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INVITED REVIEW

Driving neural regeneration through the mammalian target of rapamycin

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Abstract

Neurodegenerative disorders affect more than 30 million individuals throughout the world and lead to significant disability as well as death. These statistics will increase almost exponentially as the lifespan and age of individuals increase globally and individuals become more susceptible to acute disorders such as stroke as well as chronic diseases that involve cognitive loss, Alzheimer's disease, and Parkinson's disease. Current therapies for such disorders are effective only for a small subset of individuals or provide symptomatic relief but do not alter disease progression. One exciting therapeutic approach that may turn the tide for addressing neurodegenerative disorders involves the mammalian target of rapamycin (mTOR). mTOR is a component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) that are ubiquitous throughout the body and control multiple functions such as gene transcription, metabolism, cell survival, and cell senescence. mTOR through its relationship with phosphoinositide 3-kinas e (PI 3-K) and protein kinase B (Akt) and multiple downstream signaling pathways such as p70 ribosomal S6 kinase (p70S6K) and proline rich Akt substrate 40 kDa (PRAS40) promotes neuronal cell regeneration through stem cell renewal and oversees critical pathways such as apoptosis, autophagy, and necroptosis to foster protection against neurodegenerative disorders. Targeting by mTOR of specific pathways that drive long-term potentiation, synaptic plasticity, and β-amyl oid toxicity may offer new strategies for disorders such as stroke and Alzheimer's disease. Overall, mTOR is an essential neuroprotective pathway but must be carefully targeted to maximize clinical efficacy and eliminate any clinical toxic side effects.

Key Words: *Alzheimer's disease; apoptosis; autophagy; mTOR; necroptosis; rapamycin; stem cells; stroke*

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The current void for novel therapeutic avenues to foster neural regeneration

Both acute and chronic neurodegenerative disorders impact greater than 30 million individuals throughout the globe to result in death and disability for the majority of those afflicted. Over the course of the next ten years, the advancing age and increased lifespan of the world's population will lead to a further increase in the incidence of neurodegenerative disorders. In regards to chronic neurodegenerative disorders such as Alzheimer's disease (AD), this long-term disease affects a significant portion of the world's population (Maiese et al., 2009). Almost ten percent of the world's population over the age of 65 is affected with the sporadic form of AD. Currently with sporadic AD more than 5 million individuals suffer from this disorder and 3.5 million are under treatment at an annual cost of over 4 billion United States (US) dollars. This is in contrast to familial cases of AD that account for less than 2% of all presentations of AD. Familial AD can result from variable single-gene mutations on chromosomes 1, 14, and 21 with mutations on chromosome 1 leading to abnormal presenilin 2, mutations on chromosome 14 resulting in abnormal presenilin 1, and mutations on chromosome 21 leading to amyloid precursor protein (APP).

The impact to the global population is equally as significant when one considers the effects of acute neurodegenerative disorders. For example, at least 15 million individuals suffer some form of a stroke every year and approximately 800,000 of these cerebrovascular events occur in the US at an annual cost of 75 billion US dollars. Both AD and stroke are significant causes of death and disability throughout the world. Present therapies for AD that consist of acetylcholinesterase inhibitors or behavior modification are symptomatic and do not alter disease progression. Furthermore, therapies for stroke such as recombinant tissue plasminogen activator are only applicable for a small subset of patients. Although multiple therapeutic strategies are under consideration for a host of neurodegenerative disorders, one novel and exciting strategic avenue for neurodegenerative disease

that can affect neural regeneration involves the mammalian target of rapamycin (mTOR) (Maiese et al., 2013a).

The structural and functional basis of mTOR

mTOR in mammals is a 289-kDa serine-threonine protein kinase and controls multiple functions that involve gene transcription, cytoskeleton composition, cell metabolism, cell survival, and cell senescence (Maiese et al., 2013a). mTOR is a vital component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2). The association of mTOR with either Raptor (component of mTORC1) or Rictor (component of mTORC2) determines which protein complex mTOR associates, either mTORC1 or mTORC2. mTORC1 contains Rictor, 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). mLST8 promotes mTOR kinase activity through two important targets of mTORC1, namely p70 ribosomal S6 kinase (p70S6K) and the eukaryotic initiation factor 4E (eIF4E)-binding protein 1 (4EBP1). mTORC1 uses p70S6K to promote cell growth, mRNA biogenesis, and the translation of ribosomal proteins. In the nervous system, glutamate and leucine rely upon p70S6K to modulate synaptic signaling (Lenz and Avruch, 2005) and food intake (Cota et al., 2006). mTOR signaling also is tied to the pathways of phosphoinositide 3-kinase (PI 3-K), Akt, and AMP activated protein kinase (AMPK) (Maiese et al., 2013b).

In regards to mTORC2, this complex contains Raptor and also has similar components of mTORC1 that include mLST8 and Deptor. In addition, mTORC2 contains the mammalian stress-activated protein kinase interacting protein (mSIN1) and the protein observed with Rictor-1 (Protor-1) (Chong et al., 2012b; Maiese et al., 2013a). Rictor and mSIN1 form the structural basis of mTORC2. mTORC2 utilizes Rictor to activate and phosphorylate Akt to enhance cell survival and relies upon protein kinase C-α (PKCα) for cytoskeleton remodeling. mTORC2 also controls cell migration through the Rac guanine nucleotide exchange factors P-Rex1 and P-Rex2 and through Rho signaling.

Overcoming pathways of programmed cell death to facilitate neural regeneration

Pathways of programmed cell death that involve mTOR include apoptosis, autophagy, and necroptosis (Maiese et al., 2012). Apoptosis consists of both an early phase that involves the loss of plasma membrane lipid phosphatidylserine (PS) asymmetry and a later phase that leads to genomic DNA degradation. Since the early phase of apoptosis with membrane PS externalization alerts inflammatory cells to engulf and remove injured neurons, prevention of membrane PS externalization in injured neurons is necessary to block the loss of functional cells that may be temporarily disabled (Maiese et al., 2013b). Activation of mTOR may be necessary to prevent apoptotic cell death in the nervous system. Loss of mTOR activity can lead to apoptotic neuronal cell loss (Chen et al., 2010) and β-amyloid (Aβ) exposure can inhibit mTOR activity (Chen et al., 2009). Neurons also are protected against sepsis with application of the cytokine erythropoietin (EPO) (Maiese et al., 2005) and activation of mTOR (Wang et al., 2014). Activation of mTOR is required for EPO to prevent apoptosis in cerebral microglia that can support neuronal function during oxidative stress and Aβ toxicity (Shang et al., 2012b). Enhancement of cortical neuronal survival during ischemic preconditioning (Zare Mehrjerdi et al., 2013) or during permanent cerebral ischemia also requires mTOR activation (Shi et al., 2011). In regards to downstream signaling of mTOR, p70S6K offers growth factor neuroprotection against apoptosis (Chong et al., 2012a; Shang et al., 2012a), fosters progenitor cell induction of neovascularization in ischemic tissue (Huang et al., 2013), and prevents cortical ischemic injury (Koh, 2013).

Autophagy is a pathway that recycles cytoplasmic components and discards defective organelles for tissue remodeling (Maiese et al., 2012). Macroautophagy, which involves the classification of autophagy most commonly described, sequesters cytoplasmic proteins into autophagosomes that ultimately fuse with lysosomes for degradation and are subsequently recycled for future cellular processes. For neurodegenerative disorders, activation of autophagy through mTOR inhibition usually promotes neuronal survival. In neonatal models of ischemia (Balduini et al., 2012) or during excitotoxicity (Kulbe et al., 2014), inhibition of mTOR activity with induction of autophagy is protective. In models of Huntington's disease (Hyrskyluoto et al., 2012) or prion protein disease (Jeong et al., 2012), autophagy during mTOR inhibition results in cytoprotection. Blockade of mTOR signaling with the induction of autophagy also leads to neural tissue protection and functional improvement in models of spinal cord injury (Sekiguchi et al., 2012).

Yet, a reduction in autophagy with mTOR activation also may be necessary to foster survival in the nervous system. For example, in dopamine neurons exposed to oxidative stress, neurons are protected during the blockade of autophagy and enhancement of mTOR activity (Choi et al., 2010). Animal models of ischemic stroke show that inhibition of autophagy leads to the reduction in infarct size and the protection of cerebral neurons (Yin et al., 2013). During traumatic spinal cord injury in animal models, activation of mTOR with reduction in autophagy also leads to improved cell survival of motor neurons and improved functional capabilities (Walker et al., 2012). One potential reason for the observations that autophagy with modulation of mTOR can sometimes be protective and at other times be detrimental is the knowledge that apoptosis and autophagy do not occur in isolation. For example, during oxidative stress in neurons, WISP1, a component of the wingless pathway Wnt1, can block neuronal death through the inhibition of apoptosis with a minimal contribution in a subset of neurons that also requires the inhibition of autophagy (Wang et al., 2012).

The programmed cell death pathway of necroptosis in conjunction with mTOR signaling also is pertinent to neurodegenerative disorders (Maiese, 2014). Inhibitors of necroptosis can block neuronal cell death and improve

memory function in animal models of aluminum exposure that have disabilities consistent with AD (Qinli et al., 2013). Other pathways of programmed cell death also overlap with necroptosis. Glioblastoma cell proliferation has been tied to a number of pathways that include inhibition of mTORC1 and mTORC2 with the initiation of necroptosis and autophagy (Liu et al., 2014).

Neuronal cell renewal through stem cells

mTOR signaling is vital for neuronal stem cell development and migration. mTOR is required for insulin-induced neuronal differentiation in neuronal progenitor cells (Han et al., 2008). mTOR pathways also can control neuronal migration and cortical patterning (Malagelada et al., 2011). In the absence of mTOR signaling, arrest of embryonic stem cell proliferation ensues (Gangloff et al., 2004). Yet, the timing and intensity of mTOR signaling can affect neuronal stem cell development, since sustained activation of the mTOR pathway can result in neuronal stem cell premature differentiation and impaired maturation (Magri et al., 2011). Recently, mTORC1 has been shown to be required for neural stem cell differentiation and to target 4EBP for neural stem cell self-renewal (Hartman et al., 2013).

Neural regeneration with mTOR for acute and chronic neurodegenerative disorders

With multiple potential treatment strategies focused upon mTOR for neurodegenerative disorders, excitement is growing for the application of mTOR-mediated strategies for acute neurodegenerative diseases such as stroke. Agents that include salvianolate (You et al., 2014) as well as ferulic acid (Koh, 2013) can reduce stroke volume in animal models by activating mTOR and its signaling pathways. Activation of mTOR has been shown to be neuroprotective and improve memory function during global brain ischemia (Zare Mehrjerdi et al., 2013). In neuronal cell lines and microglia during oxidative stress, activation of mTOR signaling with the reduction of PRAS40 activity and blockade of apoptosis can lead to cellular protection (Chong et al., 2012a; Shang et al., 2012a). Yet, other studies suggest that autophagy with the inhibition of mTOR activity may be required to prevent acute neuronal injury under some circumstances. Antagonism of the histamine H3 receptor during stroke leads to neuronal protection through inhibition of mTOR activity and induction of autophagy (Yan et al., 2014). In addition, damage from excitotoxicity in hippocampal neurons can be reduced with activation of autophagy and mTOR inhibition (Kulbe et al., 2014).

In relation to more chronic neurodegenerative disorders such as AD, mTOR is involved in both the protection of neurons and the preservation of memory. Dendritic protein synthesis in hippocampal neurons is promoted through mTOR activity (Gong et al., 2006). mTOR also is necessary for the formation of long-term memory in the amygdala (Parsons et al., 2006). Loss of mTOR signaling can impair long-term potentiation and synaptic plasticity in animal models of AD that can be reversed with the up-regulation of mTOR signaling (Ma et al., 2010). In microglial cells of the nervous system, Aβ can down-regulate mTOR and p70S6K expression and foster PRAS40 inhibition of mTOR (Shang et al., 2012a, b). Additional work also has shown that increased mTORC1 activity may necessary to regulate the β-site amyloid precursor protein (APP)-cleaving enzyme 1 (β-secretase, BACE1) that promotes Aβ accumulation in AD, since elevated mTORC1 activity reduces BACE1 and is able to limit Aβ generation (Shahani et al., 2014). However, similar to studies involving cerebral ischemia and mTOR, alternate pathways that limit mTOR activity also may be beneficial for neuronal survival during chronic disorders such as AD. In the temporal cortex of patients with AD, mTOR and tau phosphorylation are increased to suggest that aberrant and increased mTOR signaling may contribute to the pathology of AD (Griffin et al., 2005). In animal models of AD, long-term inhibition of mTOR reduces levels of Aβ and slows the progression of cognitive deficits (Spilman et al., 2010). Other studies also have shown that mTOR inhibition can enhance Aβ clearance in cell lines and animal models of AD and improve spatial learning through the activation of autophagy (Jiang et al., 2014).

Neural regeneration strategies with mTOR for the future

mTOR is a critical component to multiple neuroprotective protective pathways that not only involve phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt), but also growth factors, transcription factors, wingless pathways, sirtuins, neurotransmitter modulation, and lipid metabolism (Maiese et al., 2013a; Maiese, 2014). As a result, neuronal protection and regeneration may require mTOR modulation in conjunction with multiple signaling components of mTOR such as p70S6K, PRAS40, BAD, and Bcl-xL (Shang et al., 2012a,b, 2013). However, many of these cellular pathways including mTOR are cell proliferative and have the potential to lead to tumorigenesis (Maiese et al., 2013a; Maiese, 2014). Furthermore, agents used to inhibit mTOR, such as rapamycin and rapamycin derivative compounds, can lead to side effects that limit clinical utility to include oral and respiratory infections, stomatitis, hypercholesterolemia, and immunosuppression. Given these considerations, it is imperative to target specific components of the mTOR cascade that will enhance clinical efficacy and limit clinical toxicity.

It is important to recognize that the degree of mTOR activation also appears to play a significant role for neuronal protection and regeneration. mTOR activation can prevent oxidative stress mediated autophagy in dopamine neurons (Choi et al., 2010), but prolonged activation of mTOR can lead to dyskinesia in patients with Parkinson's disease (Santini et al., 2009). In addition, inhibition of mTOR in models of AD can lead to a reduction in BACE1 (Zhu et al., 2013), reduced senile plaque formation, and prevent Aβ generation. (Spilman et al., 2010). In contrast, mTOR activation protects neuronal networks controlling memory (Parsons et al., 2006; Zare Mehrjerdi et al., 2013) while loss of mTOR activity can

impair long-term potentiation and synaptic plasticity in animal models of AD (Ma et al., 2010). As a result, therapeutic strategies for mTOR directed against neurodegenerative disorders must focus upon relevant mTOR signaling pathways that block neurotoxicity in the nervous system but at the same time foster neuronal survival and regeneration without complications that could affect overall clinical prognosis such as cognitive impairment or tumorigenesis.

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