The Prospects of RNAs and Common Significant Pathways in Cancer Therapy and Regenerative Medicine

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16.1 Introduction

Human cells normally expand and multiply via cell division to generate new cells as needed and in cancer, some cells in the body grow out of control and spread to other parts of the body. Cells die as they become old or injured, and new cells replace them. Cancerous tumours can affect adjacent tissues and spread to other parts of the body, resulting in the formation of new tumours by a process called metastasis. Regeneration is a natural mechanism by which injured or damaged tissues and organs are replaced through cell proliferation into a normal tissue. Tissue regeneration, similar to cancer, has certain hallmarks, which are restricted to lineages and are activated only during damage (Goldman and Poss 2020). Repair of an organ is the restoration of interrupted continuity of injured tissue mass and formation of scar tissue, while regeneration refers to the restoration of interrupted continuity of the damaged tissue mass with original anatomical characters and original tissue function, yet no scar formation (Mason and Dunnill 2008). Many signalling pathways play a major role in the process as well. In this chapter, the role of different signalling pathways has been discussed, which modulate both the process of carcinogenesis and regeneration. Role of different signalling pathways in cancer has been depicted in Fig. 16.1.

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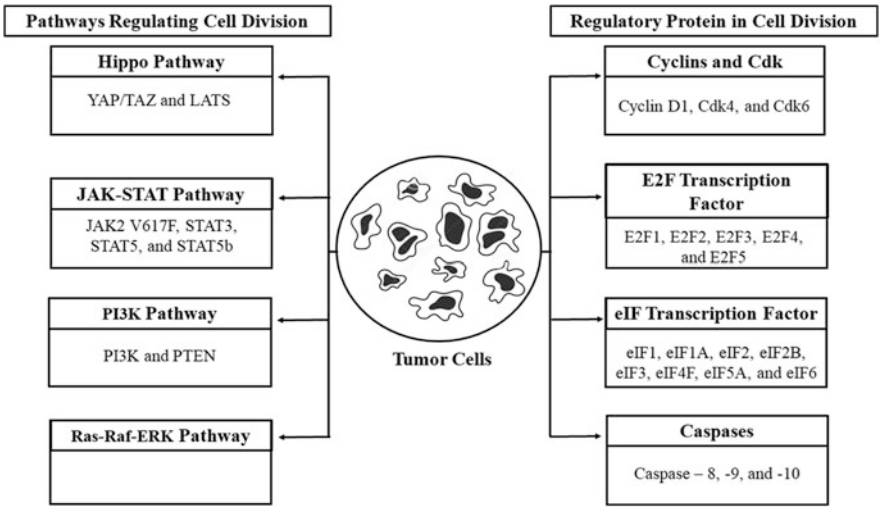

Fig. 16.1 Regulation of cancer by various signalling pathways

16.1.1 Similarities and Differences Between Cancer and Regeneration

The similarities and differences between cancer and regeneration have been shown in Table 16.1 (Charni et al. 2017; Boilly et al. 2017; Oviedo and Beane 2009; Smetana et al. 2013).

16.1.2 Significant Pathways of Regeneration and Cancer

Early signs of regeneration include:

1. A layer of epithelium covers the injured region, as one of the initial responses.
2. There is an immediate triggering of reactive oxygen species (ROS) in the injured area for wound detection.
3. The site of injury shows inflammation because of macrophages and T cells, which further direct the site of injury into a site for regeneration.
4. There is production of hydrogen peroxide.
5. Targets of ROS include vital signalling pathways like JNK, WNT and FGF. These pathways are essential for cell regeneration.
6. Mitogens are released by dying cells, by MAPK/CREB pathway, to cause the activation of tissue regeneration in the healthy cells of the injured site (Chen and Poss 2017).

There are a few hallmarks of regeneration of heart revascularization

Table 16.1 Similarities and differences between cancer and regeneration

Similarities—cancer and regeneration	Differences—cancer and regeneration
Inflammation, construction and remodelling of tissues are common in both cancer and regeneration	Tumorigenesis has surpassed one/many of the regulations and is unrestrained, while regeneration is a strictly controlled process
Various cell signalling pathways like WNT, PI3K and MEK, are commonly seen in both cancer and regeneration	Dysregulation in any one of the factors like genes/regulatory proteins/pathways can lead to cancer
Cell proliferation, cell differentiation, cell migration are commonly triggered by the same regulatory processes	Cell proliferation and cell migration, when uncontrolled, lead to cancer. Inflammation can become a pre-condition
Triggering cancer and the rate of regeneration are influenced by telomeres length and the extent of the activity of telomerase	Regeneration of organs in humans is limited and is commonly incomplete because of the formation of scar tissue, while any tissue can turn cancerous due to impairment
Blastema provides stem cells, which contributes to the regeneration of damaged tissue and also contributes to the growth of cancer cells	Cancers can be formed from improper regeneration or loss of regeneration or loss of a tissue morphogenesis
Regulation of microenvironment, such as extra-cellular matrix or cytokines, contributes to regeneration and as well as metastasis	Common pathways are strictly controlled in regeneration, while common pathways are usually unrestrained in cancer
Suppression of tumours can also lead to suppression of regeneration	End result of cancer is death, but end result of regeneration is life

1. Modulating the developmental signalling pathways
2. Directing the cell cycle regulators
3. Reprogramming resident stromal cells into required specific tissue
4. Stem cell or progenitor cell leads to paracrine effect, but this is an indirect central hallmark (Bertero and Murry 2018).

In cancer, a few pathways associated with cell cycle regulation, JNK, WNT, FGF signalling, the mTOR pathway, PI3K, JAK-STAT, Hippo signalling, modulation by miRNAs also have significant contribution and have been detailed accordingly in this study.

16.2 Cell Cycle and Checkpoints

'Antipathic pleiotropy' is a key idea in evolutionary theories of aging, which states that aging itself is not an evolutionary selected programme, but rather the result of selection for organismal fitness during development and reproductive phases (Kirkwood and Melov 2011). The aging of stem cells and progenitor cells is also influenced by checkpoint genes. Under genotoxic stress, checkpoint genes play a major role in suppressing cancer, but they also limit the ability of stem cells and progenitor cells to maintain and repair tissues under accumulated DNA damage and during physiological aging (Chambers et al. 2007; Krishnamurthy et al. 2006; Siegl-

Cachedenier et al. 2007). According to the results of checkpoint enhancement, the maintenance of physiologic control of checkpoint genes has a bearing on lifespan and cancer effects. Checkpoint activation cannot delay aging nor protect against cancer in conditions of high DNA damage accumulation, such as those found in telomere-dysfunctional mice. Enhanced expression of physiologically regulated checkpoint genes has been shown to reduce cancer formation and extend lifespan in mice with low levels of DNA damage. There may be a way to prevent the clonal expansion of mutated or transformed stem cells through increased expression of physiologically regulated checkpoints. Depletion of damaged stem cells during mouse models of low DNA damage inhibits cancer development and delays aging since abnormal stem cells are removed, and the remaining undamaged stem cells compensate for this depletion. Despite the enhanced clearance of damaged stem cells in mouse models of severe telomere dysfunction, tissue maintenance is unaffected since the functioning of undamaged stem cells diminishes and cannot compensate for the loss of damaged stem cells.

Cell cycle in eukaryotes includes the G0, G1, S, G2 and M phases. They are necessary for the division of the cell and are regulated by three checkpoints called G1/S checkpoint or start checkpoint, G2/M checkpoint and SAC (spindle assembly checkpoint). These checkpoints are critical for the completion of the cell cycle. Along with checkpoints, there are a few proteins like cyclins- and cyclin-dependent kinases (CDKs) that are also a part of the cell cycle regulation. During an injury or damage to the organ or tissue, cell division is triggered and the site of damage is repaired or regenerated. Regeneration of an organ or tissue involves cell differentiation along with cell proliferation. Some cells also might need reprogramming, meaning differentiated cells revert to pluripotent cells and then they divide it into any type of cell. Any aberration in cell cycle or checkpoints could lead to cancer.

16.3 Regulatory Proteins in Cell Division

16.3.1 Cyclins and CDK

The cyclin-dependent kinases (CDKs) are a large group of enzymes with a serine/threonine-specific catalytic core that becomes active on interaction with a cyclin regulatory protein, which modulates substrate specificity and kinase activity (Lim and Kaldis 2013; Loyer and Trembley 2020). In mammals, 30 cyclins and 20 CDKs have been identified so far (Loyer and Trembley 2020; Chotiner et al. 2019). These CDKs have been given a name from CDK1 to CDK20, and CLKs have been named from CDKL1 to CDKL5. Furthermore, cyclins are divided into three groups which include canonical, non-canonical and atypical cyclins. The canonical group contains A, B, D and E sub-families which play a significant part in cell cycle regulation, whereas the non-canonical group includes C, H, K, L, Q and T sub-families which are required in controlling transcription and pre-RNA processing. The third group consists of recently identified cyclins which include G, I, J, O, P and Y (Loyer and Trembley 2020). Studies have shown that

cyclin and CDKs (cyclin-dependent kinase) complexes are critical cell cycle regulators (Chotiner et al. 2019; Deshpande et al. 2005). In general, CDKs act as a promoter for the progression of the cell cycle, while cyclins regulate the transition between cell cycle stages. Therefore, CDK inhibitors (CKIs) serve as a barrier to cell cycle progression in adverse situations and hence regulate CDK–cyclin complex activity (Lim and Kaldis 2013).

16.3.1.1 Cyclins and CDK in Cancer

Deregulated cell cycle control is one of the hallmarks of cancer. Generally, non-cancer cells proliferate according to tissue growth requirements, while the proliferation of cancerous cells occurs uncontrollably which in turn contribute to tumour formation (Deshpande et al. 2005). The deregulation of the CDK–cyclin complex is among the leading causes of uncontrolled cell growth. Cyclins have been reported to have pivotal function in the pathogenesis of cancer (Stamatakos et al. 2010). The formation of tumour is usually linked with genetic or epigenetic alterations in key cell cycle molecules such as cyclins which regulate the activity of CDKs (Malumbres 2007).

Furthermore, cyclin D has been found to act as a carcinogen with a pathogenetic involvement in a variety of malignancies (Stamatakos et al. 2010). Among three types of cyclin D, cyclin D1 reported to be overexpressed in various types of malignancies (Fu et al. 2004). This cyclin D1 binds to *cdk4* or *cdk6* and using different mechanisms such as translocation of a chromosome, amplification of the gene, normal intercellular trafficking disruption, and proteolysis leads to an increase in tumour formation (Stamatakos et al. 2010). In addition to this, dysregulation of cyclin E has shown to be linked with various cancers such as breast, ovarian, colorectal and bladder (Geisen and Möröy 2002; Stamatakos et al. 2010). The exact method by which cyclin E is dysregulated is unknown; however, a few studies have indicated that gene amplification is involved, which results in G1 shortening, decreased cell size and the elimination of serum need for proliferation (Stamatakos et al. 2010).

CDKs are a well-validated target for cancer therapies because of their function in regulating important checkpoints of the cell cycle and transcription. In recent years, continuous attempts have been made to the development of CDK inhibitors (Whittaker et al. 2017). Due to the absence of an exact mechanism of action and relevant biomarkers, poor CDK isoform leads to failed attempts to target CDKs (Whittaker et al. 2017; Canavese et al. 2012). Furthermore, most of the CDKs inhibitors (non-selective CDKs inhibitors) have been found to lack selectivity for cancerous cells and found to be ineffective in most cancers (Whittaker et al. 2017). Despite these, researchers are trying to target CDKs to regenerate the controlled cell division potential via finding a novel molecule with more favourable pharmacokinetics, developing selective CDKs inhibitors, and using CDKIs in combination with conventional cytotoxic (Canavese et al. 2012; Whittaker et al. 2017). For instance, palbociclib is a selective inhibitor of CDK4/6 that has been certified as a therapeutics, and a combination of CDK4/6 inhibitors and hormone therapy is currently being tested for breast cancer (Lin et al. 2018; Whittaker et al. 2017). Moreover, certain

medications with the perfect balance of CDK selectivity, such as the second-generation, orally accessible inhibitor of CDK 2, 5 and 9 CYC065 developed from seliciclib, have been proven to be beneficial against cancer (Whittaker et al. 2017). Additionally, even though the significance of CDK2 in carcinogenesis is questionable, targeted *cdk2* inhibition may provide therapeutic advantage against some malignancies (Tadesse et al. 2018). Therefore, selective inhibitors alone and/or in combination can be used to target CDKs, but yet more research studies are required in this area as there are emerging hurdles such as drug resistance (Whittaker et al. 2017).

16.3.1.2 Cyclins and CDKs in Regeneration

In humans many (types of) cells remain quiescent in the gap phase between cell cycles, until they receive cell proliferation signals. The cells enter the G1 phase. This phase is linked with various cell controlling pathways such as quiescence, senescence, responses to stress and differentiation. During the S phase, a number of signals are received and DNA is replicated. The entry of a cell into the S phase is also termed as a restriction point since cells cannot decide to return to the original stage after this phase. Usually, differentiated cells enter the G0 phase after the G1 phase and perform their specialized functions. These cells must receive signals for their re-entry into the cell cycle and to undergo cell proliferation.

In mammals, such as humans, entry of cells into the restriction point is highly controlled by the retinoblastoma suppressor (RB) pathway.

Cell cycle is strictly controlled by cyclins and CDKs. Various cyclins and CDKs are expressed to regulate each phase of the cell cycle. During the G1 phase, cyclin D-*cdk4/6* is expressed, during the G1-S phase cyclin E-*cdk 2* is expressed, while in the S-G2 phase, cyclin A-*cdk2/1* is expressed, and during the mitotic phase, cyclin B-*cdk 1* is expressed.

The three cyclin-dependent kinases, *cdk4, cdk6 and cdk2*, phosphorylate pRB proteins at various sites. These CDKs signal the RB pathway and control G1 mechanism. In a normal cell, *CDK2*, *CDK4* and *CDK6* are relatively constant on their expression which allows the cell to perform various functions like quiescent, aging, terminal differentiation. Thus, cell proliferation is triggered, and cell cycle is regulated. Aberration in this signalling leads to development of most cancers. These CDKs can be regulated via balancing mRNA stability or translational control.

The most common pathway, mitogen activated protein kinase (MAPK) pathway, activates cyclin D transcription. When optimal expression of cyclins and CDKs is present, it leads to cell proliferation however, when there is overexpression of cyclin D with mitogenic growth factors in the G1 phase, it leads to tumorigenesis. This is because cyclin D triggers proto-oncogene transcription factors. Repression of cyclin D is essential for cell cycle exit, and any dysregulation in this terminal differentiation could lead to reactivation into the S phase of cell cycle (Duronio and Xiong 2013).

16.3.2 E2F

E2F is a class of transcription factors in mammals consisting of eight genes. Based on in vitro research, these genes encode ten proteins that are split into an activator of transcription (E2F1 to E2F3A) and repressor of transcription (E2F3B to E2F8) (Xie et al. 2021; Hollern et al. 2014; Xanthoulis and Tiniakos 2013). E2Fs are essential for various cellular functions such as controlling cell cycle, DNA damage response and apoptosis (Xie et al. 2021; Xanthoulis and Tiniakos 2013). Furthermore, the level of E2F1, E2F2 and E2F3A (activator protein) is found to be increased in the G1-S phase, whereas the high level of E2F7 and E2F8 (atypical repressor) is found in the late S phase and the level of E2F3B, E2F4, E2F5 and E2F6 (canonical repressor) is found to remain same throughout the cell cycle. Moreover, the expression and activity of E2Fs are firmly regulated at multiple levels, including regulation via post-transcriptional, pocket protein, subcellular localization and post-translational mechanisms (Kent and Leone 2019).

16.3.2.1 E2F Transcription Factor in Cancer

E2F transcription factors have been found to make a significant contribution to metastasis regulation (Hollern et al. 2014). High levels of E2F have been linked to a poor prognosis in malignancies of several types, including liver and pancreatic tumours (Kent and Leone 2019). Studies have shown that E2Fs have a dual function; based on the tissue, it may either promote or repress cancer (Xanthoulis and Tiniakos 2013). For instance, a study has shown that knockdown of E2F8 in transformed cells affects the target gene expression, cell survival and the tumour growth in xenograft models. In contrast to this, another study reported the tumour suppressor role of E2F8 using knockout mice, but further analysis is needed to confirm this controversy (Kent and Leone 2019). Furthermore, E2F1 is by far the most researched component of the E2F family in terms of cancers, along with the investigation of a few other genes. Elevated levels of E2F1 and E2F3 expression have been found to be linked with a worse prognosis in non-small cell lung cancer patients. In breast tumours, enhanced level of E2F1 or E2F4 is related to a worse prognosis, but increased E2F5 expression is linked to certain histological subtypes. The level of E2F1-5, E2F7 and E2F8 expression has been found to increase in cases of ovarian cancer. Additionally, higher levels of E2F4 and E2F7 have been connected to improved overall and disease-free survival, respectively, whereas E2F8 expression has been linked to worse overall survival. In prostate tumours, the expression of E2F2 and E2F3 increases whereas that of E2F1 is absent. The expression of E2F3 has been enhanced in bladder urothelial carcinomas, whereas E2F1 is dependent on invasion. Glioblastoma, thyroid cancer, lymph nodes, as well as small cell lung carcinoma metastases from malignant melanoma, have been shown to harbour higher E2F1 expression (Xanthoulis and Tiniakos 2013).

16.3.2.2 E2F Transcription Factor in Regeneration

It is one of the key regulators of cell proliferation. This is in turn controlled by intracellular and extracellular signals. It plays a very important role in maintaining

the inhibition of the cell cycle at the G0/G1 phase in embryonic as well as adult stem cells, during regeneration and cancer. As G1 cells are directed to enter the S phase or return to the G0 phase, the regulation of E2F is essential for the cells to enter into the S phase. E2F members bind to promoters of genes that regulate transcription of the G0/G1 phase. Cyclin-CDK activity is upregulated with the increase in the dissociation of repressive E2F complexes and releasing activator E2F complexes which leads to upregulation of genes with HATs. This family of transcription factors lacks nuclear localization signals, and, therefore, they depend on the RB family of proteins to arrest the cell cycle. On the whole, E2F behaves as a cell activator, while E2F4-5 are those repressors which prevent cell proliferation. During regeneration, expression of E2F4 is optimal and normal; thus, it prevents cell proliferation, while the aberration of E2F4 leads to cancer, pointing E2F4 as an onco-gene. Also, because of aberration in E2F4, cells also escape apoptosis (Hsu and Sage 2016).

16.3.3 eIF

The translation route in eukaryotes is facilitated by a group of enzymes known as eIF (eukaryotic translation initiation) factors (Efiok and Safer 2000). In eukaryotic cells, messenger RNA (mRNA) translation is essential for gene expression and occurs at the initiation stage, which is mostly controlled by eukaryotic initiation factors (eIFs). eIFs are required for mRNA translation and so serve as major targets for various signalling pathways that control gene expression (Hao et al. 2020). eIF-2 is a prominent initiation factor among eIF-1, 1A, 2, 3 and 5 because it triggers a rate-limiting initiation step of translation, that is, it stimulates the interaction of initiator met-tRNA to the 40S ribosomal subunit (Watanabe et al. 2010; Efiok and Safer 2000). As a result, most cells' overall translation rate is determined by eIF-2. Furthermore, the α subunit of eIF-2 is considered as a target for post-translational alterations which in turn contributes to protein synthesis regulation in accordance to cell cycle arrest, division, viral infection and metabolic abnormalities (Efiok and Safer 2000). Moreover, other eIFs are also involved in the initiation process of eukaryotic translation but do not have a prominent role. For instance, eIF4F is responsible for recruiting m7G-capped mRNA to the PIC (43 S pre-IC) (Watanabe et al. 2010).

16.3.3.1 eIF in Cancer

The typical characteristic of carcinogenesis is deregulated mRNA expression (Hao et al. 2020). The abnormal translational pathway promotes tumour development and cellular changes. This pathway is sensitive to cellular conditions such as nutrition availability, energy or stress, production of the ribosome and gene expressions in non-cancerous cells, but it is hyper-activated and pro-oncogenic in malignant cells (Ali et al. 2017). Furthermore, investigations conducted over the last two decades have revealed that a number of eukaryotic initiation factors (increased expression levels of eIF4A, eIF4E and eIF4G, alone with low expression of 4E-BPs or phosphorylation of eIF2) have been reported in various types of malignancies (Ali et al.

2017; Hao et al. 2020). These in turn result in the selective translation of mRNA encoding proteins involved in carcinogenesis, metastasis, or drug resistance, making eIFs a prospective therapeutic target for a variety of malignancies (Hao et al. 2020). There are a number of eIFs which are misregulated in human cancer. For instance, elF1, eIF1A, eIF2, eIF5A, eIF6, eIF2B, eIF3 and eIF4F are found to be dysregulated in most of the malignancies (Hao et al. 2020; Ali et al. 2017).

16.3.3.2 eIF Transcription Factor in Regeneration

Eukaryotic initiation factor is another important regulator during the cell cycle, cell proliferation and apoptosis. It binds to the 5′ terminal 7-methyl GTP cap of DNA transcript and affects the rate of translation. This factor is crucial for the cell cycle to progress and when overexpressed, it becomes oncogenic. In quiescent cells, eIF-4E binds to eIF-4F to act as translational suppressor (Wilkinson and Millar 2000). Under normal conditions, eIF-4E binds to eIF-4G, a translation initiation complex. When it is activated by mitogenic stimulators, it becomes phosphorylated, and it interferes with many pathways such as Ras, PI3K-AKT. In optimal conditions eIF-4E is responsible for angiogenesis, an important factor for cell proliferation (De Benedetti and Graff 2004).

16.3.4 Caspases

Caspases are cysteine-aspartic proteases which are present in an inactive form in the cells and are majorly involved in controlling apoptosis and inflammation (Shalini et al. 2015; Yadav et al. 2021). It is split into two groups—group I are inflammatory caspases which consist of caspase-1, -4, -5, -11 and -12, and group II are apoptotic caspases (Olsson and Zhivotovsky 2011; Yadav et al. 2021). Based on various structures and functions, apoptotic caspases are further separated into: (1) caspase initiators (caspase-2, -8, -9 and -10) and (2) caspase effectors (caspase-3, -6 and -7) (Yadav et al. 2021; Hounsell and Fan 2021). These enzymes are synthesized as inactive zymogens that gain catalytic activity after signalling events that encourage their aggregation into dimers or macromolecular complexes (McIlwain et al. 2013).

16.3.4.1 Caspases in Cancer

Apoptosis evasion is thought to be one of the characteristics of human malignancies. Caspases are responsible for cell death, and various upstream regulatory factors that control their proteolytic activity have been categorized as suppressor of tumour or oncogenic (Olsson and Zhivotovsky 2011). Caspases are implicated in a variety of human diseases, including cancer and inflammatory disorders, and considerable attempts to better understand how these enzymes work and might be managed are underway (McIlwain et al. 2013). Deregulation of caspase results in abnormal apoptosis which eventually leads to decreased apoptosis, irregular growth of cancer cells, and carcinogenesis (Farghadani and Naidu 2021). The dysregulation of caspase can occur via different mechanisms which include inhibition by apoptotic protein, dimerization blockage of initiator caspases etc. (Boice and Bouchier-Hayes

2020). The deficiency of initiator apoptosis has been linked to the formation and progression of cancer. Majorly, altered expression of caspase-8, -9 and -10 is known to be involved in the progress of carcinogenesis (Farghadani and Naidu 2021). In addition to this, studies have reported the dysregulation of single or multiple caspases which contributes to tumour cell growth and development. For instance, in stage II colorectal cancer, caspase-9 is found to be downregulated, whereas, in choriocarcinoma, caspase-8 and -10 are found to be downregulated (Wong 2011).

16.3.4.2 Caspases in Regeneration

Apoptosis is one of the most crucial steps for cell cycle regulation, executed by caspases. Caspases are triggered when they receive signals such as DNA damage, viral infection, loss of cell adhesion and other cellular insults (Bergmann and Steller 2010). Although their major role lies in regulating apoptosis, a few members of caspases family, like caspases-3, play an important role in cell differentiation. The caspase-3 has no role in cell death. Caspase-2 and -8 play roles in cell proliferation (tumorigenesis also). The differentiation of muscle progenitors into myotubes occurs in the presence of caspase-3 and caspase-9. But it is limited and regulated by Bcl-xL, an apoptosis inhibiting protein. The osteogenic differentiation of MSCs also happens in the presence of caspase-3, absence of which leads to decreased bone density. Caspase-3 also plays a major role in differentiating embryonic and haematopoietic stem cells; macrophage differentiation and absence of the same lead to improper differentiation. Caspase-3 and -7 are involved in liver regeneration and wound healing. They target iPLA2 (phospholipid) activity and cleave it, for the secretion of prostaglandins. These prostaglandins in turn trigger stem cell proliferation, tissue regeneration and repair. They also target the WNT (Wingless-related integration site) pathway and regulate, usually by paracrine functioning. Caspase-8 is also involved in liver regeneration, but it interferes with the NFkB (nuclear factor kappa B) pathway (Shalini et al. 2015).

16.3.5 mTOR

16.3.5.1 mTOR in Cancer

The mammalian target of the rapamycin (mTOR) pathway is composed of two complexes—(1) mammalian target of rapamycin complex 1 (mTORC1), and (2) mammalian target of rapamycin complex 2 (mTORC2). Furthermore, the function of mTORC1 is to promote cell metabolism and growth, while the role of mTORC2 is to control cell division and survival (Zou et al. 2020). The mTOR pathway has been found to have a close link with cancer as it is known to involve in cell proliferation, survival, growth, glucose metabolism, protein synthesis, autophagy and apoptosis (Tian et al. 2019). Moreover, mTOR, in healthy conditions, is a principal controller for the division of cells, whereas under cancer conditions, activated mTOR signals encourage cancer cells to expand, spread and infiltrate healthy tissues (Zou et al. 2020). Also, mTOR is a commonly affected pathway in the case of human cancer and is recognized to have a fundamental part in cancer

development and progression (Tian et al. 2019). The altered level of mTOR is seen to be related to a higher development of tumour and metastasis and generally occurs due to the following mechanism—(1) mTOR gene mutation that leads to a hyperactive mTOR signalling cascade, (2) mTORC1 and mTORC2 mutation leads to dysregulated mTOR signalling and (3) upstream gene mutation can also lead to deregulated mTOR pathway (Tian et al. 2019; Hua et al. 2019). Meanwhile, various mTOR antagonists have been discovered for cancer treatment, and a range of medicines have been demonstrated to have high activity when paired with mTOR antagonists (Zou et al. 2020; Hua et al. 2019). Hence, certain mTOR antagonists have already been certified for the treatment of cancer, whereas others are still being studied in clinical studies (Hua et al. 2019).

16.3.5.2 mTOR in Regeneration

Mammalian target of rapamycin (mTOR) is a member kinase of PI3K-PKC family (phosphoinositide 3-kinase/protein kinase C associated kinase). mTOR has two units—mTORC1 and mTORC2 where the former mTORC1sub-unit is one of the essential components for helping cells to recoup tissue damage by reviving homeostasis. Dysregulations and disruptions in mTOR can cause diseases like cancer, organ dysfunction and degenerative disorders. WNT signalling and TNFα trigger the activation of mTORC1 which then suppresses autophagy and lysosome biogenesis and promotes cell growth, metabolism in regulation with environmental factors and growth factors. mTORC2 regulates cell migration and cytoskeleton remodelling to enhance cell survival and proliferation.

mTOR promotes axial regeneration by inactivation of pTEN and suppressing cytokine signalling 3, which are negative regulators of mTOR. Pathways like JAK-STAT and JNK-MAPK also promote axial regrowth during neuroregeneration. By activating mTOR, astrocytes are inhibited, which in turn leads to promotion of retinal ganglion cells (Wei et al. 2019). Mutations in TSC genes usually cause pathway disruption for mTOR and further lead to cancer. Pathway disruption from RAS-MAPK to inhibit TCS is also shown as an obvious reason for cancer (Guertin and Sabatini 2007).

16.4 Genes Regulating Cell Division

16.4.1 p53

16.4.1.1 p53 in Cancer

Cells respond to various stress signals, such as oncogene activation, DNA damage, hypoxia and reactive oxygen species (ROS), by expressing the tumour suppressor *p53*. *p53* activates a wide range of responses within the cell, from cell cycle arrest, senescence, or ferroptosis to eliminate unrecoverable cells. Therefore, *p53* is supposed to act as the 'Guardian of the genome' by preventing the accumulation of mutations that cause cancer (Lane 1992; Levine 2020). Cancers with *p53* mutations develop in an initial stage or a late stage depending on the type of cancer and strongly

facilitate onset or progression (Levine et al. 2019). As a consequence of *p53* mutations, the remaining wild-type allele of TP53 is usually lost. This results in the loss of wild-type *p53* in late-stage cancers, which further confers a selective advantage to these cancer cells (Song et al. 2007; Amelio and Melino 2020). Many *p53* mutations alter the central DNA-binding domain, and a few points of particular interest have thus far been identified: R175, G245, R248, R249, R273 and R282 (Duffy et al. 2020). Studies have revealed an association between immune checkpoints and *p53*. The program-death receptor PD-1 (PD-1) and programmed death-ligand 1 (PD-L1) are activated by *p53* when cancerous cells and normal T cells are stressed (Thiem et al. 2019). Immune checkpoints such as PD-L1 on tissue and PD-1 on T cells act together to reduce inflammation by reducing the activation signals from T cells after antigen recognition. Utilizing this immune checkpoint mechanism, tumour PD-L1 amplification fosters tumour surveillance and immune tolerance (Alsaab et al. 2017). Thus, mutant *p53* may be useful as a biomarker for the response to immunotherapy in certain contexts and may correlate with better prognosis due to distinct immunogenic signals (Liu et al. 2019). p53-TLR regulatory axis is unique to humans and apes. In consideration of TLR-mediated cancer treatment, this evolutionary gap is significant since mouse models do not mimic the regulatory axis present in humans. Mutations of the *p53* gene not only alter TLR gene expression, but also have other consequences. These alterations modulate TLR3 sensitivity and reactivity to known ligands, resulting in downstream apoptosis (genotoxic stress) (Pradere et al. 2014). P151H and R337H, two transcriptionally active or TLR3-enhancing *p53* mutants that control TLR3 responsiveness, might inhibit TLR3-mediated immune responses, while other *p53* mutations may increase their expression (Taura et al. 2010). Several cancers can be affected by overexpression of microRNA, and another mutant-specific GOF of *p53* may be relevant. Because exosomal-mediated transfer of microRNA is crucial to many kinds of cancer, a second mutant-specific GOF of *p53* can also be important (Mantovani et al. 2019). MicroRNA transfer via exosomes can induce similarly phenotypic changes in macrophages in tumours expressing mutant *p53*. Furthermore, these reprogrammed macrophages increased degradation of the extracellular matrix and were more invasive in comparison to macrophages that were introduced to nonmutated tumour cells (Cooks et al. 2018).

16.4.1.2 p53 in Regeneration

p53 is one of the tumour suppressor genes; dysregulation of which is involved in many cancers (Duronio and Xiong 2013). *p53* acts as a coordinator to promote regeneration and inhibit tumour. It is therefore regarded as the guardian of the genome. During studies, *p53* was observed to contribute majorly in many cellular processes and also it was seen to decide the outcome of cascade of events, pointing towards its role in regeneration. In a normal cell, *p53* and its isoforms trigger regeneration after injury. Here, p53 triggers mitogenic growth factors, promoting cell division. It controls and allows the blastema of differentiated cells for their re-entry into the cell cycle. In progressive stages of wound healing, *p53* was found to suppress growth factors and downregulate cell division. It was concluded through

studies that *p53* regulates the pliability of differentiated cells and their fate during regeneration. *p53* controls cell apoptosis by transactivation of Noxa, an apoptotic protein, and regulates cell cycle arrest by interfering in MAPK and JNK signalling pathways. It can trigger regeneration only under homeostatic conditions especially in the nervous system. Mutations, cellular insults and telomeric shortening for this particular gene alone cause more than 50% of the cancers in humans (Charni et al. 2017). Recent observations have shown that p53 can also act as a cancer inhibitor. When the transcript of *p53* binds at a certain hydrophobic site of MDM2 protein, it results in protein–protein interactions that occur in the domain that inhibits cancer. As one of the strategies to prevent cancer because of *p53*, it can be inactivated by dysregulating the DNA-binding function through point mutations or other strategies. p53-DNA binding domain (DBD) is very flexible which can direct towards partial unfolding of p53 even at slightest changes of normal body temperature range, pointing towards mutation. Ligands which bind to BDB can remodel the protein folding into normalcy and stabilize it (Selivanova 2010).

16.4.2 p21

16.4.2.1 p21 in Cancer

Molecular studies of knockout mice and biochemical and functional analysis of cultured cells have been crucial to understanding the role of p21 in cancer. Initially, *p21* was found to be a potential mediator of p53's tumour suppressor activity, leading to ground-breaking research (El-Deiry et al. 1993). Further work showed that, despite eliminating DNA damage-induced and p53-dependent growth arrest, deletion of Cdkn1a did not affect p53-dependent apoptosis. Because of this, p21 can't explain the entire spectrum of p53's tumour suppressor activity (Efeyan et al. 2007). Despite that, p21 is a major determinant of tumour protection by p53, since cysteine methylation abolished the ability of p53 to induce apoptosis but preserved partial growth arrest in mice expressing a mutant form of *p53* (Trp53R172P+/+) (Barboza et al. 2006). An important insight into the role of p21 in tumour suppression was provided by a study by Shen et al. 154 that showed the existence of a prominent tumour suppressor role for this gene in genomically unstable tumours. Ataxia-telangiectasia mutated was induced by a Cdkn1a deficiency in conjunction with DNA damage checkpoint protein loss, resulting in aneuploidy prior to tumour development (Shen et al. 2005). There is an inverse correlation between *p21* downregulation in colorectal cancer and microsatellite instability regardless of *p53* status. This supports the notion that the loss of genomic stability protection by *p21* contributes to the development of human malignancies (Edmonston et al. 2000; Minucci et al. 2002). Several mouse genetic studies have also revealed that *p21* may act as an oncogene, as shown by a study that demonstrated deletion of Cdkn1a suppressed the development of spontaneous lymphomas in Trp53−/− and Atm−/− mice, as well as radiation-induced lymphomas in nuclear-type 138 and Trp53−/− mice (De la Cueva et al. 2006; Wang et al. 1997). Cdkn1a−/− mice develop lymphomas demonstrating a high level of apoptosis, suggesting that *p21*'s

anti-apoptotic activity promotes tumour growth. Apoptosis can be suppressed by *p21* in lymphocytes, but it is not clear why this activity can only be found in lymphomas. In the absence of *p21*, restricted tumour formation in the absence of cellular differentiation may result from blockage of proliferation at a phase when cells are not capable of proliferating. It has also been shown that *p21* can also promote oncogenesis without inhibiting its anti-apoptotic activity by promoting the assembly of complexes of cyclin D with CDK4 or CDK6, yet independent of its anti-apoptotic activity. p21 can also promote tumour growth independently of its antiapoptotic activity by promoting the assembly of complexes between cyclin D and CDK4 or CDK6 without negatively affecting their kinase activity (LaBaer et al. 1997).

16.4.2.2 p21 in Regeneration

p21 is involved majorly in cell cycle exit during development (Duronio and Xiong 2013). It is also observed to play a role in various cell responses for DNA damage, cytokine activities, cellular insults like oxidative stress. It is to be noted that *p21* is regulated by *p53* for tumour suppression activity and also inhibits progression of cell cycle. Another major role of *p21* is to inhibit the expression of Cdk, because of which, there is a block in the proliferation, by preventing phosphorylation, which in turns leave Rb not phosphorylated (Arthur and Heber-Katz 2011). With the understanding that p53 regulates p21, inhibitory molecules targeting sequence of *p21* were identified. A sequence of *Cdkn1a* gene was bound to p53 and was targeted to regulate 21. Though results proved to be positive, more work has to be done on this for better understanding (El-Deiry 2016).

16.4.3 Yamanaka Factors

The Yamanaka cocktail, Nobel prize–winning concept, was described by Kazutoshi Takahashi and Shinya Yamanaka. It states that adult fibroblast cells can be reprogrammed into embryonic-like states by triggering four factors—Oct-3/4, Sox2, c-Myc and Klf4. They express marker genes of embryonic stem cells as well (Takahashi and Yamanaka 2006).

The first wave is led by c-MYC/Kruppel-like factor, while the second is propelled by OCT4/SOX2/KLF4. OCT3/4, SOX2, KLF4 and c-MYC are the four transcriptional factors that make up OSKM. Overexpression of these four major transcriptional factors induces pluripotent qualities in somatic cells by modulating the signalling network required for pluripotent features in somatic cells (Takahashi and Yamanaka 2006; Huang et al. 2009; Holczbauer et al. 2013; Fiorenza and Rava 2019).

16.4.3.1 Yamanaka Factors in Cancer

Yamanaka factors reprogramme somatic cells into pluripotent cells in two phases. After the first discovery of Yamanaka factor reprogramming in mouse embryonic fibroblasts by retroviral transduction, a number of changes were made, and different

delivery techniques were tried to improve the process' sensitivity. OCT4 is a transcription factor that has been linked to CSC stemness and has been used as a biomarker in breast, colon, oral and lung cancer. Self-renewal potential, chemoresistance and a poor prognosis are also caused by it (Roy et al. 2019). Overexpression of *Sox2* has been linked to squamous cell cancer and has the ability to regulate self-renewal in embryonic stem cells (Islam et al. 2015). KLF4 is a CSC marker that is involved in a variety of tumour-related activities and has a controversial role in cancer aetiology. It is both a tumour suppressor and an oncogene, and it is required for the survival of CSCs (Roy et al. 2019). When a subset of Yamanaka factors, OCT4 and KLF4, as well as NANOG, are overexpressed in a subpopulation of radioactively challenged cancer cells, cancer stem-like cells are generated (Lagadec et al. 2012). KLF4 was discovered to be increased in cancer cells, and knocking it out inhibited tumour growth (Yu et al. 2011). According to Wolfer et al. (2010), c-MYC can aid in the preservation of cancer stemness, allowing cancer cells to survive for longer periods of time. Misregulation of c-MYC can lead to abnormal cell behaviour and accelerate the stemness process in cancer cells. CSCs are regressed, and tumour cells' apoptotic behaviour is increased when *c-Myc* expression is knocked down or silenced. If c-MYC is reactivated, the tumour may relapse. Even in the absence of c-MYC, further mutations can accumulate and aid in the self-renewal capacity of CSCs (Wang et al. 2008). Overexpression of *klf4* in the xenograft model results in higher levels of both KLF4 and EpCAM proteins, according to Firtina Karagonlar et al. (2020). Overexpression of KLF4 in the Huh 7 cell line results in considerable protein binding to the EpCAM promoter, upregulating EpCAM and E-Cadherin expression and increasing hepatic CSCs. Circular RNA was found to be important in the CSC-rich hepatoblastoma microenvironment in another investigation. Circular RNA suppresses miR-7-5p and decreases its sponge activity on KLF4, upregulating KLF4 expression and liver CSCs as a result (Chen et al. 2020).

16.4.3.2 Yamanaka Cocktail in Regeneration

Oct4, Sox2 and *NANOG* are the core components of the pluripotency circuitry. The octamer binding transcription factor 4, *Oct-4*, is one of the important genes that are present in the primordial germline cells. One of the unique properties of *Oct-4* is that it can trigger itself with the help of transcription factor Sox2. This transcription factor, *Oct-4*, has a POU domain which can interact at different sites to determine the pluripotency factor. Reduction on *Oct-4* and *Nanog* expressions leads to reduction in pluripotency and vice versa. The expression of *Nanog* is regulated by *Oct-4*, and the triggering of *Sox2* is sometimes required for *Oct-Sox* enhancers. The *Oct-4* is hence called the master switch for totipotency-pluripotency in the lifespan of humans. It is not only expressed in embryonic conditions but also expressed in adults. It is observed in the kidneys, the pancreas, the endometrium, the thyroid, the brain, the skin, and the peripheral blood. Here, *Oct-4* expression is mandatory for maintaining self-renewal property in somatic cells and maintaining homeostasis in the cells (Wu and Schöler 2014).

Sex determining region Y-box2, Sox2, is a prerequisite for the formation of various tissues and organs during the development of an embryo. Its major function is to maintain pluripotency and self-renewal of embryonic stem cells. It regulates master transcription factors, miRNA, signalling pathways without intricacy and dysregulations lead to cancer (Feng and Wen 2015, p. 2). It means that overexpression can affect cell proliferation, invasion, apoptosis and metastasis. It plays a role in pathways like WNT, PI3K, JAK-STAT3 and is shown to function in the stemness factor of adults as well as embryonic stem cells. This gene also contributes by playing an important role in deciding cell fate of pluripotent stem cells. It plays an important role in the final phase of reprogramming major fate decisions in induced pluripotent stem cells (Kretsovali 2017, p. 2).

c-Myc is a proto-oncogene which monitors and co-ordinates a variety of cellular processes like angiogenesis, apoptosis, cell growth and cell differentiation. *C-Myc*, in association with Max, forms dimers and regulates its target genes. One set of genes is triggered and activated by Myc/Max through promoters. *C-Myc* is very important for cell-lineage committed haematopoietic cell proliferation and can create equilibrium between self-renewal of cells and their differentiation (Wilson et al. 2004). By targeting G-quadruplexes in the promoter, Myc/max dimerization is prevented, leading to control of cell proliferation. This strategy is also being used and being studied further to inhibit cancer (Chen et al. 2014).

Krüppel-like factor 4, Klf4, controls cell proliferation and neural stem cell differentiation. This blocks the STAT3 pathway and contributes to regenerate the injured ganglion cells. It majorly phosphorylates STAT3 by cytokine signalling (Qin et al. 2013). Klf4 can also inhibit the proliferation in the cell cycle by inhibiting cyclins and upregulating p21 expression. This can result in loss of proliferation (Moore et al. 2011).

16.4.4 NANOG

16.4.4.1 NANOG in Cancer

NANOG is a diverse homeobox domain protein that plays a canonical role in transcriptional regulation of pluripotency and self-renewal in embryonic stem cells (ESCs). The expression of NANOG is highest in pluripotent cells, such as embryonic stem cells (ESCs), and embryonic germ cells (EGs) as well as embryonic carcinoma cells (ECs) (Chambers et al. 2003; Mitsui et al. 2003). Immunohistochemistry (IHC) in a variety of primary human tumour samples demonstrates that NANOG protein is expressed in both the nucleus and cytoplasm. There is evidence that NANOG is involved in tumour development or progression when present in neoplastic cells. Several studies suggest that NANOG influences CSC properties by imbuing subsets of cancer cells with self-renewal potential, which ensures the immortality of the entire tumour population. The NANOG mRNA and protein are found in many CSC subpopulations, including CD44+ breast cancer cell and prostate cancer cell, as well as CD133+ prostate, brain cancer and ovarian cancer cell, as well as CD24+ liver cancer cells. It is of clinical significance that higher

NANOG expression has often been linked to worse outcomes in tumours of the epithelium (Bourguignon et al. 2012; Zbinden et al. 2010). The second effect of forced *NANOG* expression is to promote the accumulation of breast cancer cells that are CD133+ and AldeFLUOR+ (Jeter et al. 2011). The RNAi-mediated NANOG knockdown, on the other hand, leads to reduced CSC properties such as sphere formation, which promotes cancer cell proliferation (Jeter et al. 2009). Immunity is another critical hurdle cancer cells must overcome. It is purported that cancer cells expressing *NANOG* can evade the immune system. NANOG generated by hypoxia protects against tumour cell killing by cytotoxic T lymphocytes, possibly by way of signal transducer and activator of transcription 3 (STAT3). A *NANOG* knockdown rendered xenograft tumours susceptible to immune surveillance when exposed to vaccine-induced evolution and immunity evasion of human papillomavirus cervical cancer cells, as the knockdown of *NANOG* reduced the growth of TC-1 cells (Hasmim et al. 2011). Proliferation of cancer cells appears to be positively correlated with NANOG levels. Increased proliferation is a hallmark of neoplastic disease despite not yet knowing whether this phenomenon is linked directly to a cell's fate (as in ESCs). Knockdown of NANOG reduced the proliferation, invasion, migration and apoptosis of human gastric cancer cells in conjunction with cell cycle arrest in the S phase during cell cycle progression (Ji and Jiang 2013).

16.4.4.2 Nanog in Regeneration

Although, in cancer, there are many downstream pathways which *NANOG* regulates, the role of *NANOG* in regeneration is majorly concerned with post-translational modification of proteins and interferes with transcriptional activity. It regulates DNA binding and sub-cellular localization as well as protein stability. *NANOG* re-activates transcription along with Oct4. Although *Oct4* and *Sox2* are stable, *NANOG* fluctuates extensively in stem cells during embryonic conditions. Also, *NANOG* requires OCT4 and SOX2 for its upregulation. *NANOG*, along with its 11 pseudo genes, participates in regulating the modifications of pluripotency and stem-cell renewal, primarily through phosphorylation (Saunders et al. 2013).

16.4.5 Hox Genes

16.4.5.1 HOX Genes in Cancer

Studies of HOX upregulation have been reported in various HOX-related fields, including leukaemia, where haplotype translocations or altered regulation lead to the malignancy known as trithorax homologue myeloid lymphoid leukaemia. A majority of the studies that have looked at invasion and metastasis caused by abnormal *HOX* gene expression have focused on solid tumours and have found that mutations in upstream regulators or loss of function mutations usually result in *HOX* gene deregulation (Del Bene and Wittbrodt 2005). Apoptosis and proliferation of cancer cells are also affected by HOX molecules, which regulate cell cycle-related proteins. Numerous studies indicate that many HOX transcription factors are abnormally expressed in cancer, and that these abnormalities contribute to tumour invasion

and metastasis. Inhibition of ZEB1 by HOXD9 suppresses HCC cell migration, invasion, as well as EMT in part by interacting with the zinc-finger Ebox binding homeobox (ZEB)-1 promoter region (Lv et al. 2015). In epithelial ovarian cancer cells, HOXA9 induces intraperitoneal dissemination by activating transcription of the *cadherin3* gene encoded by P-cadherin within the enhancer region of the gene encoding growth factor b (TGFb)-2 (Ko et al. 2012; Quéré et al. 2011). Studies have suggested HOXA9 deregulation in the temporal and spatial domains is related to primary tumours and specific histological subtypes. HOXA9 has therapeutic potential; however, its effectiveness is restricted by low membrane permeability. HOXC10 upregulates VEGFA transcription by attaching to its promoter via protein arginine methyltransferase 5 and WD repeat domain 5. These mechanisms govern the posttranslational modification of histones to promote angiogenesis (Tan et al. 2018). HOXA5 boosts Akt1 mRNA and protein expression, as well as Akt activity, through coordinating the downregulation of *PTEN*, enhancing the capsular patellar junction's stability (Feng et al. 2017). In malignancies, such as myeloid leukaemia, HCC, breast cancer and lung cancer, HOX proteins are involved in treatment resistance. HOX proteins influence cancer cell treatment resistance by regulating a variety of non-coding RNAs (ncRNAs). HOXB13 is shown to mediate chemotherapy resistance in lung cancer as an example. Through direct binding to promoters of drugs-transfer and drug-resistance-related genes, the cisplatin-HOXB13-ABCG1/EZH2/Slug network, which includes ATP Binding Cassette Subfamily G Member 1, Enhancer of Zeste 2 Polycomb Repressive Complex 2, and Slug, upregulates several genes associated with drug resistance and drug-transfer (Barresi et al. 2016; Zhan et al. 2019). In cancer, posttranslational changes of HOX proteins primarily affect protein stability, DNA binding, transcriptional activator-like effector interaction, transcriptional activation capability and unexplained cellular effects (Yu et al. 2020). The molecule networks IGF1-HOXA13-ACLY/IGF1R and CXCL12-HOXB5-CXCR4/ITGB3, which target blocking the downstream protein with small molecular drugs, are promising anticancer therapies in colorectal cancer (Qiao et al. 2021). HOXA4, HOXA9 and HOXD10 expression alterations promote aberrant colorectal cancer cell proliferation and differentiation, which contributes to tumour growth (Zhou et al. 2018; Mohr et al. 2017; Miller et al. 2018; Cheng et al. 2018). The discovery of chemical compounds that target downstream molecules has increased the possibility to precisely target the *HOX* genes intermediated network and prevent cancer development, thereby improving cancer clinical outcomes.

16.4.5.2 HOX Genes in Regeneration

Homeobox genes or HOX genes are required for embryonic development, regulating cell fate and repair of the adult body. They decide the pattern of each region of the body through Hox code. Hox genes are majorly responsible for embryonic and adult stages of life during stem cell differentiation (Seifert 2015). They can be programmed to make or change any tissue through a proper pattern, but it cannot be erased or change a fixed pattern, thus making it a limiting factor in regeneration. On the other hand, epigenetic mechanisms of transcripts of HOX make it stronger for tissue homeostasis and cell plasticity. The retention of a particular position in adult

cells for regeneration holds good for homeostasis but does not hold good for cell plasticity. This is one of the reasons for the loss of regenerative ability in humans and other mammals. In order to retain plasticity, organisms must be able to undergo changes in its polarity through specific pathways. Modulation of the WNT pathway and silencing of β-catenin results in regeneration, although it could lead to inappropriate polarity. It is essential for the organism to remember the position of the injured tissue, missing structures of the wound and understanding what type of cells, like totipotent/somatic, must be placed in those wounded sites. These functions are done by HOX genes (Wang et al. 2009). HOX genes also play a role in apoptosis, when they are expressed in normal conditions. But during an abnormal condition, when they are overexpressed, they cause abnormal development and malignancies (Shah and Sukumar 2010).

16.5 Pathways Regulating Cell Division

16.5.1 Hippo Pathway

The Hippo pathway is a revolutionary preserved pathway present in higher-level vertebrates that facilitate vital target genes in a variety of biological functions, including differentiation, cellular proliferation, cellular fate determination, survival, organ size and tissue homeostasis (Calses et al. 2019; Harvey et al. 2013). Fundamentally, it consists of MST1/2 (mammalian Ste20-like kinases 1/2), LATS1/2 (large tumour suppressor 1/2), YAP (yes associated protein) and/or its paralog TAZ (transcriptional coactivator with PDZ binding motif, also called as WWTR1 (WW domain-containing transcription regulator)) (Han 2019). The Hippo pathway mechanism involves the initiation of the Hippo kinase cascade via MST1/2 automatic phosphorylation. Furthermore, with the aid of MOB1A/B, NF2 and SAV1, active MST1/2 phosphorylates LATS1/2, which then phosphorylates YAP/TAZ. Finally, it causes the cytoplasmic retention of 14-3-3 and the destruction of YAP/TAZ by SCF. YAP/TAZ is a transcriptional coactivator that interacts with TEAD to control gene transcription (Yang et al. 2021).

16.5.1.1 Hippo Pathway in Cancer

The Hippo pathway modulates a variety of cellular activities important in cancer, such as proliferation and apoptosis (Harvey et al. 2013). The activity of the Hippo pathway has been reported to be regularly dysregulated in a broad range of cancers in humans including NSCLC (non-small-cell lung carcinoma), breast carcinoma, gastric carcinoma, hepatocellular carcinoma, renal cell carcinoma, colorectal carcinoma, osteosarcoma, rhabdomyosarcoma and angiosarcoma (Harvey et al. 2013; Han 2019). Furthermore, in human tumours, the level of components of the Hippo pathway is commonly changed, which is related to worse prognosis and shorter patient survival (Nakatani et al. 2017). According to studies, the dysregulation of YAP/TAZ and TEAD can enhance cancer (Han 2019). But the mutations within the

pathway are relatively rare and present in <10% of cancer cases (Cunningham and Hansen 2022).

In addition to this, Hippo pathway dysregulation in human tumours could be caused by molecular processes such as susceptibility to tumour mechanical characteristics and interaction with other tumour pathways (Harvey et al. 2013). Studies over the last two decades have revealed that the Hippo pathway has both tumour-suppressing and tumour-promoting functions. Studies have shown that YAP/TAZ and LATS have tumour-suppression and tumour-promoting functions, respectively, in several types of cancer, including haematological cancer, colorectal malignancies and ERα positive breast tumours. Moreover, YAP/TAZ activity in the tumour environment, such as immune cells and peritumoral cells, can influence tumour development, and their effect differs from that of YAP/TAZ activity in cancerous cells. As a result, a complex link has formed between the Hippo signalling pathway and cancer growth (Li and Guan 2021).

16.5.1.2 Hippo Pathway in Regeneration

This pathway is essential in development, homeostasis and also in regeneration of most organs of the body. It controls cell function, cell size and cell proliferation, and is also a crucial pathway for the suppression of tumour. G-protein coupled receptors play a vital role in regulation of subcellular localization of YAP and TAZ. Both YAP and TAZ are essential for defining cell structure, shape and polarity. During the embryonic stem cells phase, YAP promotes pluripotency by binding directly to the target. When YAP expression is enhanced in the embryonic stage, cells turn to be pluripotent whereas when YAP is inhibited, cells lose pluripotency. Also, studies show that YAP is increased when cells are being reprogrammed. Both YAP and TAZ are overproduced in most cancers, resistant to apoptosis. With small molecule modulators and inhibition of YAP and TAZ, suppression of cancer can be strategized. Defects in Hippo directly affect YAP and TAZ which also contribute to cancer initiation and prognosis (Johnson and Halder 2014).

16.5.2 JAK-STAT Pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is the highly preserved signalling pathway present in a wide range of species that are involved in an array of cytokines and growth factors. This pathway is important for cell differentiation, proliferation, survival and embryology (Luo and Balko 2019; Bousoik and Montazeri Aliabadi 2018). Furthermore, this route transports extracellular signals to the cell and begins the gene transcription involved in the proliferation and differentiation of the cell by a sequence of phosphorylation cascades. The JAK/STAT pathway is mainly involved in cytokine signalling, which includes erythropoietin, thrombopoietin, interferons, interleukins and granulocyte-colony stimulating factors (Luo and Balko 2019). In addition to this, the family of JAK has four members (JAK1, JAK2, JAK3 and TYK2), each with 7 preserved JAK homology domains (JH1–7); meanwhile, the family of STAT has 7 members

(STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6) (Pencik et al. 2016). The OG (oligomerization), CC (coiled-coil), DB (DNA-binding), LK (linker), SH2, phosphotyrosine tail (Y) and transcriptional activation (TA) domain are all found in STAT family members (Lim and Cao 2006). The downregulated controllers of the pathway include (1) tyrosine phosphatases (SHP1 and SHP2), which dephosphorylate JAKs, (2) suppressors of cytokine signalling (SOCS), which compete with STAT binding to the cytokine receptor and (3) the PIAS family, which obstructs with STAT binding to DNA. The downregulated regulators of the pathway suppress the JAK/STAT pathway by turning it off, hence modulating the amplitude and temporal regulation of pathway signalling (Luo and Balko 2019).

Janus kinase (JAKs) are members of non-receptor tyrosine kinases. Downstream to JAKs, signal transducer and activator of transcription (STATs) are present. They are activated together as a receptor when a ligand, such as a cytokine, binds to the site of the reception. When a receptor activates, associated JAKs are phosphorylated for specific residues. Activated JAKs then phosphorylate and select STATs. Activated STATs disintegrate from the receptor and dimerize to move into the nucleus where transcription factors regulate the target genes. This pathway is known to participate in cell proliferation, differentiation and haematopoiesis. This is one of the stable stress-response pathways that promote injury-induced apoptosis and compensatory proliferation. Activation of transcription genes due to tissue damage is associated with compensatory proliferation (La Fortezza et al. 2016).

16.5.2.1 JAK-STAT Pathway in Cancer

JAK/STAT signalling pathway is a critical component of cancer development, either as a tumour-specific driver of cancer growth and metastasis or a mediator of immune surveillance (Brooks and Putoczki 2020). This pathway is part of 12 other cancer pathways (Vogelstein et al. 2013). JAKs usually engage the receptor of tyrosine and then go into a dormant state until the binding of ligand occurs. Because of genetic abnormalities or polymorphisms, improper activation of the JAK/STAT system results in chronic activation of JAKs in the absence of cytokine signalling, which can lead to cancer or carcinogenic activity. Furthermore, while this mechanism is involved in many cellular processes relevant to cancer, each of the JAK/STAT pathway components can be activated in different ways in different forms of cancer, and the molecular and cellular environment can have diverse consequences on cancer characteristics. Moreover, whereas the importance of the JAK-STAT signalling mechanism in haematological malignancies is very well known, there is growing recognition of its role in solid tumour development (Luo and Balko 2019). JAK-STAT dysregulation has been linked to loss- or gain-of-function in certain malignancies, resulting in alterations that can begin and promote carcinogenesis (Villarino et al. 2017). Abnormal JAKs can stay active, resulting in uncontrollable transduction of the JAK/STAT mechanism. Conversely, numerous mutations in *STAT*s, including *Stat1*, *Stat3* and *Stat5*, have been discovered. Diverse haematological malignancies have been linked to somatic mutations in *Stat3*. CD4+ T-LGL oncogenesis has been associated with Stat5b mutations, with abnormal CD4+ T cell proliferation being observed in more than 55% of patients. The

V617F mutation is linked to a threefold greater risk of early death in myeloproliferative cancer patients as compared to those who do not carry the mutation (Nielsen et al. 2011). While JAK-STAT mutations are less common in solid tumours, the JAK2 V617F mutation has been found in non-small cell lung cancer (NSCLC), with GOF mutations connected to PD-L1 changes in tumour cells (Jeong et al. 2008; Li et al. 2017). Furthermore, LOF mutations in JAK1 and JAK2 have been associated with the decrease of PD-L1 expression in the TME as a result of dampened tumour-inherent IFN signalling in melanoma patients, which may lead to bad patient response to checkpoint inhibitors (Shin et al. 2017). STAT3 and STAT5 expression abnormalities in the TME are linked to tumour growth and dissemination. Upregulation of STAT5 has been related with early recurrence and worse prostate tumour patient survival, in contrary to this, a high level of STAT3 is found to be linked with low patient survival and increased recurrence risk in cancers such as renal cell tumour, glioblastoma, cervical tumour, colorectal tumour and melanoma (Owen et al. 2019).

16.5.2.2 JAK-STAT Pathway in Regeneration

JAKs and STATs are activated together as a receptor when a ligand, such as cytokine, binds to the site of reception. When a receptor activates, associated JAKs are phosphorylated for specific residues. Activated JAKs then phosphorylate and select STATs. STATs, when activated, dissociate from its receptor to move into the nucleus in dimerized form, to the target gene sites where transcription factors are regulated. This pathway is essential for the cell division, their differentiation and haematopoiesis (Jang and Baik 2013). This is one of the stable stress-response pathways that promote injury-induced apoptosis and compensatory proliferation. Activation of transcription genes due to tissue damage is associated with compensatory proliferation (La Fortezza et al. 2016).

16.5.3 PI3K Pathway

16.5.3.1 PI3K Pathway in Cancer

Phosphatidyl-inositol-3-kinases (PI3K) are a family of plasma membrane-associated lipid kinases made up of three subunits: p110 catalytic, p85 regulatory and p55 regulatory. PI3K is divided into three categories based on structural differences and specificity of substrate: classes I, II and III (Yang et al. 2019). Class I PI3Ks are the group of heterodimers that is made up of a four CAT (catalytic) and eight regulatory subunits (Porta et al. 2014, p. 27; Jean and Kiger 2014). Class I is further categorized into two isoforms—class IA and class IB PI3Ks. Class IA PI3K is composed of the p110α, p110β and p110δ catalytic subunits that are produced by distinct genes PIK3CA, PIK3CB and PIK3CD, respectively, whereas class IB PI3K consists of only p110γ catalytic subunit which is generated by PIK3CG (Yang et al. 2019). Furthermore, class II PI3K consists of only catalytic subunits—PI3KC2α, PI3KC2β and PI3KC2γ produced by PIK3C2A, PIK3C2B and PIK3C2G, respectively, whereas class III is composed of catalytic and regulatory subunits synthesized by

PIK3C3 and PIK3R4, respectively (Jean and Kiger 2014). Moreover, activation of Akt/PI3K is done by growth factor receptor protein kinases that eventually results in the regulation of various cell activity (Porta et al. 2014).

In recent years, PI3K has been investigated to be dysregulated in a variety of cancers (Yang et al. 2019). PI3K is known to have a fundamental part in human malignancies as shown by the decreased activity of PTEN and/or mutations of the kinases (Hennessy et al. 2005; Dillon et al. 2007). Nevertheless, PI3K dysregulation has been described by a number of mechanisms, including (1) inhibition of the PTEN, a tumour suppressor, (2) PI3K mutation and (3) stimulation of tyrosine kinase growth factor receptors or oncogenes upstream of PI3K (Aziz et al. 2009; Stemke-Hale et al. 2008; Zhou et al. 2000). Moreover, PI3K is considered as a fundamental therapeutic target for cancer treatment (Yang et al. 2019). PI3K antagonists are mainly classified into—(1) dual PI3K/mTOR inhibitors, (2) pan-PI3K inhibitors and (3) isoform-specific inhibitors (Yang et al. 2019). Additionally, other than PI3Ks, a range of therapies have also been discovered to suppress various proteins in the PI3K/AKT/mTOR pathway such as mTORC1, mTORC2 and AKT. Many of these medications have shown considerable therapeutic improvements in ER+ metastatic breast tumours that have progressed on previous lines of endocrine therapy, with better progression-free survival (PFS) (Nunnery and Mayer 2020).

16.5.3.2 PI3K Pathway in Regeneration

Phosphoinositide-3-kinase (PI3K) is one of the members of the lipid kinase family which phosphorylates 3′ hydroxyl groups of phosphoinositide. It is characterized by PIP3, an essential component for cell growth, cell survival, and cell proliferation (Yuan and Cantley 2008). This is a controlled process, and the pathway involves many steps. A completely activated AK strain transforming mediator (Akt) triggers angiogenesis, metabolism, proliferation, transcription, apoptosis (Hemmings and Restuccia 2012). Various oncogenic genes and tumour suppressor proteins are regulated by the AKT pathway. The proteins and transcription factors in this pathway behave oncogenic when they are either upregulated or downregulated. Most cancers formed in this manner are sporadic (Altomare and Testa 2005).

16.5.4 Ras-Raf-ERK Pathway

16.5.4.1 Ras-Raf-ERK Pathway in Cancer

The ERK is a kinase cascade pathway and one of the well-studied pathways in human cancers (McCubrey et al. 2007). The pathway is initiated either by growth factors or mutation of proteins involved in the pathway; the most common proteins are RAF and RAS. Dysregulation of this pathway is common, and it performs a vital function in malignancies namely pancreatic, melanoma, colorectal and lung cancer (Neuzillet et al. 2014). Targeting these kinases has already been found to be fruitful in cancer treatment (Huang et al. 2017).

16.5.4.2 Ras-Raf-ERK Pathway in Regeneration

This pathway is one of the first kinase cascade pathways to be discovered and characterized in pathways. This pathway is a part of various cellular processes which include proliferation, cell cycle inhibition, terminal differentiation of stem cells and apoptosis. They signal from the cell membrane into the nucleus for many physiological processes such as mitogenic signals and differentiation signals. Raf proteins activate MAP kinase kinases (MAPKK) and MAPK or ERK kinases (MEK) pathways which in turn activate MAPKs and ERKs. These ERKs move into the nucleus and phosphorylate transcription factors to control them. The Ras and Raf are also linked with oncogenes (Peyssonnaux and Eychène 2012).

16.5.5 Wnt Pathway

16.5.5.1 Wnt Signalling Pathway in Cancer

WNT is considered as a crucial signalling pathway that is known to regulate tissue morphogenesis during embryogenesis and repair and has also been firmly linked with cancer (Patel et al. 2019; Sharma et al. 2021). This pathway has been predominantly shown in the case of human colorectal cancer, but an altered WNT signalling pathway has already been reported in other kinds of human tumours namely oral, lung, breast, cervical and haematopoietic malignancies (Zhan et al. 2017). The WNT pathway is a vast network of proteins that coordinates the regulation of molecular processes in a systematic manner. Furthermore, any disturbance in the regulation results in the emergence of various diseases and tumorigenesis (Bugter et al. 2021). Also, the important characteristic of the dysregulated WNT pathway is the integral nuclear localization of β-catenin. Several studies have investigated the mutations in β-catenin's serine and threonine residues that prevent phosphorylation by GSK3 and CK1 kinases, resulting in WNT signalling pathway hyperactivation (Sparks et al. 1998). Moreover, high throughput cancer genomics studies have revealed that the WNT pathway also gets activated by gene mutation, receptors, ligands and intracellular components which include APC, CTNNB1 and AXIN1 (Sharma et al. 2021; Patel et al. 2019). Additionally, the essential components of the WNT pathway, namely, (1) receptor–ligand interface of WNT, (2) destruction complex of β-catenin and (3) transcription complex of TCF/-catenin have been found to be a prospective target for cancer treatment and are now being studied in preclinical and clinical trials. Hence, targeting the WNT/β-catenin pathway has been identified as a possible candidate for customized cancer treatment techniques. To confirm the feasibility, effectiveness, patient stratification and drug delivery of new WNT/β-catenin focused therapies in human cancer, more research is needed (Zhang and Wang 2020).

16.5.5.2 Wnt Signalling Pathway in Regeneration

Wnt are a group of secretory factors, which along with frizzled receptors make a pathway in cells which are majorly involved in cell homeostasis and cell development. It regulates many cellular activities in adult tissues like axis patterning, cell division, cell fate decisions, self-renewal of somatic cells (Jansson et al. 2015). It is

essential in tissue regeneration with signals between adjacent cells (Clevers et al. 2014). Studies also show that signals from the WNT signalling pathway induce epidermal and haematopoietic stem cells development and dysregulation might lead to abnormality in self-renewal of progenitors thus directing towards cancer. Inhibiting the Wnt pathway also showed that uncontrolled cell renewal and proliferation can be interrupted (Reya and Clevers 2005).

16.6 Influence of Microenvironment

16.6.1 DNA Methylation and Epigenetic Regulation in Cancer

To sustain normal growth and development, as well as gene expression in various organs, epigenetic mechanisms are essential. Gene expression and function can be altered by abnormal epigenetic regulation, which can lead to illnesses like cancer. Human tumours are essentially a genetic illness, as a huge number of genes are altered or improperly active during cancer growth. Cancer is caused by a combination of accumulative genetic mutations, epigenetic modifications and environmental influences. Much research has focused on describing the genomic landscape of malignancies, ranging from oncogene-driven signalling pathways to the mutation spectrum in various cancer subtypes. Epigenetic effects, unlike genetic mutations, refer to changing gene expression without causing permanent changes in the genomic sequence. They're used more frequently in cancer cells because epigenetic changes are reversible and easier to control than genomic evolution (Easwaran et al. 2014). DNA methylation is the most well-studied epigenetic mechanism, and it primarily occurs in CpG islands (CGIs), which are found in the 5′ promoter region of more than half of all human genes (Lister et al. 2009). It plays a key role in X chromosome inactivation, embryonic development, genomic imprinting, epigenetic reprogramming, cell identity establishment and lineage specification, among other things. It works by covalently attaching methyl groups from *S*-adenosylmethionine (SAM) to the 5 position of the cytosine pyrimidine ring to silence genes. The 5-methylcytosine (m5C) structure can either restrict transcriptional factors (TFs) from accessing DNA-binding sites or recruit methyl-binding domain proteins (MBDs) to remodel chromatin in conjunction with histone changes, resulting in repressive gene expression (Robertson 2005). The catalysis of DNA methylation is regulated by three DNA methyltransferases (DNMTs), notably DNMT1, DNMT3a and DNMT3b. The maintenance DNA methyltransferase, DNMT1, has a greater catalytic activity and is primarily responsible for maintaining the DNA methylation status by preferentially methylating hemimethylated DNA during replication (Goyal et al. 2006). While 'de novo' methyltransferases DNMT3a and DNMT3b generate and support the precise DNA methylation status in the genome, they both prefer to bind to previously unmethylated DNA regardless of replication (Liang et al. 2002). DNA demethylation, on the other hand, is a reversible process that restores silenced genes damaged by DNMTs. It is catalysed by a family of ten-eleven translocation methylcytosine dioxygenases (e.g. TET1, TET2 and TET3), which can convert 5mC

to 5-hydroxymethylcytosine (5-hmC) and then further oxidise 5-hmC to 5-formylcytosine (5-fC) and 5-carboxylcytosine (5-caC) (Scourzic et al. 2015; Zhao and Chen 2013). In numerous types of cells, homeostasis between demethylation and methylation of the genome occurs as a dynamic mechanism of gene expression.

16.6.2 Role of DNA Methylation and Epigenetics in Regeneration

Gene expression is largely dependent on one or many of these factors—transcription regulators such as lncRNA, miRNA, DNA modifications and epigenetic code. It was understood through experimentation that because of tissue damage or injury, a change in the transcriptome can be observed. This change is due to epigenetic changes in the new, regenerating tissues. It is observed that the polycomb repressor complex, PRC, is playing a major role in regeneration of skin and intestine, regulates the regeneration when the repressive mark H3K27me3 pattern is expressed on the gene (Zhang et al. 2021).

16.6.3 Role of Extracellular Matrix in Cancer

An extracellular matrix (ECM) is an environment that surrounds a tumour and consists of cellular components (fibroblasts, endothelial cells, adipocytes, immune cells etc.) as well as noncellular components. Cancer progresses as carcinoma cells recruit host stromal cells, altering their metabolism and characteristics, and together they form a unique microenvironment within which they collaboratively remodel the surrounding matrix and facilitate tumour invasion (Rowe and Weiss 2009). Proteolytic enzymes (such as matrix metalloproteinases) remodel the ECM, increasing stiffness and changing its composition (Piperigkou et al. 2021) and enzymes that influence the modification and cross-linking of extracellular matrix proteins (such as lysyl oxidases (LOX)) (Ye et al. 2020). These vesicles, which contain nucleic acids, lipids and proteins, play a significant role in tumour progression and behaviour, including reshaping the environment around tumours, stimulating fibroblast activity, stimulating angiogenesis, modulating immunity and forming neoplastic niches (Dong et al. 2021; He et al. 2021). In addition to matrix degradation, the release of matrix-bound growth factors and matrikines regulates signal transduction and tumour growth and migration by interacting with surface receptors (Manou et al. 2019; Niland and Eble 2020).

16.6.4 Role of Extracellular Matrix in Regeneration

Extracellular matrix usually regulates the behaviour of cell proliferation, shape and survival. It remodels the cell as well as degrades the cell. Sometimes, its contributions, when mis-utilized or overpowered, become a reason for diseases

like cancers. The ECM is composed of structural proteins, specialized proteins, matricellular proteins, glycoproteins etc. These help it to build and rebuild cells for repair and regenerate. The ECM is cleaved by proteolytic members such as proteases. They release small signalling molecules and growth factors to degrade the matrix proteins. These proteases must always be regulated and, when not under control, the tissue homeostasis is disturbed. It can be therefore inferred that when there is a mis-regulation of protease activity, it could lead to many diseases such as cancers (Daley et al. 2008).

16.6.5 Inflammation

16.6.5.1 Role of Inflammation in Cancer

In the tumour microenvironment, IL-6 encourages the recruitment of immune cells, which further stimulates the production of proinflammatory cytokines. As a result, IL-6 contributes to the growth of chronic inflammation and tumour. The presence of elevated IL-6 levels is observable in a variety of cancer types, similar to patients with arthritis and those with Castleman disease. Elevated IL-6 levels are observed in a variety of different forms of cancer, just as they are in patients with arthritis, Castleman disease, or following infection (Dethlefsen et al. 2013; Kotowicz et al. 2016; Chung and Chang 2003; Chen et al. 2013; Jinno et al. 2015; Riedel et al. 2005; Macciò and Madeddu 2013; Sanguinete et al. 2017; Miura et al. 2015; Culig and Puhr 2012; Altundag et al. 2005; Chang et al. 2013). The Cancer Genome Atlas (TCGA) (Gao et al. 2013; Cerami et al. 2012) has detected no clinically relevant alterations in IL-6, IL-6R, or gp130 genes in tumour types studied to date. A majority of surgical specimens from patients with inflammatory hepatocellular adenomas were found to contain activating mutations in gp130. An additional polymorphism ($-174G > C$) in the promoter region of the IL6 gene has been shown to result in an increase in its expression. IL-6/IL-6R/JAK/STAT3 pathway activation occurs due in large part to epigenetic alterations, and transcription factor expression and activation might play a major role in elevated levels of IL-6 in cancer (Rebouissou et al. 2009). Epigenetic alterations are believed to play a major role in aberrant activation of the IL-6/IL-6R/JAK/STAT3 pathway in cancer, and transcription factor expression and/or activation may play a major role in abnormal expression of IL-6 in cancer. Over 70% of human cancers exhibit abnormally elevated STAT3 activity (Frank 2007; Roeser et al. 2015). STAT3 hyperactivity has been observed in malignancies including acute myeloid leukaemia (AML), multiple myeloma and solid tumours of the bladder, breast, brain, cervix, colon, oesophagus, head-and-neck, kidney, liver, lung, ovary, pancreas, prostate, stomach and uterus. Many of these cancers have been shown to have high levels of phosphorylated and/or activated STAT3. An exogenous form of STAT3 encoded by a constitutively active form confers growth and tumour-inducing properties on fibroblasts, demonstrating the ontogenetic properties of this protein (Chen et al. 2008; Sonnenblick et al. 2012; Takemoto et al. 2009; Zhang et al. 2016). STAT3 activation and phosphorylation have been associated with poor clinical prognosis in multiple

types of cancer. STAT3 expression leads to anchorage independent growth and tumorigenicity in fibroblasts, thus proving STAT3's oncogenic activity (Bromberg et al. 1999).

16.6.5.2 Role of Inflammation in Regeneration

Inflammation is defined with its five characters like dolor, calor, rubor, tumour, functio laesa (Karin and Clevers 2016). It is a part of one of the initial lines of defence of the body against pathogenic organisms. This mechanism is a response to infection. Inflammation is a kind of hallmark for cancer, but its role in regeneration is not very prevalently known.

Certain signalling pathways are triggered during inflammation that leads to regeneration. Pro-inflammatory cytokines like IL-6 and IL-11 trigger the activation of STAT3 and enhance intestinal epithelial cell proliferation and cell regeneration. IL-6 also triggers YAP and Notch pathways, through STAT3 independent signalling cascade, suppressing cell death and promoting cell proliferation (Pesic and Greten 2016).

Macrophages play a crucial role in regeneration. They activate surrounding cells to trigger cytokines (Crupi et al. 2015). They perform phagocytosis which later results in scar tissue formation. The most accepted hypothesis for macrophages playing a role in healing of wounds and regeneration is the transition of pro-inflammatory phenotype (M1) to a regulatory anti-inflammatory phenotype (M2). This mechanism leads to a complete regeneration unlike the scar formation. After an injury, macrophages differentiate among themselves and turn into M1 phenotype. This is because they get exposed to pro-inflammatory cytokines and necrotic cells. Because of this initial response and shift into M1, dormant satellite cells are triggered for activation and are expanded into the injured site. Once the initial inflammatory response is subsided, they transit into M2 phenotype. This transition could be because of IL-10. By transition to M2 phenotype, it subsequently releases anti-inflammatory cytokines and promotes tissue repair and remodelling (Brown et al. 2014). Any abnormality in M2 would, therefore, promote tumour than M1, in comparison (Mills 2015).

Along with STAT3 and macrophages, NF-κB and AP1 are also important for regulating immune responses. They are also primary inflammatory response regulators that control regeneration and wound healing. TNF inhibits apoptosis by activating NF-κB as NF-κB inhibits necrosis. IL-6 and TNF together stimulate intestine and liver regeneration by targeting epithelial cells. TNF triggers epithelial cells in the notch pathway. IL-6, a cytokine member, stimulates cell proliferation and cell subsistence. IL-22 stimulates proliferation, prolongs the differentiation of cells in final cell division, and constrains cell death. Also, IL-22 directly activates STAT3 and MAPK.

Reactive oxygen species (ROS) that are produced during inflammation trigger the proliferation of intestinal stem cells by activating Jun-N-terminal kinases (JNK) and other transcription factors. The transcription factors are activated by the growth factor EGF family. This pathway also interacts in cell migration during tissue injury for wound closure.

Self-limiting acute inflammation is essential for proper regeneration and restoration for injured tissue since it is the primary stage of a wound to heal and it is followed by tissue repair and tissue remodelling (Karin and Clevers 2016).

16.7 Growth Factors

Growth factors are polypeptide molecules, which are secreted by cells, to aid them in regulating, proliferating, differentiating and migrating for healing. They usually bind to very specific target molecules and regulate the downstream processing of the cell. Although these molecules are receptor specific, their function is cell specific since their action is much localized. Off-target effect or over expression of growth factors is one of the major contributing reasons for cancers (Cheah et al. 2021).

16.7.1 Growth Factor Receptor in Cancer

Growth factors and their receptors (GFR)s, which are located on cell membranes or in the cytoplasm, play important roles in cell growth, survival, angiogenesis and metastasis. GFR amplification results in both innate and acquired resistance to traditional and targeted chemotherapies and drugs. To prevent apoptosis, or programmed cell death, escalating growth impulses interact differently with death signals. Role of different GFRs in cancer has been depicted in Table 16.2.

16.7.2 Growth Factors in Regeneration

Growth factors play a role in regeneration through growth factor gradients causing chemotaxis. This process is observed as an illustration in platelet-derived growth factors where growth factors scatter out from clots of blood platelets and macrophages, and this scatter behaves as primary chemotactic signal for fibroblast cells. Also, the gradient in growth factors is the reason for cell migration (Cheah et al. 2021).

16.7.2.1 Transforming Growth Factor Beta (TGF-β)

The TGFβ is a signal transducer that has a key role in healing of wounds and regeneration specific to tissues. It transcribes three isoforms—TGFβ1, TGFβ2 and TGFβ3—which are structurally similar to cytokines and regulate embryonic development through autocrine and paracrine mode. They are usually inactive in state and are activated in the extracellular matrix. Once it is in active state, TGFβ binds to its target ligand's transmembrane receptor through kinase activity. It plays a pleiotropic role by behaving as a crucial factor in cell proliferation, differentiation, migration, invasion and chemotaxis during inflammation and in endothelial cell proliferation, migration, invasion, cell maturation during angiogenesis. It acts as a very able chemo-attractant and inflammatory mediator for neutrophils, basophils and mast

Table 16.2 Role of different GFRs in cancer

GFR family	Role in cancer	References
EGFR/ ERB/HER	*HER2* gene associated to poor prognosis was observed in diverse cancers; aggressive metastatic breast (15–30%), gastric (10–30%), ovarian (20–30%), endometrial (1–47%), esophageal (0–83%), lung (20%) and invasive urothelial bladder (20%) (0–80%) carcinomas In breast cancer (20–78%), constitutive expression of active truncated *EGFR* vIII lacking the extracellular domain was identified, which was linked to tumour aggressiveness. Patients had mutations in the *HER2* gene in lung cancer, the *Her3* gene (somatic) in breast, colon and gastric cancer and the *Her4* gene in melanoma, colorectal, gastric, lung and breast cancer	Witsch et al. (2010)
TGF-βR	*TGF-RII* gene mutations are found in 58–82% of colon and pancreatic cancers, are absent in 24% of prostate cancers, and are downregulated in breast and lung cancers	Elliott and Blobe (2005)
IGFR	*IGF1R* gene amplification has been found in a small number of breast and melanoma cases Squamous cell carcinomas of the lung were shown to have mutations in the *IGF2R* gene	Witsch et al. (2010)
PDGFR	Amplification of the *IGF1R* gene has been discovered in a small proportion of breast and melanoma cases Mutations in the *IGF2R* gene have been discovered in lung squamous cell carcinomas	Demoulin and Essaghir (2014)
VEGFR	*VEGFR1-3* gene expression has been found to be high in a variety of cancers, including bladder, brain, breast, colon, gastric, lung, ovarian, prostate and head-and-neck carcinomas	Goel and Mercurio (2013)
FGFR	*FGFR1-3* gene amplification has been seen in a variety of cancers. For example, the *FGFR1* gene is found in 20% of lung cancer cases, 10% of breast cancer cases, 5% of ovarian cancer cases and 3% of bladder cancer cases; the *FGFR2* gene is found in 10% of gastric cancer cases and 4% of breast cancer cases in triple negative cases; and the *FGFR3* gene is found in bladder and salivary adenoid cystic cancer cases Mutations in the *FGFR1-4* genes have been discovered. For example, *FGFR1* gene in melanoma (rare), gliblastoma; *FGFR2* gene in endometrial (12%), lung (5%), gastric (rare); *FGFR3* gene in bladder (50–60% nonmuscle invasive, 10–15% muscle invasive), cervical (5%), prostate (3%), colorectal; *FGFR4* gene in rhabdomyosarcoma (7–8%) cancer	Dieci et al. (2013)

cells. It can also act as an antagonizer for other neutrophil chemo-attractants like IL-8 to neutralize immune cells and to migrate to the injured site of the tissue.

During an injury, margins are more activated to get altered phenotypically to alter their cytoskeleton and dissolute cell–cell interactions. Through their autocrine and paracrine signalling, it instructs cells from the margin to migrate and proliferate for

healing. If these TGFβ isoforms and their signals are absent at the injury site, then the wound healing is disturbed and diminished. TGFβ plays a vital role as a growth suppressant also. It is regulated by SMAD3, and decline in SMAD3 also results in loss in growth suppressive effect of TGFβ. Hence, they both are proportional in expression. It also interacts in the Hippo pathway to ensure wound healing properties. Dysregulations in *SMAD3* interactions and Hippo pathway lead to cancer. Another important role of TGFβ is to facilitate and regulate the capillary sprout creation during angiogenesis at the site of injury. It helps in production of haemopoietic effector cells and promotes angiogenesis. Ideally, TGFβ signals margin cells from dermis at site of injury to promote fibroblasts and produce extracellular matrix. By the end of wound healing fibroblasts turn into myofibroblasts and undergo apoptosis leaving a scar. But in mammals, a scar-free cutaneous healing is observed in fetal development due to the established role of TGFβ. The TGFβ1 and TGFβ2 are high, but TGFβ3 is low in adults at the wound site but it is inverse in case of foetus. Also, to prevent fibrosis, various integer-mediated non-proteolytic activation of TGFβ1 is required.

TGFβ also has a crucial role in tissue regeneration. Stage one of tissue regeneration is the formation of blastema. Blastema has a mass of undifferentiated cells, from a heterogeneous pool of lineage restricted progenitor cells. Wound epithelium forms the epidermal layer around the site of injury and allows cells to migrate for healing. As the epithelium begins to cap, by thickening, it becomes stratified in appearance with basal keratinocyte polarity and basal lamina. Studies have shown that blastema induction and proliferation are triggered and controlled by wound epithelium (Gilbert et al. 2016).

16.7.2.2 Fibroblast Growth Factor (FGF)

Fibroblast growth factors (FGFs) act through tyrosine kinases to play a vital role in cell proliferation, survival, metabolism, morphogenesis, cell differentiation, tissue repair and regeneration. Pathways like MAPK and PI3K-AKT are regulated by these growth factors. Basic FBF (bFGF) promotes angiogenesis, an important wound healing character. Also, it catalyses tissue remodelling. Granulocyte macrophage colony stimulating factor (GM-CSF), a bFGF, was studied and was shown to be most prominent in wound healing as it contains higher bFGF, TGF-1 in wound fluids. FGF 15/19, FGF21, FGF23 are hypothesized to promote regeneration. FGF 11 contributes to angiogenesis in hypoxia conditions, while FGF21 is involved in spine repair.

FGFR1 and FGFR2 delay wound healing. Cancer associated FGF23 is a biomarker and is observed to be upregulated in osteoclasts (Farooq et al. 2021).

16.8 Autophagy

16.8.1 Autophagy in Cancer

Autophagy is a cytoplasmic catabolic mechanism of cells that have evolved over time and is driven by ATG (autophagy-related genes). It takes part in the removal of degraded cell organelles, abnormal proteins, pathogens and mass cytoplasm from the cell, while aids in recycling the cell nutrients (Yun and Lee 2018). There are four main phases in the process of autophagy. The first phase, induction, the mTOR pathway is involved in the initiation of this phase along with a few autophagic proteins, namely, ULK1, ATG13, ATG101 and FIP200. The second phase, phagophore, which is generated by BECLIN1-linked PIP3 kinase III. The third phase, autophagosomal membrane, which is guided by 2 ubiquitin-like conjugation systems and requires autophagic components such as ATG3, ATG4, ATG5, ATG7 and ATG12. The cellular machinery is recycled until the maturation stage, with the exception of a piece of LC3II that attaches to the membrane. The fourth phase, maturation, is involved in the merging of the autophagosome and lysosome. ATG6 or BECLIN 1 has been known to govern early autophagosome development (Barnwal et al. 2022). As a result, autophagy is involved in both tumour initiation and control (Yun and Lee 2018).

Furthermore, in the case of healthy cells, autophagy helps in maintaining biological function homeostasis, cell quality control and the clearance of old proteins and degraded organelles (Mizushima 2007; Yu et al. 2018). But in the case of cancerous cells, autophagy has been reported to perform a dual role—(1) under certain conditions, it involves in spreading of cancer by inducing proliferation of cancer cells via catabolic processes during situations like drugs administration and deficiency of nutrients and (2) in another condition, it involves in inhibiting cancer cell progression by inhibiting the survival of cancer cells, which eventually results in apoptosis (Yun and Lee 2018; Barnwal et al. 2022). Moreover, mTOR and AMPK have been found to negatively control tumour suppressor factors, resulting in the activation of autophagy and prevention of cancer development (Comel et al. 2014). On the other hand, cancer genes can be stimulated by mTOR, class I PI3K, and AKT, which in turn suppress autophagy and promote cancer growth (Choi et al. 2013). Nevertheless, it is known that mutations in essential autophagy proteins limit tumour growth. For example, BIF-1 proteins, which are connected to BECN1, have been found to become aberrant or absent in a range of cancer types, including colorectal and gastric cancer. UVRAG proteins are likewise related to *BECN1* and serve as the controller of autophagy. UVRAG mutation is known to impair autophagy, which causes an increase in the proliferation of colorectal cancer cells. On the contrary to this, certain forms of RAS-activated malignancies, such as pancreatic tumours, have a high level of autophagy. Further, high-level autophagy inhibition reduces cell proliferation and facilitates tumour suppression in certain malignancies. In conclusion, autophagy is a promising therapeutic cancer target, and researchers are exploring the utilization of autophagy stimulators as adjuvant therapy (Lim et al. 2021).

16.8.2 Autophagy in Regeneration

Autophagy is the process of degradation of cytoplasmic contents in lysosomes. It is one of the major approaches, by cell, to remove cellular waste. This process prevents cells from becoming toxic or damaged. It is to be noted that apart from playing a crucial role in tissue regeneration and cell reprogramming. It promotes induction of pluripotency by counteracting with cellular senescence and apoptosis. Also, degradation of mitochondria through autophagy is believed to improve the reprogramming of cells and promote tissue regeneration. Since autophagy is also important for protein control, maintenance of tissue homeostasis, it is implied that cellular aging is controlled by autophagy (Pan et al. 2013). The JNK pathway, when dysregulated, increases phosphorylation and further induces autophagic cell death, thus preventing cell from tissue homeostasis and reprogramming. Also, NFκB upregulates certain genes like *Beclin 1*, which stimulates autophagy.

mTOR negatively regulates autophagy. mTORC1 acts downstream of the Ras-PI3K pathway, signalling Ras to suppress autophagy, while mTORC2 also has a negative feedback loop, inhibiting transcriptional activity, in Ras senescence. Irregularity in autophagy contributes to tumour survival (Young et al. 2009) (Table 16.3).

16.9 miRNA

16.9.1 miRNAs in Cancer

miRNAs are small, endogenous, single-stranded and revolutionary conserved ncRNAs (non-coding RNAs) of 19–25 nucleotides in length encoded by introns, exons, intersection between introns and exons, or their genes. They can be either cancerous or tumour-suppressor, and contribute to silencing of RNA and post-transcriptional gene regulation. However, multiple reports have found that numerous miRNAs are inhibited in tumour phenotypes because of defective miRNA synthesis (Paul and Banerjee 2022). Studies have also reported that expression of miRNA is aberrant in human cancer due to a variety of mechanisms, which include (1) miRNA gene amplification or deletion, (2) aberrant miRNA transcriptional control, (3) abnormal epigenetic changes, (4) alteration in the biogenesis of miRNA, (5) genomic abnormality and (6) epigenetic factors (Peng and Croce 2016; Di Leva et al. 2014). Moreover, investigations have shown that miRNAs can be carcinogenic or tumour suppressive under certain circumstances (Peng and Croce 2016). Hence, numerous researches have illustrated that miRNAs have a function in tumour cell drug resistance by either targeting drug-resistance-related genes or affecting genes present in apoptosis, cell division and cell cycle. An individual miRNA can modulate multiple genes and has tissue-specific effects (Si et al. 2019). A list of miRNAs involved in cancer and regeneration has been provided in Table 16.4.

Table 16.3 mRNAs/proteins involved both in cancer and regeneration (identified by KEGG pathway)

mRNA/protein	Target	Role of mRNA/protein
WNT-4, WNT5A, WNT10B, β-CATENIN, LRP5/6, PAX7 GSK3β, DKK-1 SURVININ	WNT signalling	Promotes cell proliferation Inhibits Wnt signalling Helps in evading apoptosis in cancer cells
TGF-β, CCN2, SMAD-4, C-myc, BMP2, ACTIVIN SMAD-7 TGFβR,SMAD-2/3 inhibition	TGF-β signalling	Promoting differentiation, angiogenesis, gonadal growth, embryo differentiation Inhibits TGF signalling Causes insensitivity of anti-growth signals in cancer
SHH, GLI, PTC, HHIP, CCND, BCL2 GLI inhibition	Hedgehog signalling	Activates cell proliferation, tissue patterning, stem cell development and maintenance Promotes cell proliferation in cancer
MAP2K1, CREB, NFKB, RAS, FOS, C-myc, ERK, RAF Suppression of DAPK-mediated ERK inhibition	MAPK signalling	Promotes cell proliferation and anti-apoptosis Causes sustained angiogenesis in cancer
YAP/TAZ, TEAD	Hippo signalling	Helps in controlling cell proliferation, apoptosis and fate
m TOR, RHO, PKC, SGK1, AKT, CASP9, PTEN Suppression of AKT inhibition	mTOR signalling	Promotes cytoskeletal organization and cell survival Helps cancer cells in evading apoptosis
P13K, AKT, MYC, CCND, CDK, FASL, BIM, BCL-2, MCL-1, C-myb, BRCA1 Suppression of PTEN-mediated inhibition	P13K-AKT signalling	Promotes cell survival and cell cycle progression Promotes evading apoptosis, proliferation in cancer
JAK, STAT, SOCS, PIMI, BCL2, MCL 1, BCL-XL, C-myc, cyc-D	JAK-STAT signalling	Promotes cell cycle progression and anti-apoptosis

16.9.2 miRNAs in Regeneration

It was identified through sequencing that embryonic stem cells which have a different expression of miRNAs when compared with epiblast stem cells, like miR-290-295, miR-17-92, miR-302/367 clusters are expressed differentially along with another repetitive cluster on chromosome 2 (Sen and Ghatak 2015).

miRNAs play roles in different types of cells. In stem cells, a few miRNAs, especially from miR-290 family, are expressed for regulation of regeneration. The cell proliferation is observed to be seemingly low in the G1 phase when DICER was inhibited and DROSHA was deleted. miRNA like let-7, when expressed in proliferating and self-renewing cells like embryonic stem cells, its stemness is blocked. *Let-7* is also observed in differentiated cells, but regeneration depends only on the stemness and, therefore, it can be concluded that *let-7* is switched off when stemness is required. miR-1 and miR-133 are expressed in cardiac muscles and

Table 16.4 List of miRNAs involved in cancer and regeneration

miRNA	Target	Role of miRNA	Reference
miR 17-92, miR-21	*pTEN*	Oncogenic role in cancer	Farazi et al. (2011)
Let-7/miR-98, miR-141/200	*Ras*	Tumour suppressor in cancer	Farazi et al. (2011)
miR-34a, miR-48,miR-49	*TP53*	Transcriptional regulation of cancer and regeneration	Farazi et al. (2011)
miR-21,miR-29,miR-50,miR-51	Ras pathway	Tumour suppression in cancer	Farazi et al. (2011)
miR-17-92 cluster	*Myc*	Suppress apoptosis in regeneration (usually)	Farazi et al. (2011)
miR-34	*TP53*	Cell cycle arrest in cancer	Farazi et al. (2011)
miR-290-205, 17–92, 302/367	*Bcl*	Anti-apoptosis in cancer and regeneration	Sen and Ghatak (2015)
miR-290-295	*Myc*	Suppressing autophagy in regeneration	Thatcher and Patton (2010)
Let-7	*Ras*	Loss of self-renewal in cancer	Thatcher and Patton (2010)
miR-1	Cardiac muscle	Cell cycle termination in cancer and regeneration	Thatcher and Patton (2010)
miR-133	Skeletal muscle	Promoting differentiation in regeneration	Thatcher and Patton (2010)
miR-27b	Skeletal muscle	Muscle cell differentiation in regeneration	Thatcher and Patton (2010)
miR-15a, miR-16, miR-195	*Ngn3*	Downregulation of translation in regeneration	Thatcher and Patton (2010)
miR-23	*Hes-1*	Downregulation of Hes-1 in regeneration	Thatcher and Patton (2010)
miR-17, miR-302 families	Yamanaka cocktail	Induction of pluripotency in regeneration	Pedroza-Torres et al. (2019)
miR-290	Yamanaka cocktail	Enhance pluripotency in regeneration	Pedroza-Torres et al. (2019)
miR-93, miR-106b, 302a-d	Ras-induced senescence	Cell programming in regeneration	Pedroza-Torres et al. (2019)
miR-200c, miR-302a-d, miR-369	Somatic cells	Activate fibroblast in regeneration	Pedroza-Torres et al. (2019)
miR-29b	AMPK pathway	Tumour proliferation in cancer	Pedroza-Torres et al. (2019)
miR-125, 33, 190	*HIF-1*	Suppressing tumour in cancer	Pedroza-Torres et al. (2019)
pre-miR-17, miR-34a, miR-96, miR-125b	Pro-apoptosis caspase	Translational reduction in cancer	Reddy (2015)
miR-143/145	*Ras* gene	K-Ras activation in cancer	Reddy (2015)

skeletal muscles. The miR-1 expression terminates cell cycle in mammals, thus promoting differentiation in progenitors. While miR-206 is expressed only in muscle cells, its induction by MyoD and myogenin promotes muscle differentiation. miR-27b is essential for the initiation of muscle differentiation. miR-15a, 16, 195 downregulates the translation of *ngn3*, a gene which transcribes NGN3 (neurogenin 3 protein). This protein is called the master controller of pancreatic development. miR-23 downregulates *hes1*, an enhancer of Notch signalling effector. Improper amount of *hes1* results in improper cell count and premature differentiation. *miR-34* when overexpressed, it induces apoptosis and inhibits cell growth and tumour invasion. When the same miRNA is downregulated, the pancreas escapes the cell cycle and it leads to cancer (Thatcher and Patton 2010). miR-17 and miR-302 families are found to be expressed in Yamanaka genes, and their induction of pluripotency is disrupted when these miRNAs are disrupted. It is hypothesized that miR-290 may increase the efficiency of Yamanaka factors in inducing pluripotency, majorly as a substitute for *c-Myc*. miR 290–295 are predicted to bind to c-Myc. It was also found that miR-93, 106b, 302 also enhance cell reprogramming. It is also observed that the absence of miR-302a-d does not allow epithelial marker expression on Yamanaka factors. A group of miRNAs 200c, 302a-d, 369 activate the human fibroblast and reprogramme it as an induced pluripotent stem cell. While miR-133 controls unnecessary ossification, miR-675, 221 promote collagen-II expression in chondrocytes. When satellite cells of the human genome are induced with miR-1, 206, the cells were seen to improve in their differential potential (Sen and Ghatak 2015).

miRNAs not only regulate genes but also regulate metabolic pathways. miR-320, 123a, 422, 506, 136 regulate the glucose uptake and cancer metabolism, influencing the PI3K pathway. miR-33a/b regulate enzymes of the AMPK pathway, fatty acid metabolism pathway, while miR-29b regulates amino acid metabolism that helps in regulating metabolism of tumour growth and cell proliferation. Also, Hypoxia inducible factor-1 (HIF-1), a pathway that suppresses cancer growth, can be controlled by miR-125-5p, miR-33-5p, miR-190-5p (Pedroza-Torres et al. 2019).

In Fig. 16.2, each node represents one protein and the lines connecting the circles represent the interactions. It is evident that cancer may be caused by dysfunction of at least 200 proteins, whereas regeneration is ensured when at least 60 proteins work properly and interact with each other. The network comparison shows that almost 80% of proteins involved in regeneration are shared in cancer-causing pathways, and cancer is a much more complicated system than the process of regeneration. mRNAs/proteins found to be associated both in cancer and in regeneration (identified by the KEGG pathway) have been provided in Table 16.3 and corresponding references of each molecule and pathways have been provided in the respective sections of the chapter.

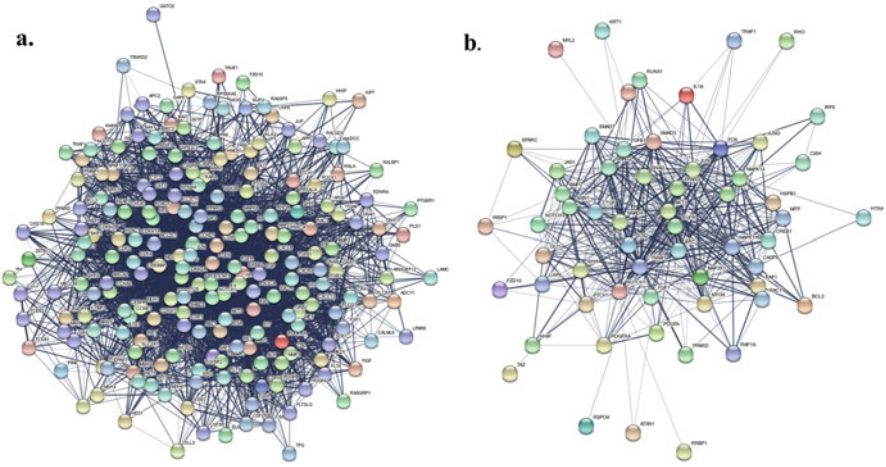

Fig. 16.2 Protein–protein interaction (PPI) network of proteins corresponding genes identified in KEGG pathway database for (**a**) cancer and (**b**) regenerative processes using string database (https://string-db.org/)

16.10 Applied Therapeutics

16.10.1 Regenerative Medicine

The human body has the ability to regenerate complex tissues to a limited extent. For example, the skin and the blood are continuously restored, and the bone, the muscle, the liver and the blood vessels have capacity to self-repair. However, they often fail to regenerate after extensive trauma or injury as they are capable of repairing only unicell lining like epidermis or intestinal mucosa. Regenerative medicine involves comprehending the complex regenerative mechanism in nature to enhance the restoration of tissue damage in the human body (Gurtner et al. 2007; Petit-Zeman 2001). Regenerative medicine is often mediated by the micro-environment that is mostly an extracellular matrix (ECM). ECM plays a significant role in the restoration by providing cell adhesion and transducing signals to dictate their function of cell migration, proliferation and cellular communication by various signalling mechanisms (Walker et al. 2018). For example, integrins, a transmembrane receptors bind to ECM by receptor-ligand binding regulates epidermal stem cell fate by regulating ERK and MAPK signalling and also by controlling orientation of spindle fibres (Watt and Fujiwara 2011). In addition, the sub-types of β integrin contribute to osteoclast migration in bone remodelling. Apart from this, the ECM-Cell adhesion mechanism, variation in signalling pathways, cytokines, growth factors, or other biomolecules lead to developing interesting therapeutic strategies for regenerative medicine which has to be evaluated in detail.

16.10.2 Cancer Therapy

As discussed earlier, mutations or defects of certain transcription factors (TF), signal modulators and other regulatory proteins cause cancer worldwide. Moreover, reports suggest that microenvironment homeostasis has a major role in tumour cell progression. Minimum change in concentration of ECM proteins especially collagen leads to cancer cell proliferation. During initiation of cancer progression, adjacent cancer-associated fibroblast secrete collagen and cancer cells at the site release lysyl oxidase (LOX) which causes cross-linking of collagen at tumour site and eventually increased integrin signalling leads to cancer proliferation over the matrix region (Walker et al. 2018). This makes an effort to use regenerative medicine in treating cancer to restore tissue homeostasis. Ongoing therapies like chemotherapy have been used to treat cancer for decades along with surgery and irradiation to eliminate cancer. These have several limitations in selection of the tumour cell over the normal cells, leading to deficient drug concentrations in tumours, systemic toxicity and development of drug resistance. Lately various strategies and formulations have emerged for cancer therapy per se, liposomal formulation, resistance modulation (e.g. PSC833), antidotes/toxicity modifiers (e.g. ICRF-187), monoclonal antibodies, cell-based therapy and gene therapy. Recent literature on targeted therapy using biomaterial-based delivery systems claimed the improved effectiveness in terms of specificity towards the tumour cells as well as their regulatory factors. These broad strategies in both preclinical and clinical therapeutics are classified into categories.

16.11 Biomaterial-Based Therapies

Synthetically engineered materials which mimic the native cellular environment can be considered as the biomaterials. These materials play an extensive role in providing a matrix environment in the damaged site to enhance cell attachment and proliferation. However, some of the earliest attempts of regenerative medicine included decellularized tissues and organs obtained from allogeneic or xenogeneic sources. Extracellular matrix remains the active component of such practices; of course, it is a biomaterial. Recently, in vitro grown tissue-constructs using organ specific cells grown on decellularized tissues were developed and propounded to be a more promising alternative to decellularized matrix alone in regenerative medicine. These decellularized grafts can further be transplanted into hosts to improve accurate function of the diseased organ. Decellularized materials without recellularization can also be used for the treatment of regeneration as they contain the matrix components like collagen and elastin to facilitate the growth of cells. The studies suggest that fish skin decellularized by hypertonic and hypotonic and triton solutions is similar to human skin properties and involves enhancing epithelial cell adhesion in decellularized material (Kamalvand et al. 2021). Recently, researchers reported perfusion-seeding and culture technique for decellularized liver matrix to attain a vascular matrix which are involved in circulation and facilitate oxygen and nutrient supply after transplantation (Uygun et al. 2010). This proves that decellularized

materials can be a potential strategy for regenerative medicine. However, due to the degradation of ECM proteins during decellularization, a loss in mechanical strength is shown.

Hence, fabrication of scaffold or hydrogel-like biomaterials using naturally derived ECM polymers (collagen, elastin etc.) or synthetic polymers (poly (ethylene glycol), Poly (lactic acid-*co*-glycolic acid) etc., act as ECM analogues and help in attaining the structural and functional properties of tissues. Additionally, these can also be utilized as a cargo medium for the persistent release of drug or growth factors. For example, injectable poly (ethylene glycol) PEG hydrogel was developed to deliver Avastin for ocular treatment (Yu et al. 2014). Polymers are biodegradable, enabling its replacement with the host tissue.

The field of tissue engineering and regenerative medicine is seeing a new age. The field of 3D bioprinting has emerged as a technique with high control over cell placement in the engineered structures (Mao and Mooney 2015). These structures have a definite altitudinal patterning of cells and other biomolecules which is based on computer-aided assembling in layer-by-layer tactic to develop a tissue or organ structure. Although 3D engineered structures attain the cellular assembling and structure of aimed tissue or organ, they fail to mimic the kinetics of usual vascularization and other cellular functions (Ozbolat 2015).

Moreover, biomaterial-based therapies have several limitations such as low engraftment and micro vascularization in engineered structures; lack of cellular signalling and function and limited organ donors are also rendering this therapy unattainable. Hence, incorporation of biomimetics with immune modulators will be a potential strategy to attain regenerative medicine feasibly.

16.12 Newer Therapeutic Aspects

16.12.1 Gene Therapy

The European Medicines Agency (EMA) explains gene therapy-based products or biological medical products as active substances consisting of nucleic acids in order to regulate or repair the genetic sequence and should also possess therapeutic, prophylactic or diagnostic effects on the host (Ma et al. 2020). In practice, this is a complex operation where the transgene should overcome several barriers to express in the target cell-nucleus. The ultimate goal of the regenerative medicine is to attain biocompatibility at the damaged tissue without immune rejection. It clearly emphasizes that modulating the immune system plays a prominent role in regulating regeneration by augmenting the healing process and engraftment (Eming et al. 2007). Processing of cells in regeneration indirectly induces immune response by releasing growth factors and cellular signalling. Cell therapy and gene therapy predominantly fall under the category of altering the immune system. Gene therapy includes techniques for passing the transgene through the plasma membrane and its entry into the cell nucleus without degradation (Luo and Saltzman 2000). Gene therapy is divided under two main subtypes based on the nature of target cells as

germline gene therapy and somatic gene therapy where former includes the transfer of functional gene in reproductive cells and the latter in non-reproductive cells which means modified expression is within the generation and will not pass on to the next generation as in germline gene therapy (Stribley et al. 2002). Nucleic acids involved in gene therapy are majorly plasmid DNA (pDNA) and various types of RNAs. Although pDNA-based studies have shown extensive results for decades, there are difficulties such as nuclear trafficking and low efficiency. Unlike pDNA, RNAs exercise their function only in cytoplasm thereby effectively transfecting cells (Wang et al. 2019b). Therefore, gene therapy using RNA is found to be more effective, and a number of researches are carried out on the same.

16.12.2 RNA-Based Therapy

RNA-based therapies involve both positive and negative regulation of RNA in cancer or regeneration as mentioned. Delivery of messenger RNA (mRNA) encoding regulatory proteins or growth factors of pathway end up in accelerating the pathway or the mechanism, whereas micro-RNA (miRNA) and small interfering RNA (siRNA) follow RNA interference (RNAi) mechanism of gene silencing. RNAi is the phenomenon of sequence-specific degradation of mRNA followed by suppression of associated biological function (Davidson and McCray 2011).

miRNA mediates post-transcriptional gene silencing, but before that it is processed via a complex engagement of endogenously expressed transcripts like drosha and dicer. This processed strand enters an RNA-induced silencing compartment (RISC) guided towards mRNA targets where it binds to the 3′UTR, and the pairing is highly complementary at seed regions of 2–8 base pairs. The miRNA–mRNA complex will be transported to cytoplasmic processing bodies where deadenylation and mRNA degradation takes place. Although miRNAs have an effective role in gene silencing, they have numerous target mRNAs. Hence, it is essential to screen the miRNA and their targets to attain specific function rather than targeting other targets (Elbashir et al. 2001).

The siRNAs are processed from double stranded RNA by dicer. They are 20–24 nucleotides in length. One strand is ‘passenger’ strand, and the other strand is ‘guide’ strand which initiates silencing by binding to mRNA with full complementarity. The cleavage occurs at the 10–12 base pairs from 5′ end of the siRNA binding site. siRNA differs from miRNA by their high complementarity to mRNA that helps in increased specificity towards the target (Zamore et al. 2000).

In most cases, nucleic acids are delivered with cationic or lipid-based complexes to the target site for gene silencing inside the cell. For example, ligand-targeted injection of siRNA with PEGylated poly-plex in tumour bearing mice shows anti-tumour effect with decreased uptake in the lung and the liver (Li and Huang 2006). Similarly, an appropriate delivery system for RNA therapeutics will help in achieving target-specific immune response by either enhancing or supressing the proliferation of cells.

16.12.3 Gene Delivery System

As gene therapy involves the transfer of nucleic acids, it is essential to ensure its reach in the target site without degradation as they are very sensitive to nucleases and their expression after binding to the site. The pertinent delivery system which gives the cellular environment will help in preventing denaturation of nucleic acids. It also satisfies several features.

- It should not involve in immune response and deliver genetic cargo in sustained manner which leads controlled expression.
- It should prevent biodegradation and help in target-specific release.
- It should be inexpensive and commercially available (Ibraheem et al. 2014).

16.12.3.1 Viral Vectors

A virus is a pathogenic microorganism that can survive by releasing their genetic material in the host organism to replicate and transmit to the adjacent cells (Kay et al. 2001). Researchers use their mechanism to carry therapeutic RNA into the nucleus as vectors. These viruses should be modified by genetic engineering to use as a vector. The pathogenicity of the virus is killed and replaced by therapeutic genes (Bouard et al. 2009). However, it retains the ability to infect the cell. These modified viruses are known to be viral vectors which have high transfection efficiency and thus are used till date. But they have certain drawbacks as follows:

1. It causes acute immune responses which can be fatal.
2. The large-scale production of viral vectors is very challenging and highly expensive.
3. The limitations in the size of genes that can be transported by the virus (Nagasaki and Shinkai 2007).

The commonly used viral vectors are retroviruses, adenoviruses, adeno-associated viruses (AAV) and simple herpes virus (Walther and Stein 2000).

16.12.3.2 Non-Viral Vectors

The limitations of viral vectors specifically to severe acute reaction have led to finding safer replacements. Non-viral vectors are safer, cause lower acute response, are inexpensive, and can be prepared in large quantities efficiently. Additionally, they have larger stability and can transfer genes of various sizes (Munier et al. 2005). But because of their low transfection efficiency, they cannot be produced on a large scale. Non-viral vector systems are classed into two groups as physical methods in which nucleic acid (DNA, -miRNA, siRNA) is delivered without any carrier, by preparing competent cell to enhance the permeability of transgene using physical forces (Gao et al. 2007) and chemical methods wherein nucleic acid is transfected into the vector of biological or synthetic origin. The principle of physico-chemical methods of biomolecule delivery which are emphasized in RNA theraupeutics are further elucidated in detail.

Electroporation

This physical technique termed as electro-permeabilization or electric pulse-based gene transfer is a technique in which an electric pulse is used to infuse DNA into viable cells (Golberg 2020). Electroporation is a process of increasing the cell permeability under controlled electric fields to stimulate the uptake of injected DNA into the cell (Niidome and Huang 2002). This effect of electric pulse causes temporary destabilization of the cell membrane, allowing DNA to enter the cell easily. Both physical factors like pulse duration, field intensity and electrode geometry and biological factors such as cell size, shape and density affect the efficacy of gene transfer. Although electroporation in the nucleic acid delivery system has advantages of safety and efficiency, its use in vivo is limited because of difficulties in transferring DNA to large tissue areas, requires surgery to apply electrodes in organs and causes incurable harm in the treated tissues.

Gene Gun

Gene gun technology was first employed in 1987 to present genes into cells (Gehl 2003). It's basically a technique which delivers transgene into a cell or tissue using accelerated particle carriers which are biocompatible heavy metals like gold, tungsten and silver. These carriers should be inactive and smaller in size of about 1–1.5 μm (Mehier-Humbert and Guy 2005). These carriers are treated with plasmid DNA by providing needed acceleration by either vaporizing water under high-voltage electric spark or using helium discharge (Ibraheem et al. 2014). This method can be hired in most fields such as genetic vaccination, immune therapy and suicide gene therapy to treat cancer (Lin et al. 2000). Gene gun transfer method offers many advantages like higher and sustained gene expression (Ajiki et al. 2003) as well as it is achieved without injury to the surrounding cells (Muangmoonchai et al. 2002). Due to its poor competence while transferring the entire gene into tissue by penetration of metal particles, surgery is often needed for deep tissues.

Inorganic Particles

Inorganic particles involve nanomaterials that can be synthesized in varying their physical nature in order to make entrapped molecules survive from degradation by the immune system. Calcium sulphate, silica, gold and magnetic compounds are some of the most commonly studied inorganic particles.

1. Calcium: Initially used delivery systems are calcium phosphate particles as it has a vital role in cellular signalling, it has the benefit of passing through the membrane by receptors, and also has high binding affinity in the cell. They are highly biocompatible and biodegradable. However, calcium phosphate nanocrystals cannot be stored as it grows with time, a drawback which was later overcome by combining other particles.
2. Silica: One of the major components of sand and glass, which are widely used in our daily life. It is used as a gene delivery vehicle because it is relatively easy to functionalize with amino silicanes due to its minimal toxicity. However, the limiting factor is its reduced delivery efficacy in media containing serum as due to non-specific binding.

3. Magnetic nanoparticles, such as (like magnetite), soluble carbon molecules, carbon nanotubes, quantum dots and supramolecular systems, are claiming some promising results in in vitro as well as in animal models. In these nanoparticles, DNA binding is aided by the coating which is applied on the surface. Small particle size helps in passing most of the cell membrane barriers to generate excessive transfection efficiency. However, reviews are required on chronic reactions of safety, plane functionalization effect on physical characterization, its transfection efficiency etc., to improve its clinical application (Al-Dosari and Gao 2009).

Lipid-Based Therapy

Several classes of lipid-based formulations are opted for the delivery of RNA notably liposomes, solid lipid nanoparticles, and nanostructured lipid carriers. Unlike other lipid-based systems, liposomes can be used for loading hydrophilic and ionic molecules. It undergoes similar transportation of fusing into plasma membranes like other biomolecules to reach the target cell then bear endocytosis process to release their drug or nucleic acids in cytoplasm. Cationic liposomes complexed with anionic siRNA forms 'lipoplex' which provides stability of the siRNA. However these cationic liposomes react with negatively charged proteins causes non-specific interactions. Hence, to reduce these complications, PEGylations can be applied on the surfaces that help in enhancing half-life siRNA. Also, pH-sensitive liposomes can be formulated by phosphatidylethanolamine (PE) with pH-sensitive lipids (Fan et al. 2017). This formulation helps in delivering the molecules or drug in low pH microenvironments like tumour sites. RNAi molecules can be incorporated into solid lipid nanoparticles (SLNs) to provide a sustained release to the targeted cell. Nanostructured lipid carriers are modified formulations of SLN where lipid is either solid phase or in liquid phase but in SLNs it is solid core. These can be surrounded by surfactants which give positive surface potential to bind with nucleic acids. Compared to SLNs, nanostructured carriers have high loading space so that combinations of siRNA can also be transported by nanostructured lipid carriers.

Polymer-Based Therapy

Polymers of an amine group when modified to cationic can be used for RNA delivery via electrostatic interaction of RNA and polymers to form a complex. These can be chemically modified to attain biocompatibility. For example, nanoparticles synthesized with PEG-grafted PEI (polyethylenimine) deliver mRNA into lung cells (Ke et al. 2020). Another class of cationic polymers, poly (beta amino esters) PBAEs are prepared by coupling amine monomers to diacrylates to improve biodegradation and cytotoxicity relative to amine group polymers. These PBAEs are used to deliver siRNA to tumour mice models (Kozielski et al. 2019). Research on lipid-PBAE's hybrid polymer synthesis shows improved serum stability and delivery. Dendrimers consisting of branched monomers are also used for RNA delivery when synthesized with cationic groups to form a complex. In addition, its structure has been modified to resist enzyme degradation of nucleic acids. Alkyl

substituted amines with dendrimer-based nanoparticles deliver siRNA to endothelial and hepatocytes in vivo (Khan et al. 2014).

Extracellular vesicles secreted by cells are considered as micro-vesicles (100–1000 nm), exosomes (40–100 nm), or apoptotic bodies (1–4 μm) based on their size range. Exosomes can be isolated from mesenchymal stem cells (MSCs), epithelial cells, mast cells, dendritic cells, even cancer cells and purified by ultrafiltration followed by affinity purification. Exosomes include different transmembrane proteins, heat shock proteins and around 1300 types of RNAs and miRNAs. Most of the functional miRNAs found in exosomes undergo RNAi. Hence, it emerged as a natural carrier for RNAi molecule delivery due to their non-immunogenicity and stability. Native miRNA of the exosomes or miRNA and siRNA can be transfected to exosomes, and they are transported to the target cell by ligand-receptor mechanism via endocytosis (Yu et al. 2016). For example, the upregulation of exosomal miR-146a downregulates Erbb4, Notch1 and Irak1, which leads to a decreased metabolism and improper contractile function in cardiomyocyte; it also inhibits angiogenesis by downregulating TNF receptor-associated factor 6 (TRAF6) expression (Ailawadi et al. 2015). Researchers proved the effective delivery of siRNA by exosomes to silence the functional oncogenes in head and neck cancer. Exosome/transient receptor potential polycystic 2 (TRPP2) siRNA complexes inhibit the expression of TRPP2 in FaDu cells, a cell line of human pharyngeal squamous cell carcinoma (Wang et al. 2019a).

16.13 Cell Therapy

16.13.1 Stem Cell Therapy

Stem cell therapy has proved itself as a non-replaceable and unique candidate for cancer therapeutics because of its regenerative potential and enhanced target on tumours. Although iPSC has evolved as compensation for embryonic stem cell (ESC) application because of ethical barriers, enough studies proved the use of adult stem cells like mesenchymal stem cell (MSC), haematopoietic stem cell (HSC) and neural stem cell (NSC) (Chu et al. 2020). The migration of HSC into their defined niches, called the homing process, leads to an engraftment of marrow tissues. This process occurs prior to differentiation into specialized blood cells. The molecular mechanism of HSC homing process involves an association between stem cell CXCR4 receptor and gradient SDF-1 secreted from the cells lining the bone marrow niches. Similarly, another mechanism is the tumour tropic effect, which involves the secretion of various chemoattractant factors that favour the movement of MSC into the tumour microenvironment. Apart from the above two mechanisms, other mechanisms are paracrine factors secreted from stem cells (Vakhshiteh et al. 2019) and CSC signalling. Researchers are using the above properties of stem cells by different means to use for therapeutic applications. The strategy of using stem cells as therapeutics in HSC transplantation, MSC transplantation after cancer treatment, will show the advantages over side effects, efficiency and degradation

due to the intrinsic tumour-targeting effect of stem cells, genetically modified stem cells, stem cell-derived exosomes, nanoparticles carrying stem cells and stem cell-based anti-cancer vaccine which can be created from oncofetal protein, CSC/ESC, or iPSC-based whole cells.

16.13.2 CAR-T Cells Therapy

Chimeric antigen receptor (CAR) T cell therapy is a class of immunotherapy which employs in the cancer treatment domain. CAR T cell therapy edit the immune response of T cell to produce a receptor which is specific for tumour antigen. In this immunotherapy procedure, autologous T cells are isolated from the sufferer then it is harvested in ex vivo. All the harvested cells undergo viral and non-viral transfection by which T cells are genetically transformed to produce antigen receptors. Once CAR-T cells are able to synthesize the product, these cells are transfused back to the patient body (Gross et al. 1989). CARs possess antigen binding moiety and spacer on their outer cell membrane. Single chain fragment variable (scFv) is a variable monoclonal antibodies which derived from human Abs, humanized Abs, or mouse monoclonal antibody(mAbs) which displayed on the outer membrane and are able to act against tumour-associated antigens (TAAs) (Sadelain et al. 2013). CAR T cell does not follow antigen processing and presentation (MHC class I and class II restriction) directly but CD4+ and CD8+ subset recognize processing antigen from the tumour cell. CD4+ and CD8+ identify the carcinogenic cell and do cytolysis by granzyme and perforin exocytosis (Miliotou and Papadopoulou 2018).

16.13.3 NK Cells-Based Therapy

Natural killer cells are group-I lymphocytes, which control many infections, tumours by preventing their spread and damage through their innate cytotoxicity. They detect various cell-surface receptors and identify healthy cells and self-cells from the other cells. The property of cytotoxicity has been exploited in the past few years to develop many mechanisms. They can be activated by distress by stress-induced ligands like KNG2D, Toll-like receptor ligands. NK cells can show MHC class-I-specific receptors and fail to receive inhibitory signals when they interact with class-I-deficient haematopoietic cells. This means that NK cells can recognize the missing 'self'. The inhibitory receptors have killer cell immunoglobulin-like receptors (KIRs), CD94-NKG2A heterodimers (Vivier et al. 2008).

NK cells act as the first line of defence by playing two major roles—cytotoxic effect and immune regulation. Because of their capability to act in the absence of MHC immunosurveillance, they can function as cancer suppressors. But they can also get suppressed because of surrounding factors in a tumour microenvironment. The suppression itself denotes that NK cells are representing a site of tumour or cancer, thus making them promising strategies for immunotherapy. NK cells are

stimulated killing activating receptors (KARs) which in turn induce ligands-like tumour necrosis factor-alpha (TNFα), Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL) and lead to activate apoptotic pathway. They diagnose and cause cell death in unhealthy cells by perforin and granzymes. They have higher cytotoxicity as compared to other cells, which makes them more resistant to cancer cells and have higher immune surveillance capability. The different therapeutic approaches using NK cells are allogeneic cell infusion therapy to trigger alloreactivity of NK cells, enhancing activity through cytokines IL-2 or IL-15 and inhibiting checkpoints of immune response by releasing dominant inhibition, blocking immune tolerance signal, or targeting emerging inhibitory checkpoints to induce the activity of NK cells in vivo (Du et al. 2021).

16.14 Conclusion

It is believed that every minute several cancer cells are born in the human body. Cell division events in regenerative processes occur even more frequently. Almost all the molecular tools used for regenerative processes could be misused for cancer development. Analogously, it can be put as cancer rides on the same horse as regeneration does, however, with diminished systemic controls. Yet, all of the human population may not die of cancer. That indicates homeostatic mechanisms of the human body have the ability to pull back the reign to maintain order and reverse the cancerous condition. This discipline is imposed at many scales viz., molecular scale, molecular-network scale, cellular scale and systemic scale.

The general idea is, genetic mutation followed by malfunctioning molecules results in a tumour cell formation. Proteins like p53, cyclins, Wnt, members of Hippo, Ras-raf and PI3K, pathways often promote regeneration and homeostasis. However, such proteins, upon miscoding or malfunctioning, promote cancerous growth. At a cellular scale and systemic scale, immune cells that are generally trained to eliminate cancerous phenotypes start supporting the growth of cancer tissues, when stimulated with certain cytokines that in turn might be the result of malfunctioning proteins sitting inside a cancer cell. However, certain proteins such as certain caspases, mTORs, p21, certain FGFs and some of the Yamanaka factors seem to have an exclusive role in regeneration. They also have a crucial role in embryonic development as well. Talking about embryology, gene and gene products such as hox and polycomb have exclusive roles in early developmental stages. Effectively modulating these genes for the purpose of regenerative medicine is a herculean challenge in recent times.

At an intra-cellular molecular scale, miRNAs have newfound but crucial regulatory roles. They can modulate the overall molecular interaction network and derive desirable epigenetic changes. These changes are brought however by modulating the translation of many of the aforesaid proteins. Many miRNAs are now being discovered having crucial roles in promoting regeneration and inhibiting cancer progression and vice versa. Cellular scale controls, however, include autophagic cell deaths that are usually meant for maintaining tissue homeostasis. Dysregulation of certain

autophagic mediators can cause chaos in the surrounding tissues. Similarly, the pro-tissue role of ECM can turn wry and pro-cancerous if its composition varies. This can happen due to paracrine actions of surrounding cells. Systemic restrictions on cancer cells and promotion of regeneration are mostly exerted by the nervous and immune systems as identified in lower vertebrates like amphibians. However, tumorigenic events in the said systems bring out the most complex challenges.

In cancer therapy and regenerative medicine, the most promising therapy is cell therapy. As discussed earlier, this included stem cells, gene-corrected cells, gene-overexpressed cells and immune cells, with a mode of delivery being primarily local or systemic injection. Immunomodulation or immune-restoration aiming cell therapies generally designed for cancer treatment nowadays are identified as regenerative medicine because the end result is regeneration or restoration of a normal immune system. This is achieved mostly by cell therapeutic strategies. However, cell therapy has not been able to deliver the desired results.

Molecular therapy in both the cases depended on identification of right molecular targets followed by right molecules and right modalities to deliver it. The rawest form appears in the form of ECM therapy, performed in most regenerative medicine approaches. In addition, protein therapies using a varied formulation are explored as an effective mechanism. Proteins, such as FGFs, BMPs, TGFs and monoclonal antibodies targeted to inhibit specific pathways are mostly in use. Gene- or nucleic acid-based therapy, using a viral vector or non-viral delivery systems, has been recently and most successfully explored in COVID19 vaccination in many countries. The scepticism underlying the safety of nucleic acid medication has majorly been cleared up with the pandemic. This opens an opportunity to explore stringently designed pDNA, mRNA, snRNA and miRNA molecules for cancer therapy and regenerative medicine.

The confusions and dilemmas are mostly cleared up. Cancer and regeneration that originally seemed to be a mesh of convoluted crossroads alone actually have certain segregated flyovers. Careful selection of bypasses and therapeutics most likely will land us in mutually exclusive destinations.

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