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REVIEW

Stem cell guidance through the mechanistic target of rapamycin

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Abstract

Stem cells offer great promise for the treatment of multiple disorders throughout the body. Critical to this premise is the ability to govern stem cell pluripotency, proliferation, and differentiation. The mechanistic target of rapamycin (mTOR), 289-kDa serine/threonine protein kinase, that is a vital component of mTOR Complex 1 and mTOR Complex 2 represents a critical pathway for the oversight of stem cell maintenance. mTOR can control the programmed cell death pathways of autophagy and apoptosis that can yield variable outcomes in stem cell survival and be reliant upon proliferative pathways that include Wnt signaling, Wnt1 inducible signaling pathway protein 1 (WISP1), silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1), and trophic factors. mTOR also is a necessary component for the early development and establishment of stem cells as well as having a significant impact in the regulation of the maturation of specific cell phenotypes. Yet, as a proliferative agent, mTOR can not only foster cancer stem cell development and tumorigenesis, but also mediate cell senescence under certain conditions to limit invasive cancer growth. mTOR offers an exciting target for the oversight of stem cell therapies but requires careful consideration of the diverse clinical outcomes that can be fueled by mTOR signaling pathways.

Key words: Apoptosis; Autophagy; Cancer; Cardiovascular; Erythropoietin; Mechanistic target of rapamycin; Neurodegeneration; Progenitor stem cells; Silent mating type information regulation 2 homolog; Wnt1 inducible signaling pathway; Wnt

Core tip: Mechanistic target of rapamycin, the mechanistic target of rapamycin, can directly impact stem cell maintenance, proliferation, and differentiation to offer new therapeutic strategies for multiple disease entities.

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MECHANISTIC TARGET OF RAPAMYCIN SIGNALING

The mechanistic target of rapamycin (mTOR) is a

289-kDa serine/threonine protein kinase that is encoded by a single gene *FRAP1*[1,2]. mTOR, also known as the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1, oversees a complex array of cellular functions that involve gene transcription, cellular proliferation, senescence, metabolism, survival, and cellular death. The target of rapamycin (TOR) was initially identified in *Saccharomyces cerevisiae* with the genes *TOR1* and *TOR2* that encode two isoforms in yeast Tor1 and Tor2 through the use of rapamycin-resistant TOR mutants[3]. Rapamycin is a macrolide antibiotic derived from *Streptomyces hygroscopicus* that that can inhibit TOR as well as mTOR activity.

mTOR is a vital component for the function of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) (Figure 1)[4-7]. Rapamycin primarily inhibits mTORC1 by blocking mTOR phosphorylation[8]. However, mTORC2 activity can be limited during chronic administration of rapamycin. mTORC1 is composed of Raptor (Regulatory-Associated Protein of mTOR), the proline rich Akt substrate 40 kDa (PRAS40), Deptor (DEP domain-containing mTOR interacting protein), and mLST8/GβL (mammalian lethal with Sec13 protein 8, termed mLST8). Phosphorylation of Raptor through the protein Ras homologue enriched in brain (Rheb) leads to mTORC1 activation. PRAS40 is inhibitory to mTOR activity and can prevent the binding of mTORC1 to Raptor[9]. Phosphorylation of PRAS40 by protein kinase B (Akt) frees PRAS40 from Raptor and allows PRAS40 to be sequestered by the cytoplasmic docking protein 14-3-3 to activate mTORC1[4-7]. Similar to PRAS40, Deptor inhibits mTORC1 activity through the binding of the FAT domain of mTOR (for FKBP associated protein, Ataxia-telangiectasia, and Transactivation/transformation domain-associated protein). In contrast to PRAS40 and Deptor, mLST8 fosters mTOR kinase activity through p70 ribosomal S6 kinase (p70S6K) and the eukaryotic initiation factor 4E (eIF4E)-binding protein 1 (4EBP1) that bind to Raptor[10]. PRAS40 can block mTORC1 activity by preventing p70S6K and 4EBP1 to associate with Raptor[9,11].

mTOR activity also is controlled by Akt and AMP activated protein kinase (AMPK) through the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex (Figure 1)[12,13]. TSC2 is considered to be a principal site to govern the activity of the TSC1/TSC2 complex that is an inhibitor of mTORC1. As a GTPase-activating protein (GAP) that can convert Ras homologue enriched in brain (Rheb-GTP) to the inactive GDP-bound form (Rheb-GDP), TSC2 prevents the activity of Rheb-GTP and blocks mTORC1 activity by limiting binding of 4EBP1 to mTORC1. Akt can phosphorylate TSC2 to disrupt the TSC1/TSC2 complex, force TSC2 to be sequestered by the cytoplasmic protein 14-3-3, and activate mTORC1[14]. It should be noted that under some cellular protection scenarios, a limited activity of TSC2 as well as AMPK appears necessary since complete knockdown of TSC2 can prevent cellular protection[15].

AMPK also provides a mechanism to control the activity of the TSC1/TSC2 complex, but in contrast to Akt serves to promote TSC2 activity and block mTORC1 function. AMPK phosphorylates TSC2 to enhance GAP activity to process Rheb-GTP into Rheb-GDP that can then block mTORC1 activity. Interestingly, AMPK can influence sirtuin (silent mating type information regulation 2 homolog) 1 (*S. cerevisiae*) (SIRT1) activity that can be critical for stem cell survival and proliferation[16]. AMPK increases the cellular NAD^+/NADH ratio that results in the deacetylation of the SIRT1 targets peroxisome proliferator-activated receptor-gamma coactivator 1 (PGC-1α) and forkhead transcription factors FoxO1[17] and FoxO3a[18]. AMPK also can increase nicotinamide phosphoribosyltransferase (NAMPT) activity that catalyzes the conversion of nicotinamide to nicotinamide mononucleotide[19], increases nicotinamide adenine dinucleotide (NAD^+) levels, decreases levels of the SIRT1 inhibitor nicotinamide, and promotes SIRT1 transcription[20-22]. SIRT1 up-regulation in combination with AMPK activation promotes the induction of autophagy that can protect endothelial cells exposed to oxidized low-density lipoproteins[23]. Similar to AMPK that is an inhibitor of mTOR, SIRT1 appears to exert its effects over cellular proliferation through blockade of mTOR[24]. SIRT1 inhibits mTOR activity to preserve the integrity of embryonic stem cells during oxidant stress[25]. SIRT1 also inhibits mTOR signaling to foster neuronal growth[26] and assist with mesangial cell proliferation during high glucose exposure[27].

In relation to mTORC2, this complex consists of Rictor (Rapamycin-Insensitive Companion of mTOR), mLST8, Deptor, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1)[28-33]. Rictor and mSIN1 through mTORC2 can activate Akt to promote cell survival[11,29,34]. Protor-1 is a Rictor-binding subunit of mTORC2 and is believed to activate serum and glucocorticoid induced protein kinase 1 (SGK1), since loss of Protor-1 reduces the hydrophobic motif phosphorylation of SGK1 and the substrate N-Myc down-regulated gene 1 in the kidney (NRDG1)[35]. mTORC2 is a member of the protein kinase A/protein kinase G/protein kinase C (AGC) family of protein kinases and is activated by growth factors to control ion transport. mTORC2 also controls cytoskeleton remodeling through protein kinase C-α (PKCα) and oversees cell migration through the Rac guanine nucleotide exchange factors P-Rex1 and P-Rex2 and through Rho signaling. In contrast to mTORC1, mTORC2 is activated by the TSC1/TSC2 complex through the N-terminal region of TSC2 and the C-terminal region of Rictor[36].

MECHANISTIC TARGET OF RAPAMYCIN AND STEM CELL PROGRAMMED CELL DEATH

mTOR is an important component in the control of

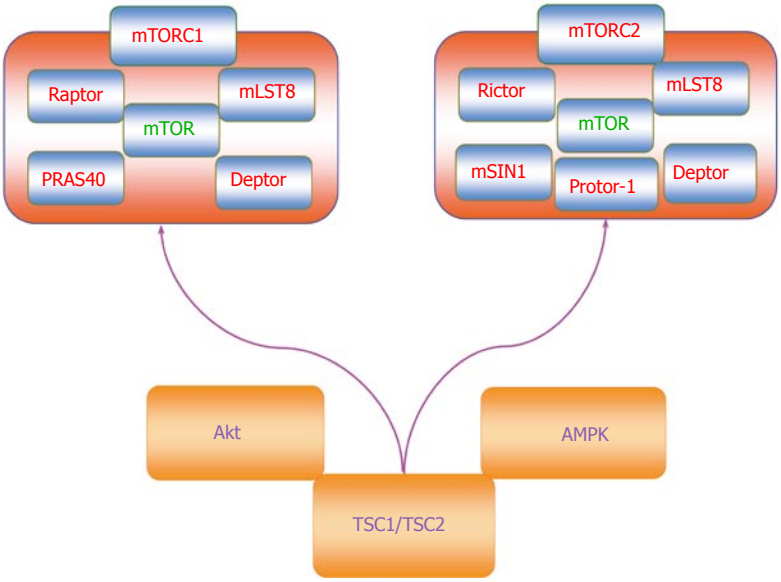

Figure 1 The components of the mechanistic target of rapamycin regulatory pathways. The mechanistic target of rapamycin (mTOR) is an important component of mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2). The function and activity of mTOR is controlled by multiple pathways that include protein kinase B (Akt), AMP activated protein kinase (AMPK), and the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex. mTORC1 is consists of Raptor (Regulatory-Associated Protein of mTOR), the proline rich Akt substrate 40 kDa (PRAS40), Deptor (DEP domain-containing mTOR interacting protein), and mLST8/GβL (mammalian lethal with Sec13 protein 8, termed mLST8). mTORC2 is composed of Rictor (Rapamycin-Insensitive Companion of mTOR), mLST8, Deptor, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1).

programmed cell death that involves autophagy and apoptosis for stem cell proliferation and survival (Figure 2). The process of autophagy recycles cytoplasmic components to remove defective organelles that can no longer be used by the cell[37]. Autophagy has three categories of chaperone-mediated autophagy, microautophagy, and macroautophagy[38]. Chaperone-mediated autophagy uses cytosolic chaperones that transport cytoplasmic components across lysosomal membranes[39]. Microautophagy sequesters components of the cytoplasm through invagination of the lysosomal membrane for digestion[40]. The most prevalent of the three categories is macroautophagy that sequesters cytoplasmic proteins and organelles into autophagosomes. These autophagosomes then fuse with lysosomes for degradation and are recycled for future use[24,41].

In yeast and mammalians, TOR and mTOR are associated with genes that control autophagy[4,6,42]. At least 33 autophagic related genes (*Atg*) have been identified in yeast that can affect multiple disorders including cancer, diabetes, vascular disease, and neurodegenerative disorders[37,38,40,43-48]. In this group, Atg1 and Atg13 (also known as Apg13) are associated with phosphoinositide 3-kinase (PI 3-K), Akt, and the TOR pathways. When Atg13 is dephosphorylated such as during starvation, Atg1 is active to promote autophagy. Phosphorylation of Atg13 through a TOR dependent pathway releases it from Atg1 and lessens Atg1 activity. In mammals, the homologues of Atg1 are UNC-51 like kinase 1 (ULK1) and ULK2[4]. Mammalian Atg13 binds to ULK1, ULK2, and FIP200 (focal adhesion kinase family interacting protein of 200 kDa) to activate ULKs, promote phosphorylation of FIP200 by ULKs, and lead to the induction of autophagy[49]. Activation of mTOR prevents the induction of autophagy by phosphorylating Atg13 and ULKs to inhibit the ULK-Atg13-FIP200 complex.

Autophagy can become a vital determinant for stem cell survival and proliferation. In some stem cell populations, activation of autophagy can lead to stem cell demise. Breast cancer stem cells have been shown to succumb to apoptosis during the activation of autophagy and the inhibition of Wnt signaling[46]. Wnt proteins are cysteine-rich glycosylated proteins that oversee stem cell proliferation and tumor cell growth[50-56]. Reduction in autophagy also may prevent the development of cellular senescence[57]. Endothelial progenitor cells that lead to the regeneration of vascular endothelium become dysfunctional during exposure to elevated glucose as a result of autophagy activity[58].

However, under other conditions, autophagy appears critical for stem cell survival. In endothelial progenitor cells, SIRT1 activity prevents apoptotic cell death during oxidative stress through the induction of autophagy[59]. In human embryonic stem cells challenged with oxidative stress, autophagy was found to be protective and required SIRT1 activity with the down-regulation of mTOR[25]. Furthermore, activation of SIRT1 is necessary to promote autophagy to maintain proteostasis, produce energy during nutrient deprivation, and maintain muscle stem cell activation[60]. In such cases, SIRT1 may have an inverse relationship with mTOR to foster stem cell survival[16,20].

The programmed cell death pathway of apoptosis also has an important role with mTOR signaling and

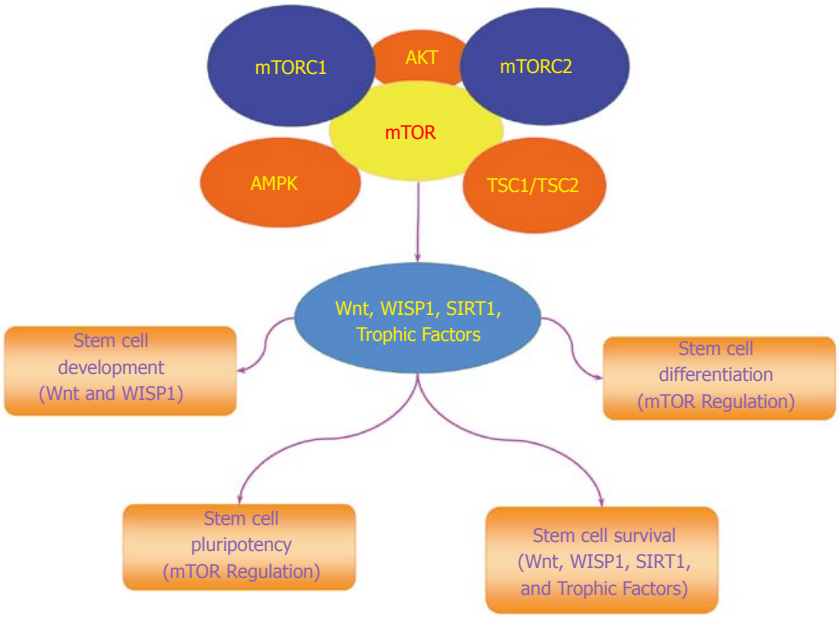

Figure 2 Mechanistic target of rapamycin governs stem cell development, pluripotency, survival, and differentiation. The mechanistic target of rapamycin (mTOR), mTOR Complex 1 (mTORC1), mTOR Complex 2 (mTORC2), protein kinase B (Akt), AMP activated protein kinase (AMPK), and the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex each play a role in stem cell development and proliferation with downstream pathways. Stem cell maintenance and survival is reliant upon mTOR signaling pathways that work in concert with Wnt signaling, Wnt1 inducible signaling pathway protein 1 (WISP1), silent mating type information regulation 2 homolog) 1 (*S. cerevisiae*) (SIRT1), and trophic factors such as erythropoietin (EPO). Stem cell development is under the regulation of Wnt and WISP1. Regulation of mTOR can control stem cell differentiation and stem cell pluripotency. As a result, mTOR signaling pathways have oversight of stem cell development, pluripotency, survival, and differentiation.

stem cell survival[61]. During the early stages of apoptotic cell injury, the loss of plasma membrane lipid phosphatidylserine (PS) asymmetry occurs[62-64]. If membrane PS externalization is not reversed and allowed to remain, inflammatory cells are activated that seek out membrane PS positive cells to engulf and remove these cells. Under such circumstances, these membrane PS positive cells may remain functional but their ultimate loss leads to tissue injury[65-71]. During the later phase of apoptotic cell injury, cellular DNA is destroyed which is usually not considered a reversible process[72-75]. During most conditions, activation of mTOR and its related pathways of PI 3-K and Akt can block apoptotic cell death in stem cells. Inhibition of mTOR, such as with rapamycin, leads to endothelial progenitor cell apoptotic death that may be related to inhibition of growth factor signaling[76]. Growth factors that include erythropoietin (EPO)[77,78] are cytoprotective against apoptosis through mTOR activity against sepsis-associated encephalopathy[79], oxidative stress[80], cerebral microglial injury[81], and beta-amyloid (Aβ) toxicity[82]. EPO has been shown to protect retinal progenitor cells from apoptotic cell death during oxidative stress through activation of the PI 3-K, Akt, and mTOR pathways (Figure 2)[83]. Interestingly, protection with EPO and mTOR may be lost with high exogenous EPO concentrations, since elevated concentrations of EPO result in decreased phosphorylation and activity of mTOR with subsequent increased apoptotic cell death[84]. Similar to EPO, other growth factors rely upon mTOR to maintain stem cell integrity (Figure 2). In murine experimental models, mTOR is used by the growth factors epidermal growth factor (EGF) and fibroblast growth factor (FGF) that are protective of stem cells and neurons[85-89] to maintain the proliferation of neural stem and progenitor cells[90]. EGF also uses the PI 3-K, Akt, and mTOR pathways to block cell injury such as during metabolic stress[91] and prevent memory impairment[92]. The growth factor brain derived neurotrophic factor (BDNF) relies upon mTOR activation for memory consolidation[93]. However, in some experimental models with growth factors, mTOR blockade with the induction of autophagy may take precedent over the inhibition of apoptosis to prevent cellular injury. During oxygen deprivation, cortical neurons are protected by BDNF through the induction of autophagy and the inhibition of mTOR[94].

MECHANISTIC TARGET OF RAPAMYCIN CONTROL OF STEM CELL PROLIFERATION AND MAINTENANCE

mTOR governs the proliferation and maintenance of stem cell in multiple systems of the body (Figure 2)[4]. The loss of the *mTOR* gene leads to limited trophoblast growth, faulty implantation, and inability to establish embryonic stem cells[95]. A decrease in proliferation of embryonic stem cells occurs during the deletion of the C-terminal six amino acids of mTOR that blocks the kinase activity of mTOR[96]. mTOR can maintain long-term undifferentiated growth of human embryonic

stem cells. Inhibition of mTOR promotes pluripotency, cell proliferation, and blocks mesoderm and endoderm activities in embryonic stem cells[97]. mTOR activity also leads to mesenchymal stem cell senescence[98]. Yet, under some conditions, activation of mTOR signaling components can lead to cell differentiation. In embryonic stem cells, mTOR signaling with p70S6K is limited, but once this signaling is increased, differentiation ensues[99].

In the nervous system, loss of mTORC1 activity in neural stem cells leads to reduced lineage expansion, prevention of differentiation, and blocked neuronal production[100]. Loss of mTOR activity during aging may influence decreased neurogenesis. In the aged brain, mTOR signaling is reduced which leads to a reduction in the proliferation of active neural stem cells[101]. mTOR activity appears important for the timing and control of neurogenesis. Inhibition of mTOR through the RTP801/REDD1 pathway delays neuronal differentiation. However, in newborn and mature neurons, levels of RTP801/REDD1 are diminished with increased mTOR activity to allow for the maturation of neurons[102]. Expression of mTOR is necessary for the neuronal phenotype of post mortem neuronal precursors[103]. Yet, the degree of mTOR activity may independently affect different populations of stem cells since in this model inhibition of mTOR activity leads to cell differentiation into astrocytic cells[90]. Akt and mTORC1 inhibition also has been shown to result in reduced neuronal stem cell self-renewal and earlier neuronal and astroglial differentiation[104]. Neighboring cells also may influence the growth of neuronal stem cells. Endothelial cells can promote mTOR activity and lead to the expansion of long-term glioblastoma stem-like cells[105].

In the cardiovascular system, mTOR is one of several components necessary for the proliferation of human embryonic stem cell-derived cardiomyocytes[106]. The activity of mTOR also controls the proliferation of hematopoietic stem and progenitor cells[107]. Maintenance of hematopoietic stem cells and inhibiting differentiation is tied to mTOR signaling and the reduction in phosphorylation of p70S6K[108]. Failure of endothelial progenitor cell development may be the result of decreased growth factor signaling and loss of mTOR activity[76]. Growth factors such as EPO have been shown to require mTOR activation to regulate bone homeostasis with osteoblastogenesis and osteoclastogenesis[109]. Differentiation of neural precursor cells that may be used for neurodegenerative disorders also is dependent upon EPO and mTOR[103]. mTOR may be necessary to increase angiogenesis from endothelial progenitor cells that may provide neuroprotection during cerebral ischemia[110]. The ability of human amniotic fluid stem cells to influence the differentiation of embryonic kidney cells is dependent upon mTOR activity[111].

During tumorigenesis, mTOR activation may affect neural precursor and oligodendroglial precursor cells to promote high-grade glioma proliferation[112]. Blockade of mTOR can prevent the conversion of astrocytoma cells to oligodendroglioma cells that can lead to glioblastoma multiforme[113]. Inhibition of mTOR signaling may reduce the population of cancer stem cells that can lead to disease recurrence and therapeutic resistance[114].

Under some conditions, mTOR may be protective against tumor cell growth by inhibiting proliferative pathways of Wnt. Wnt signaling can lead to rapid cell proliferation and cancerous growth, but in epithelial stem cells this process is blocked by mTOR that maintains cell senescence and prevents tumor growth[115]. Wnt may result in malignant melanoma[116], metastatic disease[117-120], and glioma proliferation[121,122]. It should be recognized that Wnt signaling also leads to beneficial and cytoprotective effects[52,54,123-125]. Loss of Wnt can result in human monocyte injury[126], impairment in bone repair[127], spinal cord injury[125], loss of neurogenesis[128], inhibition of wound healing[129], loss of stem cell differentiation[130], programmed cell death[38,66,131], and defects in placental development[132]. Wnt signaling activation can block inflammatory cell loss during neurodegenerative disorders[66,70,82,133], prevent cerebral ischemia[134,135], and protect cells during experimental diabetes[136-138]. Furthermore, trophic factors employ cytoprotective pathways of Wnt to prevent cerebral endothelial cell injury[137], preserve mesenchymal stem cells[139], block apoptosis during forkhead transcription factor activation[136,140], promote the maintenance of immune cells in the nervous system[81], and prevent Aβ toxicity in cerebral microglia[82]. However, prolonged exposure of growth factors such as EPO that rely upon Wnt signaling can have ill effects with the proliferation of cancer[141-143], inflammation, and blood-brain barrier injury[144].

In the Wnt signaling pathway, Wnt1 inducible signaling pathway protein 1 (WISP1), also known as CCN4, is a member of the six secreted extracellular matrix associated CCN family of proteins that are involved in cellular survival and stem cell proliferation[145]. WISP1 can activate the components of the mTOR pathway that determine stem cell survival (Figure 2)[21]. WISP1 increases mTOR activity by blocking the inhibitory actions of the mTOR component PRAS40[146]. WISP1 controls the post-translational phosphorylation of AMP activated protein kinase (AMPK), a pathway involved in stem cell proliferation and cellular metabolism[12,147]. WISP1 differentially decreases phosphorylation of TSC2 at Ser^{1387}, a target of AMPK, and increases phosphorylation of TSC2 at Thr^{1462}, a target of Akt[15].

As a tightly linked pathway to mTOR, WISP1 can significantly influence stem cell survival and proliferation. During stem cell migration, WISP1 expression is increased[148]. WISP1 is differentially regulated during human embryonic stem cell and adipose-derived stem cell differentiation. WISP1 expression is increased during human adipocyte differentiation[149] and is repressed in adipose-derived stem cells during hepatic differentiation[51]. WISP1 can modulate induced pluripotent stem cell reprogramming[150,151]. WISP1 is

one of several genes that are over-expressed during pancreatic regeneration[152]. WISP1 also may support vascular regeneration during saphenous vein crush injury[153]. WISP1 oversees cellular senescence[154] and does not appear to foster excessive cellular proliferation under circumstances involving aging vascular cells[155]. However, as a proliferative agent, WISP1 can lead to excessive cell growth. WISP1 may promote distant metastatic disease[156] and WISP1 expression is increased in neurofibromatosis type 1 tumorigenesis[157]. Variants of WISP1 can be extremely aggressive in promoting cell growth[158] in comparison to non-variant WISP1 expression that may be protective under specific scenarios and block tumor cell invasion, motility, and metastases[159].

FUTURE CONSIDERATIONS

Stem cells represent an important strategy as well as a vital experimental tool for the treatment of multiple disorders that can affect diverse systems of the body that include the brain, cardiovascular system, metabolism, and tumor cell growth. mTOR, a 289-kDa serine/threonine protein kinase and a critical component for the protein complexes of mTORC1 and mTORC2, oversees cellular development, proliferation, and senescence that can directly impact stem cell maintenance, proliferation, and differentiation.

Although mTOR is a highly attractive target to control stem cell maintenance and differentiation, the complexity of this system raises a number of considerations. How does mTOR interface with programmed cell death pathways that can directly affect stem cell populations? mTOR regulates the programmed cell death pathways of autophagy and apoptosis that have a complex outcome in stem cell survival. Through the modulation of Wnt signaling, activation of autophagy that necessitates inhibition of mTOR can block breast cancer stem cell growth. Yet, activation of autophagy that may work in concert with SIRT1 has been shown to play a vital role to maintain muscle stem cell activation and the protection of endothelial progenitor cells. Apoptosis that consists of both an early stage with membrane PS externalization and a late stage involving the destruction of genomic DNA usually relies upon activation of mTOR and its related pathways of PI 3-K, Akt, and growth factors such as EPO, EGF, FGF, and BDNF to block apoptotic cell death in stem cells. However, during some toxic environments, stem cells that become differentiated may require the induction of autophagy with mTOR inhibition to prevent apoptotic cell death.

Another consideration for mTOR is its variable role in the maintenance of stem cell populations and the eventual differentiation of cells into specific phenotypes. mTOR is necessary for trophoblast growth, implantation, the establishment of embryonic stem cells, and the maintenance of pluripotency. Loss of mTOR, such as in the aged brain, may be a factor that results in the reduction of the proliferation of active neural stem cells. Yet, mTOR signaling that can involve p70S6K also affects the modulation of stem cell genesis and cellular differentiation. The activation of mTOR rather that its inhibition can be necessary for stem cell differentiation as well as the ability to selectively promote the maturation of specific cell phenotypes. The control of stem cell development, migration, and proliferation by mTOR can be dependent upon both Wnt and WISP1 signaling.

Ultimately, consideration also must be given for the role mTOR plays to block tumorigenesis and the ability of mTOR signaling to at times accelerate tumor cell growth. Given its proliferative role, mTOR can foster cancer stem cell development and the conversion of differentiated cells into cells that have invasive growth. The degree of mTOR activity may be critical during tumorigenesis, since mTOR in some cell populations can either maintain cell senescence and prevent tumor growth or conversely promote cancer stem cell development that can lead to disease recurrence and therapeutic resistance. By clearly addressing the challenges that lie ahead, targeting mTOR and its signaling pathways offer an exciting approach to translate the development and utilization of stem cells into new therapeutic strategies for multiple disease entities.

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