D dishes or in 3D fibrin hydrogels (Rao et al. 2018). The authors demonstrated that using a 2D culture system, skeletal muscle was partially formed, while usage of the 3D culture system gave rise to mature muscle bundles that expressed adult myosin heavy chain isoforms (Rao et al. 2018). Strikingly, the muscle bundles were functional in vitro and in vivo as demonstrated by induction of

contractions and calcium transits using electrical and chemical stimuli (Rao et al. 2018).

Collectively, the findings described thus far illustrate eminent advancements in skeletal muscle cell organization in vitro; however engineering functional muscle tissue is expected to require vascularization and innervation of the muscle constructs. In the next sections we will briefly describe methods to vascularize or innervate in vitro engineered muscle cells.

8.2 Vascularization of Skeletal Muscle Tissue Constructs

Skeletal muscle is a highly vascularized tissue, as blood vessels are essential for in vitro formation of large-sized tissue since they enable nutrient and oxygen supply across large tissue segments (Kaully et al. 2009). Several studies have therefore investigated the ability to vascularize tissue-engineered muscle constructs by in vivo endothelial cell recruitment or in vitro pre-vascularization (Gilbert-Honick and Grayson 2019). With respect to the first approach, some studies reported on host vessel infiltration into small muscle constructs (Juhas et al. 2014; Kang et al. 2016); albeit for larger muscle constructs this is deemed a limiting factor. To address this limitation, several studies documented recruitment of host blood vessels by engineering cells or scaffolds to secrete growth factors such as VEGF to facilitate vessel migration (Zhou et al. 2015; Koffler et al. 2011; Osaki et al. 2018a; Borselli et al. 2010). In one notable study, muscle constructs consisting of myoblasts that ectopically express VEGF have been reported to induce robust vascularization in vivo (Zhou et al. 2015). Furthermore, interactions between C2C12-derived muscle bundles that ectopically express angiopoietin-1 and endothelial cells have been studied (Osaki et al. 2018a). Angiopoietin-1 secretion evoked endothelial cell sprouting toward the muscle fiber bundles, and this interaction increased myofiber contraction force strength (Osaki et al. 2018a).

Whereas enhancement of host cell infiltration is a promising research direction, replacing a muscle tissue in vivo may be more advantageous for therapy if the tissue is composed of multiple cell types with different physiological roles. Co-culturing myoblasts together with endothelial cells is an established method to improve vascularization of muscle grafts (Levenberg et al. 2005; Koffler et al. 2011; Gholobova et al. 2019; Nakayama et al. 2019). For example, co-culturing murine myoblasts with endothelial cells and fibroblasts have been reported to form muscle constructs consisting of vascular networks in vitro (Levenberg et al. 2005), and these findings were further recapitulated using human cells (Gholobova et al. 2015, 2019; Maffioletti et al. 2018). In a recent study, Kaufman and colleagues investigated vascularization of muscle grafts consisting of C2C12, endothelial cells, and fibroblasts in mice afflicted with injured abdominal walls (Kaufman et al. 2019). Utilizing this approach, robust graft integration into host muscles has been documented, consisting of parallel donor-derived myotubes and absence of fibrotic structures (Kaufman et al. 2019). Similarly, using human umbilical vein endothelial cells (HUVECs) with human myoblasts reportedly created endothelial cell networks in

BAM constructs, highlighting the importance of vascularization of myotubes for production of larger bio-artificial muscle constructs (Gholobova et al. 2019). Lastly, patterned scaffolds seeded with myoblasts and vascular endothelial cells have been recently demonstrated to positively guide parallel myotube alignment and organize microvasculature of engineered skeletal muscle constructs (Nakayama et al. 2019). In comparison to randomly aligned myotubes, these parallel aligned myofibers gave rise to coordinated contractions, upregulation of myogenic genes, and exceedingly improved integration into VML lesions in a mouse model (Nakayama et al. 2019). This work highlights the potential of combining endothelial cells in concert with unique scaffolds to induce vascularization in addition to muscle regeneration upon engraftment.

8.3   Innervation of Skeletal Muscle Tissue Constructs

Motor neurons induce muscle contractions via secretion of neurotransmitters in neuromuscular junctions (Slater 2017). This intricate molecular crosstalk allows muscle innervation by motor neurons, a process which plays a pivotal role in skeletal muscle function, and its derailment rapidly elicits muscle atrophy (Afshar Bakooshli et al. 2019; Osaki et al. 2018b; Kaufman et al. 2019). Generation of tissue-engineered muscle constructs therefore may require extensive innervation to enable optimal graft function inside host muscles. To this end, multiple factors have been assessed with respect to their capacity to innervate muscle constructs including neurotization (Dhawan et al. 2007; Kaufman et al. 2019), chemicals (Wang et al. 2013; Ko et al. 2013), co-culture with neural cell types (Larkin et al. 2006; Morimoto et al. 2013; Afshar Bakooshli et al. 2019), and exercise (Quarta et al. 2017).

Neurotization is a well-established method that can elicit tissue innervation via transfer of host nerves into a de-innervated tissue. For example, attaching an engineered muscle construct to femoral nerves reportedly increases innervation of flaps (Kaufman et al. 2019). Innervation of muscle tissue is key for achieving therapeutic success as lack of innervation in muscle flaps culminates in adipogenic or fibrotic tissue replacement (Chang et al. 2018). Furthermore, proper innervation of muscle constructs has also been associated with enhanced muscle maturation and increased force production (Dhawan et al. 2007).

Aside from neurotization, "preconditioning" innervation in vitro could also provide means to accelerate innervation in vivo, particularly for large muscle constructs (Ko et al. 2013). This can be achieved by inducing expression of acetylcholine receptors which are pivotal for neuromuscular junction function (Ko et al. 2013). To this end, multiple studies have reported on beneficial effects for utilizing the motor neuron secreted factor agrin on skeletal muscle cells (Bian and Bursac 2012; Bentzinger et al. 2005; Bezakova and Ruegg 2003). Agrin is an acetylcholine receptor cluster-inducing factor and accordingly muscle constructs that were pre-treated with agrin prior to transplantation demonstrated an increase in acetylcholine receptors as well as large quantities of neuromuscular junctions both in vitro and in vivo (Ko et al. 2013). In addition to chemical stimulation, co-culturing

muscle and neural cells was also studied as a method to enhance innervation of muscle constructs (Morimoto et al. 2013; Cvetkovic et al. 2017; Happe et al. 2017; Martin et al. 2015; Larkin et al. 2006). In one such study, Morimoto and colleagues reported on a technique to co-culture mouse muscle bundles with neural stem cells that were further differentiated into motor neurons (Morimoto et al. 2013). This co-culture system enabled formation of neuromuscular junctions and muscle contraction following chemical stimulation (Morimoto et al. 2013).

Human iPSC-derived neural and muscle cells have similarly been co-cultured in 3D, reportedly enabling maturation of neuromuscular junctions by such technique (Osaki et al. 2018b; Afshar Bakooshli et al. 2019; Maffioletti et al. 2018). In a recent study, innervated skeletal muscle constructs have been generated by co-culturing human muscle progenitors cells and pluripotent stem cell-derived motor neurons inside a fibrin/Geltrex hydrogel (Afshar Bakooshli et al. 2019). Following 2 weeks of culture, motor neuron clusters were detected at the periphery of the newly formed muscle bundles (Afshar Bakooshli et al. 2019). Importantly, an epsilon acetylcholine receptor subunit, indicative of adult synapse formation, was detected in the newly formed neuromuscular junctions in 3D but not in a 2D co-culture system (Afshar Bakooshli et al. 2019). In line with these results, the authors detected calcium transits in response to motor neuron stimulation in the fibers, which suggests functional innervation (Afshar Bakooshli et al. 2019). Collectively, these results highlight the importance of 3D co-culture systems for production of functional neuromuscular junctions in vitro.

8.4   Integrative Tissue Engineering Approaches to Treat VML

The extent by which current therapeutic interventions assist in treating VML in humans is still not completely understood. However, a recently published large-scale meta-analysis comparing different VML regenerative medicine-based treatment options in animal models concluded that interventions improve functional recovery in comparison to untreated injury (Greising et al. 2019). Importantly, of all examined interventions, delivery of acellular biomaterials seeded with cells was deemed the most beneficial therapeutic approach (Greising et al. 2019). However, previous works have revealed the potential of ECM based-scaffolds to treat VML. Acellular scaffolds alone have been implanted in rodents and humans to counteract VML; however, these constructs solely depend on infiltration of host cells, which presents a challenge (Greising et al. 2019; Sicari et al. 2014; Dziki et al. 2016; Corona and Greising 2016). An alternative approach is engineering skeletal muscle constructs in vitro for the treatment of VML or late stage DMD. Notably, success of this approach depends on integration of different techniques and approaches, such as combining different cell types with various biomaterials. Such an approach involves selection of an appropriate biomaterial, the type of muscle precursor cell to utilize, as well as methods to innervate and vascularize the muscle constructs. In the last section, we will introduce several studies that successfully assimilated different techniques to

produce engineered skeletal muscle tissue constructs in vitro that further demonstrated functional therapeutic outcome in vivo.

A powerful approach to engineer muscle tissue involves combination of acellular scaffolds with live cells prior to implantation, thus circumventing the dependency on host cell-infiltration. Therapeutic applicability of this approach has been successfully investigated in rodent VML models (Mintz et al. 2019; Quarta et al. 2017; Nakayama et al. 2019). In one recent study, engineered muscle bundles have been created from adult rat myogenic cells seeded with bone marrow-derived macrophages, an essential cellular component for muscle regeneration (Novak et al. 2014; Bencze et al. 2012; Lesault et al. 2012; Juhas et al. 2018). The incorporation of macrophages into engineered muscle constructs was deemed a critical step following cardiotoxin injury in vitro, enabling extensive structural and functional tissue repair (Juhas et al. 2018).

Directed differentiation of iPSCs is an elegant approach to produce muscle cells or other cell types that comprise skeletal muscle tissue. Indeed, a few recent studies reported on new disease models for muscular dystrophies using iPSC-derived muscle cells (Long et al. 2018; Maffioletti et al. 2018). In one notable study, Maffioletti and colleagues cultured human iPSC-derived muscle progenitors together with endothelial cells and pericytes inside a fibrin hydrogel, demonstrating formation of vessel-like structures inside muscle bundles (Maffioletti et al. 2018). Furthermore, iPSC-derived neural precursors were incorporated into these engineered muscle bundles and gave rise to motor neurons (Maffioletti et al. 2018). This artificial skeletal muscle tissue-like construct consist of multiple human iPSC-derived cell types that conjunctionally mimic physiological muscle tissue, offering an elegant platform for disease modeling or a tissue source to treat VML lesions (Maffioletti et al. 2018).

A growing number of new studies have unearthed the roles of muscle resident cells (MRCs) in mediating skeletal muscle tissue regeneration and repair (Wosczyna and Rando 2018). In a recent elegant study, Quarta and colleagues assessed the MRCs capacity to assist engineered muscle constructs in repairing VML lesions in a mouse model(Quarta et al. 2017). As first step, freshly isolated satellite cells were suspended in collagen I or ECM hydrogel solutions and seeded onto decellularized muscle scaffolds (Quarta et al. 2017). To test the effects of MRCs on muscle regeneration, FACS-purified MRCs including hematopoietic, endothelial, fibro-adipogenic, and fibroblast-like cells were coalesced with muscle stem cells and engineered muscle constructs and further delivered into VML lesions (Quarta et al. 2017). Remarkably, combination of muscle stem cells and MRCs dramatically increased the regeneration potential of the engrafted constructs, culminating in increased muscle mass and force production of treated lesions compared to control mice treated with constructs consisting of muscle stem cells alone (Quarta et al. 2017). Moreover, this bioconstructs restored biomechanical properties in a murine model of VML and reduced fibrosis (Quarta et al. 2018). Lastly the potential of running exercise to assist in the regeneration process was further assessed, demonstrating improved innervation of the muscle constructs in lesions, which facilitated functional recovery of treated mice (Quarta et al. 2017). It will be of interest to

further delineate the molecular mechanisms that enable exercise to potentiate muscle regeneration in this model and whether it can be harnessed to assist other engraftment paradigms such as stem cell delivery into dystrophic muscles.

Reconstructing skeletal muscle tissue in vitro is a formidable feat that involves a plethora of cellular and acellular components as well as engineering techniques. The breadth of recent research in the tissue engineering field is spearheading efforts to achieve this goal. Novel approaches to grow cells on scaffolds or hydrogels, improved methods to vascularize or innervate engineered tissues as well as harnessing muscle resident cells for repair streamline novel assistive means to engineer muscle tissue. This melting pot of different techniques and approaches is expected to yield new therapeutic applications to treat VML and other muscle-associated diseases.

9   Conclusions

Healthy skeletal muscle tissue harbors a prodigious regenerative capacity to restore muscle loss during injury or disease states. However, this capability is often derailed in patients with severe pathological conditions such as muscular dystrophies, sarcopenia, cachexia, and VML. Intramuscular transplantation of muscle stem or progenitor cells provides an attractive approach to treat some of the aforementioned conditions, albeit significant challenges still inhibit use of this approach in clinical settings. Notably, for therapeutic interventions to succeed, it will be imperative to formulate methods to match a treatment to a specific disease condition, while taking into consideration the severity grade of the affliction. For example, muscle stem cells are expected to engraft better when delivered into early-stage dystrophic muscles which contain sufficient amount of myofibers that could enable donor-derived cells to engraft. Contrastingly, late-stage DMD and VML is characterized by extensive muscle lesions and replacement with fibrotic or adipogenic tissues, rendering muscle stem cell transplantation futile in the absence of sufficient muscle volume. In such occurrences, incorporation of 3D tissue-engineered skeletal muscle constructs could provide a more valuable therapeutic method to restore muscle mass.

An additional important criterion to consider for cell replacement therapy is the choice of engrafted cells. To date, a majority of research studies have focused primarily on relatively undefined myoblast cultures for human transplantation. Rapid advances in isolation and ex vivo culture of human satellite cells could provide a superior cell source for engraftment, thus allowing a long-term therapeutic effect. It is therefore of interest to assess whether direct injection of freshly isolated satellite cells, or in vitro expanded satellite-like cells, could promote dystrophin restoration and potential recovery in DMD patient's muscles. Building upon decades of myoblast transplantation trials in humans can lend useful insights when embarking on such new translational endeavors and assist in overcoming current translational roadblocks. Moreover, novel studies have also recently illustrated ways to generate unlimited number of therapeutically applicable myogenic precursors, either from PSCs or by direct reprogramming of somatic cells. It is of interest to

further investigate these new conversion paradigms and compare the generated myogenic precursors molecularly and functionally to satellite cells and myoblasts. Such comparison could assist in finding the most suitable cell type for therapeutic applications.

Lastly, the role of muscle resident cells in mediating muscle tissue repair has been increasingly elucidated in recent years. Single cell sequencing technologies have helped map the various cell types that comprise muscle tissue, shedding new light on the cellular and molecular pathways involved in muscle regeneration. From a translational perspective, it will be of interest to investigate in detail whether injections of MRCs with muscle stem cells could better alleviate dystrophic symptoms and increase therapeutic outcomes in animal models. It is foreseeable that regenerating a patient's dystrophic muscles may require injections of three to five different cell types, each carrying a unique role in mediating tissue repair. Further research is also warranted in respect to tissue engineering of bioconstructs by incorporating MRCs and muscle stem cells. The majority of research to date has incorporated myoblasts into muscle constructs, whereas recent work nicely implemented muscles stem cells and MRCs to achieve muscle regeneration utilizing tissue-like constructs. Transplantation of an in vitro engineered muscle-like tissue that harbors satellite cell niches and consists of multiple cell types could provide a promising treatment strategy for patients suffering from VML or late-stage muscular dystrophies.

In conclusion, muscle-associated diseases inflict tremendous burden and pain on patients, their families, and society. New research in stem cell biology, biomaterials and tissue engineering immensely elevates our ability to remedy degenerative muscle tissue, bringing new hope for novel therapeutic treatments. It is anticipated that a synergistic approach combining different disciplines and assimilating various techniques will provide the most suitable way for achieving this goal.

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