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Erythropoietin and mTOR: A "One-Two Punch" for Aging-Related Disorders Accompanied by Enhanced Life Expectancy

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Abstract

Life expectancy continues to increase throughout the world, but is accompanied by a rise in the incidence of non-communicable diseases. As a result, the benefits of an increased lifespan can be limited by aging-related disorders that necessitate new directives for the development of effective and safe treatment modalities. With this objective, the mechanistic target of rapamycin (mTOR), a 289-kDa serine/threonine protein, and its related pathways of mTOR Complex 1 (mTORC1), mTOR Complex 2 (mTORC2), proline rich Akt substrate 40 kDa (PRAS40), AMP activated protein kinase (AMPK), Wnt signaling, and silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1), have generated significant excitement for furthering novel therapies applicable to multiple systems of the body. Yet, the biological and clinical outcome of these pathways can be complex especially with oversight of cell death mechanisms that involve apoptosis and autophagy. Growth factors, and in particular erythropoietin (EPO), are one avenue under consideration to implement control over cell death pathways since EPO can offer potential treatment for multiple disease entities and is intimately dependent upon mTOR signaling. In experimental and clinical studies, EPO appears to have significant efficacy in treating several disorders including those involving the developing brain. However, in mature populations that are affected by aging-related disorders, the direction for the use of EPO to treat clinical disease is less clear that may be dependent upon a number of factors including the understanding of mTOR signaling. Continued focus upon the regulatory elements that control EPO and mTOR signaling could generate critical insights for targeting a broad range of clinical maladies.

Keywords

Akt; aging; aging-related disorders; Alzheimer's disease; AMP activated protein kinase (AMPK); apoptosis; autophagy; cardiovascular disease; caspase; diabetes mellitus; epidermal growth factor; erythropoietin; hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2); Huntington's disease; hypoxia-inducible factor 1; insulin; lifespan; mechanistic target of rapamycin (mTOR); mTOR Complex 1 (mTORC1); mTOR Complex 2 (mTORC2); nicotinamide; nicotinamide adenine dinucleotide (NAD^+); non-communicable diseases; oxidative stress; phosphoinositide 3–kinase (PI 3-K); programmed cell death; proline rich Akt substrate 40 kDa (PRAS40); silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1); sirtuin; stem cells; wingless; Wnt; Wnt1 inducible signaling pathway protein 1 (WISP1)

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Increased Lifespan, Degenerative Disorders, and Cell Injury

Throughout the globe, both lifespan and the incidence of non-communicable diseases (NCDs) are increasing (1). The world's population is becoming older (2) and the number of individuals over the age of sixty-five has more than doubled during the previous fifty years. Life expectancy is approaching eighty years of age and has been marked by a one percent decrease in the age-adjusted death rate from the years 2000 through 2011 (3). In addition, the incidence of non-communicable diseases (NCDs) is rising and according to the World Health Organization more than sixty percent of the fifty-seven million global deaths are attributable to NCDs (4). This rise in NCDs closely follows the increase in life expectancy of the world's population (Table 1).

With increasing age, various systems of the body can become affected by disease. Accumulation of senescent cells with increased age is believed to contribute to loss of tissue and organ function (5, 6). Oxidative, metabolic, and mechanical stressors also increase with age that can promote tissue injury (7–11). Systems of the body may become affected with age-related disorders disorders, such as lung disease and increased inflammation, which can become detrimental to overall lifespan (12). Cardiovascular disease (13, 14), musculoskeletal disease (15, 16), and psychiatric disorders (17) also can progress with aging. Equally important is the impact of aging on the nervous system (18). Learning and memory capacity can decline with loss of hippocampal and cortical neurons (19, 20) and may ultimately result in progressive neurodegenerative disease (21–25).

As a result of progressive cellular and system insults in the body, clinical disease can ensue. For example, infections of prion agents lead to progressive and fatal neurodegenerative diseases (26). Cardiovascular disease and diabetes mellitus (DM) can lead to acute neurodegenerative diseases such as stroke (27, 28). In regards to neurodegenerative disorders (29, 30), 800,000 strokes occur per year in the United States (US) at an annual cost of 75 billion US dollars (29). Traumatic brain injury (TBI) (31, 32) can have multiple effects resulting in acute injury to the nervous system as well as subsequent chronic aging-related impairment (33–35). Approximately 50,000 individuals die every year as a result of TBI and more than 100,000 individuals suffer with chronic disability (36). Furthermore, at least ten percent of the global population over the age of sixty-five are affected with sporadic Alzheimer's disease (AD) (37, 38). In contrast, familial cases of AD represent less than 2 percent of all presentations (24), usually occur prior to age 55 (39), and represent an autosomal dominant form of a mutated amyloid precursor protein (APP) gene as well as mutations in the presenilin 1 or 2 genes (40).

Closely tied to the progression of clinical disease with advanced age are metabolic disorders (1, 10, 11, 41, 42) that includes DM (8, 43). In particular, DM is increasing in incidence throughout the world (28, 41) and it is predicted that greater than 350 million individuals currently have DM (44–48). Approximately an additional eight million individuals are considered to suffer from metabolic disorders but are yet to be identified as having DM (49–51). Overall, per reports by the Centers for Medicare and Medicaid Services (CMS), the care for patients with DM consumes 17 percent of the Gross Domestic Product in the US as reported by (52).

Disorders such as DM affect all systems of the body (10, 11, 53–60). For example, DM can negatively impact the immune system, musculoskeletal function, hepatic metabolism, and renal clearance (50, 53, 55, 59, 61–64). In the cardiovascular system, DM can lead to impaired angiogenesis, platelet dysfunction, atherosclerosis, endothelial progenitor cell injury, cardiac impairment, and loss of vascular cells (8, 14, 27, 62, 65–68). In the nervous system, DM results in cortical injury and stroke (62, 67, 69–72), retinal disease (50, 73–75), dementia (76), AD (51, 61, 71, 77), peripheral neuropathy (78, 79), and psychiatric disorders (80, 81).

The mechanistic target of rapamycin (mTOR)

Multiple cellular targets may be at the root of degenerative disorders that occur with increased lifespan and advanced aging, but it is the mechanistic target of rapamycin (mTOR), a 289-kDa serine/threonine protein, that has generated considerable excitement for developing novel therapies to avert cellular dysfunction and cell death (82–86) (Table 1). mTOR is considered a vital component that affects multiple cellular pathways during the aging process (6, 19, 87–90). mTOR also is known as the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1 (37). The target of rapamycin (TOR) was first documented in *Saccharomyces cerevisiae* with the genes *TOR1* and *TOR2* (90). *TOR1* and *TOR2* were found to encode the Tor1 and Tor2 isoforms in yeast through the use of rapamycin-resistant TOR mutants. Both TOR and mTOR activity can be blocked by rapamycin, a macrolide antibiotic in that exists in *Streptomyces hygroscopicus*.

Encoded by a single gene *FRAP1*, mTOR is the principal component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) (37, 87, 91, 92). mTORC1 contains the components Raptor, Deptor (DEP domain-containing mTOR interacting protein), the proline rich Akt substrate 40 kDa (PRAS40), and mammalian lethal with Sec13 protein 8, termed mLST8 (mLST8/GβL) (90). As noted, rapamacyin can block mTOR activity. Without the presence of rapamaycin, mTOR fosters Raptor activity. This involves the binding of p70 ribosomal S6 kinase (p70S6K) and the eukaryotic initiation factor 4E (eIF4E)-binding protein 1 (4EBP1) to Raptor. mLST8 also promotes mTOR kinase activity. In contrast, Deptor is inhibitory and blocks mTORC1 activity by binding to the FAT (FKBP12 -rapamycin-associated protein (FRAP), ataxia-telangiectasia (ATM), and the transactivation/transformation domain-associated protein) domain of mTOR. In addition, PRAS40 blocks mTORC1 activity by preventing the association of p70S6K and 4EBP1 with Raptor (93, 94). mTORC1 becomes active once PRAS40 is phosphorylated by protein kinase B (Akt) to release PRAS40 from Raptor and sequester PRAS40 with the cytoplasmic docking protein 14-3-3 (95–99). mTORC2 contains Rictor, Deptor, mLST8, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) (87, 100). mTORC2 activates protein kinases, such as glucocorticoid induced protein kinase 1 (SGK1), a member of the protein kinase A/protein kinase G/protein kinase C (AGC) family of protein kinases. Protor-1, a Rictor-binding subunit of mTORC2, activates SGK1 (101, 102). The kinase domain of mTOR phosphorylates mSIN1 to prevent lysosomal degradation of this protein. Rictor (103) and mSIN1 (104) promote cellular

survival by phosphorylating Akt at serine^{473} and leading to threonine^{308} phosphorylation by phosphoinositide-dependent kinase 1 (PDK1).

Vital in the signaling cascade of mTOR and cell survival is AMP activated protein kinase (AMPK) (1, 105, 106). Under some conditions, AMPK may be protective for cell survival and also regulate cellular metabolism through its inhibition of mTOR (106, 107). Metformin, an agent that controls hyperglycemia in DM, blocks mTOR activity through AMPK and leads to the induction of autophagy. As a result, cardiomyopathy is limited in experimental models of DM (108) and endothelial cell senescence is reduced during applications of metformin (109). AMPK maintains metabolic function of cells, prevents atherosclerosis, modulates immune system activity, and can prevent β-amyloid (Aβ) accumulation (25, 40, 110–113). AMPK activation also may improve memory retention in models of AD and DM (114). With silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1) (13, 62), AMPK can protect endothelial cells through the induction of autophagy against oxidized low-density lipoproteins (115). Yet, limited AMPK activity also may be required for cellular protection. For example, reduced AMPK activity can lead to the protection of pancreatic islet cells in mice (116), limit Aβ toxicity in cerebral microglial cells (117), and prevent inflammation in the nervous system (118).

AMPK blocks mTORC1 activity through the activation of the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex. TSC2 is a GTPase-activating protein (GAP) converting G protein Rheb (Rheb-GTP) into the inactive GDP-bound form (Rheb-GDP). Once Rheb-GTP is active, Rheb-GTP combines with Raptor to control the binding of 4EBP1 to mTORC1 and increase mTORC1 activity (119). AMPK phosphorylates TSC2 to increase GAP activity to change Rheb-GTP into the inactive Rheb-GDP and to inhibit mTORC1 activity (120). As noted above, AMPK also functions with SIRT1 (13, 62). In addition, AMPK can increase nicotinamide phosphoribosyltransferase (NAMPT) activity to convert nicotinamide to nicotinamide mononucleotide (57, 121, 122). This conversion of nicotinamide increases nicotinamide adenine dinucleotide (NAD^+) levels, decreases levels of the SIRT1 inhibitor nicotinamide (46, 121), and promotes SIRT1 transcription (28, 123, 124).

In addition to AMPK, phosphoinositide 3-kinase (PI 3-K) and Akt also play significant roles in the mTOR signaling pathway (9, 21, 85). The terminal domains of mTOR oversee the catalytic activity, binding, and phosphorylation of mTOR (90). The C-terminal domain of mTOR has a sequence homology to the catalytic domain of the PI 3-K family and contains several phosphorylation sites that regulate mTOR. Downstream from PI 3-K, Akt can block activity of the TSC1/TSC2 complex that inhibits mTORC1 (125–128). Akt controls TSC1/TSC2 complex and its phosphorylation of TSC2 (29). Other pathways, such as extracellular signal-regulated kinases (ERKs), protein p90 ribosomal S6 kinase 1 (RSK1), and glycogen synthase kinase -3β (GSK-3β) also can modulate the activity TSC1/TSC2 complex. It should be noted that under some conditions that promote cell survival, a limited activity of TSC2 and AMPK is necessary since complete knockdown of TSC2 can result in cell death (117). Although the TSC1/TSC2 complex inhibits mTORC1 activity, mTORC2 activity is increased during activation of the TSC1/TSC2 complex through the amino (N)-terminal region of TSC2 and the C-terminal region of Rictor (129).

Targeting cell death through mTOR

mTOR oversees pathways of cell death through apoptosis and autophagy, two mechanisms that can determine cell survival through programmed cell death (105, 130, 131) (Table 1). Apoptosis results in the activation of nucleases and proteases involving caspases (132). These processes impact both the early phase of apoptosis with the loss of plasma membrane phosphatidylserine (PS) asymmetry and a later phase that leads to genomic DNA degradation (133–135). Loss of membrane PS asymmetry activates inflammatory cells to engulf and remove injured cells (136–139). However, if the engulfment of inflammatory cells can be prevented, functional cells expressing membrane PS residues can rescued (50, 140–142). In contrast, the destruction of cellular DNA, once it occurs, is usually not considered to be completely reversible (143).

Activation of mTOR usually blocks apoptotic cell death in the nervous system (87, 144). Loss of mTOR activity (105) or components of this pathway, such as mTORC2, can result in apoptotic cell death (130). Activation of either mTOR or downstream pathways that involve p70S6K can protect against Aβ toxicity (21, 25, 97, 117, 145–148), cerebral ischemia (149, 150), and oxidative stress exposure (151, 152). During metabolic disease such as DM (28), mTOR activation can prevent the development of atherosclerosis (153) and through glucagon-like peptide-1 agonists can protect pancreatic β-cells from cholesterol mediated apoptotic cell injury (152). In addition, mTOR activation can prevent neural apoptotic cell loss during DM through the epidermal growth factor receptor (154) and foster pancreatic β-cell proliferation (155)

Yet, in some cases, limiting the activity of mTOR may be necessary to block apoptotic cell death (156). In such cases, induction of autophagy during mTOR inhibition leads to the prevention of cell death. At least 33 autophagic related genes (*Atg*) have been identified in yeast with TOR and can affect multiple disorders (57, 157). Atg1, Atg13 (also known as Apg13), and Atg17 are associated with the PI 3-K, Akt, and TOR pathways (158). Autophagy recycles components of the cell cytoplasm for tissue remodeling and to remove non-functional organelles (30, 131, 159, 160). Macroautophagy is the classification of autophagy that recycles organelles and consists of the sequestration of cytoplasmic proteins and organelles into autophagosomes that combine with lysosomes for degradation and recycling (93, 161, 162). Other categories of autophagy involve microautophagy that uses the invagination of the lysosomal membrane for the sequestration and digestion of cytoplasmic components (131). Chaperone-mediated autophagy uses cytosolic chaperones to transport cytoplasmic components across lysosomal membranes (163).

Autophagy with the inhibition of mTOR activity can be protective for cells. Inhibition of mTOR with the induction of autophagy can increase cell survival in neonatal models of ischemia (164) and during excitotoxicity (165). Autophagy protects cells during prion protein disease (166) and in models of Huntington's disease (HD)(90, 167). Autophagy activation can reduce Aβ production and improve memory function in animal models of AD (168). In a similar manner, loss of autophagy may be detrimental. In experimental models of AD, disease progression and duration increases with dysfunctional autophagic processes and reduction in mTOR activity (159). Vascular cell injury occurs during cerebral ischemia if

autophagy is blocked (169). In regards to metabolic disease, consumption of a high calorie diet can block autophagy and facilitate hippocampal neuronal loss in mice (20). In addition, autophagy haploinsufficiency with deletion of an essential *Atg7* gene in mouse models of obesity promotes increased insulin resistance with elevated lipids and inflammation (170). Similar to disorders such as HD, autophagy also may be necessary for the removal of misfolded proteins and to eliminate non-functioning mitochondria to maintain β-cell function and prevent the onset of DM (171). Autophagy also can improve insulin sensitivity during high fat diets in mice (172).

Induction of autophagy may be regulated not only through mTOR, but also through SIRT1 (173, 174). SIRT1 increases lifespan in higher organisms and provides protection against oxidative stress (175). SIRT1 is protective, such as with erythropoietin (EPO) growth factor protection (46, 176–180), and has an inverse relationship with mTOR (62). SIRT1 inhibits mTOR pathways and promotes autophagy to protect human embryonic stem cells against oxidative stress (181). SIRT1 blocks mTOR signaling to promote neuronal growth (182) and can oversee cellular metabolism during caloric restriction (183). In endothelial cells exposed to oxidized low density lipoproteins that can lead to atherosclerosis, SIRT1 up-regulation in combination with AMPK activity and mTOR inhibition results in autophagy that is necessary for cell protection (115).

Yet, autophagy is not always beneficial and may lead to cell injury. During Wnt1 inducible signaling pathway protein 1 (WISP1) signaling, autophagy may be a component of cell death in addition to apoptosis (184). Increased activity of autophagy can lead to loss of cardiac and liver tissue in diabetic rats during attempts to achieve glycemic control through diet modification (185). During periods of elevated glucose, advanced glycation end products (AGEs), agents that can result in complications during DM, can result in the induction of autophagy and vascular smooth muscle proliferation with atherosclerosis progression (186) as well as cardiomyopathy (187). With periods of elevated glucose exposure, autophagy can injure endothelial progenitor cells, lead to mitochondrial oxidative stress (188), and block angiogenesis (189). Furthermore, a reduction in autophagy with the activation of mTOR in animal models of traumatic spinal cord injury leads to improvement in function and increased survival of motor neurons (190). Inhibition of autophagy also reduces infarct size and protects cerebral neurons during experimental stroke (191). Blockade of autophagy and activation of mTOR protects dopaminergic neurons during oxidative stress exposure (192, 193). In tri-cultures of neurons, astrocytes, and microglia that are exposed to inflammatory stressors and Aβ, cell injury is worse during the induction of autophagy (194).

Erythropoietin and the modulation of mTOR

It is evident that a fine balance is required between apoptotic and autophagic pathways to achieve optimal cell survival and disease reduction. Growth factors are one avenue to consider to achieve fine control over cell injury pathways of apoptosis and autophagy. Growth factors are advocated for the treatment of both acute and chronic disorders (71, 195–199). In particular, the growth factor EPO is considered to offer an exciting therapeutic strategy for the treatment of disorders that result in cell injury and cell death especially since

it is intimately involved with mTOR signaling (Table 1) (85, 200–207). EPO has the capacity to offer protection against a number of disease entities (208–212) as well as enhanced biological activity (213, 214). For example, EPO has been reported to improve clinical outcome during development (215), neurodegenerative disorders (216), stroke (217–222), aging (223), TBI (32, 224), vascular disease (217–222), depression (208, 225), and metabolic disturbances (63, 211, 226, 227).

Structure and Biological Activity of Erythropoietin

Currently, erythropoiesis-stimulating agents (ESAs), which include EPO, are approved for the treatment of anemia that results from chronic kidney failure, human immunodeficiency virus, and chemotherapy. In addition, EPO can be administered to reduce blood transfusions for surgery (228, 229). The *EPO* gene is located on chromosome 7 and is a single copy in a 5.4 kb region of the genomic DNA. The gene encodes for a polypeptide chain protein that has initially 193 amino acids (230). EPO is then processed and cleaved of a 27 amino acid hydrophobic secretory leader at the amino-terminal to result in a 166 amino acid peptide protein (231). With the removal of a carboxy-terminal arginine^{166} in the mature human and recombinant human EPO (rhEPO), a protein of 165 amino acids with a molecular weight of 30.4 kDa is subsequently generated (226, 227, 232, 233).

EPO has four glycosylated chains that include three *N*-linked and one *O*-linked acidic oligosaccharide side chains (71). The *N*-linked glycosylation sites exist at aspartyl^{24}, aspartyl^{38}, and aspartyl^{83}. The *O*-linked glycosylation site occurs at serine^{126} (209). It is postulated that the *N*- and *O*-linked chains are for the production and secretion of the mature EPO (234). In addition, the carbohydrates are needed for the clearance of EPO, since EPO molecules with high sialic acid content can be easily cleared by the body through the liver (235).

In regards to the biological activity of EPO, the glycosylated chains protect EPO from free radical oxygen degradation (71). The oligosaccharides in EPO can offer protection from free radical activity as well (236) and the carbohydrate chains can stabilize the EPO protein (237). The disulfide bonds determine EPO activity since reduction of the two disulfide bonds formed between cysteine^{7} and cysteine^{160} and between cysteine^{29} and cysteine^{33} leads to functional loss of EPO. Alkylation of the sulfhydryl groups results in irreversible loss of the activity of EPO. Re-oxidization of EPO after reduction by guanidine restores almost 85 percent of the biological activity of EPO (238).

Expression and Production of Erythropoietin

EPO is present in the brain, uterus, and liver (239–243), but the primary site for the production and secretion of EPO is the kidney peritubular interstitial cells (243). Production of EPO and the EPO receptor (EPOR) are changed during development (233). EPO production and EPOR expression in gestation are increased, but later EPO and EPOR are reduced following birth with EPO regulated by the tissue oxygen supply.

EPO expression is controlled by changes in oxygen tension and not by the concentration of red blood cells (50, 239, 244). Hypoxia-inducible factor 1 (HIF-1) regulates the expression of EPO and EPOR to increase the production of EPO as required (230, 239, 245, 246). After

HIF-1 activation, gene transcription of EPO and EPOR occurs and is controlled through the transcription enhancer region in the 3′-flanking region of the EPO gene that binds to HIF-1 (230, 233).

Interestingly, EPO production can be controlled through other mechanisms not directly tied to hypoxia (247). For example, agents that limit inflammation in cerebral microglia have been demonstrated to lead to the release of EPO (248). Infections. such as malaria, also can result in significant serum levels of EPO (249). EPO serum concentrations are elevated during xenon anesthesia in cardiac surgery (250). Cytokines, including insulin-like growth factor, tumor necrosis factor-α (TNF-α) (251), interleukin-1β (IL-1β), and interleukin-6 (IL-6) can raise EPO and EPOR expressions (230, 242, 252). Other factors, such as cadmium exposure, intracellular calcium, and neuronal depolarizations, can alter EPO expression (71, 217, 240).

Cellular protection with Erythropoietin and mTOR

Several cell survival pathways that EPO oversees are intimately tied to mTOR signaling (205–207, 209, 247, 253, 254). For stem cell development and the maturation of cells, EPO relies upon mTOR for the differentiation of neural precursor cells to achieve a neuronal phenotype (254). EPO also has been shown to promote adult hippocampal neurogenesis that is considered to be important for effective antidepressant treatment and requires mTOR activity to resolve affective disorders (225). EPO also plays a role in osteoblastogenesis and osteoclastogenesis that is dependent upon pathways of mTOR (255).

In regards to cellular protection, retinal progenitor cells are protected from oxidative stress by EPO and mTOR pathways (205). EPO requires mTOR activation for prevention of cognitive loss in models of sepsis-induced encephalopathy (256). EPO oversees mTOR and down-stream signaling pathways that involve PRAS40 to increase neuronal survival during oxygen-glucose deprivation (95). EPO also increases mTOR activity during hypoxia-reoxygenation stress to protect hippocampus-derived neuronal cells (204).

As part of the mTOR pathway, AMPK is closely associated with the protective capacity of EPO. EPO controls inflammation in the nervous system through AMPK (248). Yet, it is necessary for EPO to control a specific level of AMPK and mTOR activity to protect cells under some conditions of oxidative stress (117). In addition, EPO can rely upon AMPK pathways for anti-oxidant gene expression (122).

In regards to cellular protection with EPO and mTOR during programmed cell death, EPO blocks apoptotic cell death through the activation of mTOR (46, 57, 205–207, 257). EPO can block Aβ toxicity through Wnt signaling and mTOR pathways to prevent caspase activation and apoptosis (97). EPO also fosters microglial survival during oxidative stress through mTOR (206). Given that Wnt signaling and WISP1 are also involved in metabolic pathways (60, 244, 258–261), EPO also provides cellular protection during metabolic disorders through Wnt signaling (262–265).

In relation to autophagy, EPO inhibits autophagy through the activation of mTOR (20, 57, 266). Activation of mTOR blocks autophagy by phosphorylating autophagic related genes

(*Atg*) and proteins that include Atg13 and ULKs to inhibit the UNC like kinase complex ULK-Atg13-FIP200 (37). EPO can promote cellular protection during hypoxia and oxidative stress in retinal progenitor cells by limiting the induction of autophagy (205). EPO can prevent excessive autophagy that precedes apoptosis during experimental neonatal necrotizing enterocolitis (207). EPO also can modify the activity of autophagy and limit neonatal brain damage in the developing rodent during hyperoxia exposure and oxygen toxicity (267). In some cases, EPO also relies upon the beneficial effects of autophagy. In neuronal cell line models, EPO can suppress apoptotic cell injury through the increased activity of AMPK and increasing autophagy-related signaling pathways (257). In addition, the concentration of EPO may affect mTOR signaling and apoptotic cell death. Elevated concentrations of EPO can lead to cellular damage and lessen the activity of mTOR (253).

Future Perspectives

The interest generated with EPO has led to the initiation of multiple clinical trials for EPO. Yet, the role mTOR may play with EPO in treating clinical disease requires further investigation. Currently, EPO appears to have efficacy in treating conditions that involve the developing brain. Elevated EPO concentrations during infant maturation have been correlated with increased Mental Development Index scores (268). In a randomized, double-blind placebo-controlled study involving preterm infants, EPO was demonstrated to improve white matter development assessed by diffusion tensor imaging and tract-based spatial statistics (269). High-dose erythropoietin treatment within forty-two hours after birth in preterm infants has been associated with reduced risk of brain injury documented through magnetic resonance imaging (215, 270). Hypothermia combined with high-dose erythropoietin also appears to be protective against hypoxic-ischemic encephalopathy with improved one-year motor function (271).

In mature populations that are affected by aging-related disorders, the conclusion for the use of EPO to treat clinical disease is less clear. In a small study with twenty-six Parkinson's disease patients, recombinant EPO administration improved cardiovascular autonomic dysfunction and cognition, but did not alter motor function (216). Increased expression of the EPO receptor in temporal cortical and hippocampal astrocytes in sporadic AD patients has been observed and considered to be an early neuroprotective pathway (272). The biosimilar epoetin α (Binocrit) administered in elderly patients with myelodysplastic syndromes also have experienced improved cognitive function that may be related to resolution of anemia (273). Yet, in relation to TBI, neither the administration of EPO or maintaining hemoglobin concentration above 10 g/dL led to improvement in neurological outcome at six months (274). In a large clinical trial with close to six hundred patients that experienced brain injury, EPO did not significantly affect six-month mortality, reduce severe neurological dysfunction, or increase the occurrence of deep venous thrombosis of the lower limbs (275). In addition, administration of human choriogonadotropin alfa followed by EPO did not show improvement in neurological recovery in patients with ischemic stroke (276). Similar to prior studies with cardiovascular disease (229, 250, 277–279), additional work suggests that high concentrations of EPO may not be effective for cardiac protection. Recent studies with out-of-hospital cardiac arrest demonstrate that EPO did not confer a benefit and was associated with a higher thrombotic complication rate (280, 281).

It is possible that lower doses of EPO or different times of administration may be more effective for clinical disease especially since new work suggests a role for EPO and EPOR autoantibodies for disease progression (282, 283). Additional studies suggest that low concentrations of EPO may be beneficial to the cardiovascular system (284–286) and also may benefit neurological function. However, only modulating the concentration or timing of administration of EPO may not offer the greatest gains to translate experimental *in vitro* and *in vivo* studies with EPO and mTOR into clinical success. Targeting the ability of EPO to govern specific cellular pathways such as mTOR signaling pathways would increase our understanding substantially and potentially yield new treatment modalities for multiple clinical disorders (Table 1). mTOR oversees critical pathways of programmed cell death that involve apoptosis and autophagy that can markedly impact clinical disease and aging-related disorders. For example, increased mTOR signaling may be required to regulate the β-site amyloid precursor protein (APP)-cleaving enzyme 1 (β-secretase, BACE1) that promotes Aβ accumulation in AD. Elevated mTORC1 activity reduces BACE1 and limits Aβ generation (145). However, additional studies suggest that some degree of inhibition of mTOR may be necessary to enhance Aβ clearance and improve spatial learning through the activation of autophagy (287). Greater emphasis upon the regulatory pathways controlling EPO and mTOR signaling could offer significant fruits for targeting several clinical disorders.

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Table 1

Highlights for Designing Novel Treatments with Erythropoietin and mTOR

• Both life expectancy and the incidence of non-communicable diseases are increasing throughout the globe that necessitates new strategies to treat aging-related disorders.
• The mechanistic target of rapamycin (mTOR), a 289-kDa serine/threonine protein, and its related pathways of mTOR Complex 1 (mTORC1), mTOR Complex 2 (mTORC2), proline rich Akt substrate 40 kDa (PRAS40), AMP activated protein kinase (AMPK), Wnt signaling, and silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1), offer exciting prospects for the design of therapies for multiple disorders.
• Closely coupled to the ability of mTOR signaling to govern cell survival is the oversight of the programmed death pathways of apoptosis and autophagy.
• A fine control of mTOR is necessary over apoptotic and autophagic pathways to achieve desired biological and clinical outcomes.
• Erythropoietin (EPO) offers an exciting prospect to couple with the benefits of mTOR signaling, since EPO relies upon mTOR pathways and can implement control over apoptosis and autophagy to foster potential treatment for multiple disease entities.
• Although EPO is gaining clinical acceptance in cell and animal studies as well as clinical studies for the developing brain, applications of EPO for mature and aging adults require further clarification that can benefit from continued elucidation the regulatory elements that control EPO and mTOR signaling.