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The mechanistic target of rapamycin (mTOR) and the silent mating-type information regulation 2 homolog 1 (SIRT1): oversight for neurodegenerative disorders

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Abstract

As a result of the advancing age of the global population and the progressive increase in lifespan, neurodegenerative disorders continue to increase in incidence throughout the world. New strategies for neurodegenerative disorders involve the novel pathways of the mechanistic target of rapamycin (mTOR) and the silent mating-type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1) that can modulate pathways of apoptosis and autophagy. The pathways of mTOR and SIRT1 are closely integrated. mTOR forms the complexes mTOR Complex 1 and mTOR Complex 2 and can impact multiple neurodegenerative disorders that include Alzheimer's disease, Huntington's disease, and Parkinson's disease. SIRT1 can control stem cell proliferation, block neuronal injury through limiting programmed cell death, drive vascular cell survival, and control clinical disorders that include dementia and retinopathy. It is important to recognize that oversight of programmed cell death by mTOR and SIRT1 requires a fine degree of precision to prevent the progression of neurodegenerative disorders. Additional investigations and insights into these pathways should offer effective and safe treatments for neurodegenerative disorders.

Neurodegenerative disorders

Neurodegenerative disorders are expected to continue to increase. This is a result of the advancing age of the global population and the progressive increase in lifespan. For example, the incidence of sporadic cases of Alzheimer's disease (AD) is expected to significantly increase throughout the globe [1–3]. Cognitive disorders such as AD can affect greater than 5 million individuals in the USA alone [1,4]. In addition, ~50 million people suffer from some form of dementia with ~60% of these cases resulting from AD [1,5–7]. The availability of definitive treatments to resolve or prevent the onset of cognitive loss is limited and for the most part such definitive treatments are non-existent [8,9]. Many pathways may lead to cognitive impairment such as cellular injury from β -amyloid (A β), tau, excitotoxicity, mitochondrial damage, acetylcholine loss, astrocytic cell injury, oxidative

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Author Contribution

K.M. solely conceived and designed the research, analyzed the results, and completed the writing of the manuscript.

Competing Interests

The Author declares that there are no competing interests associated with the manuscript.

stress, and metabolic dysfunction [10–17]. New strategies for neurodegenerative treatments involve novel pathways of the mechanistic target of rapamycin (mTOR) and the silent mating-type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1) that can modulate pathways of apoptosis and autophagy.

Programmed cell death

Programmed cell death involves autophagy and apoptosis [18–20] each with different mechanisms [21] (Figure 1). Autophagy recycles components of the cytoplasm in cells for tissue remodeling and eliminates non-functional organelles [18,20,22–24]. Macroautophagy recycles organelles and consists of the sequestration of cytoplasmic proteins and organelles into autophagosomes. Autophagosomes then combine with lysosomes for degradation and recycling [2,25]. Microautophagy involves the invagination of the lysosomal membranes for the sequestration and digestion of cytoplasmic components [26]. Chaperone-mediated autophagy [27] uses cytosolic chaperones to transport cytoplasmic components across lysosomal membranes [28]. Autophagy can be important for clinical aging pathways. Studies with *Drosophila* demonstrate that neural aggregate accumulation observed with aging is linked to a reduction in the autophagy pathway. These neural aggregates lead to behavior impairments that can be resolved with the maintenance of autophagy pathways in neurons [29]. In addition, autophagy is involved in many degenerative disorders such as cognitive decline [15,16,30], AD [1,31–34], Parkinson's disease [28,35–37], Huntington's disease [38–40], diabetes mellitus [15,23,32,41–43], aging processes [44–48], and cardio-renal disease [49]. Autophagy may be particularly important for memory processes in individuals. In some cases, activation of autophagy may decrease neurofibrillary tangles and tau in animal models that suggests a potential treatment for some forms of dementia [31,36,50,51]. Modulation of autophagy also may be important in clinical disorders such as Huntington's disease to reduce mitochondrial dysfunction and improve motor function [39,40].

Apoptosis has an early phase that involves the loss of plasma membrane phosphatidylserine (PS) asymmetry and a later phase that leads to genomic DNA degradation [52–54]. Apoptosis is a process of a series of cascade activation of nucleases and proteases that involve caspases [55,56]. These processes affect both the early phase of apoptosis with the loss of plasma membrane PS asymmetry and a later phase that leads to genomic DNA degradation. Membrane PS asymmetry loss activates inflammatory cells to target, engulf, and remove injured cells [57–60]. Yet, if the engulfment of inflammatory cells can be prevented, functional cells expressing membrane PS residues can be rescued and not be removed from the nervous system [61–64]. Once the destruction of cellular DNA occurs, it is usually not considered to be completely reversible [40]. Apoptosis in the nervous system can be involved in retinal degeneration [62,65], Parkinson's disease [36,37,66–68], pain sensitivity and neuronal injury [69], A β injury [2,70–74], epilepsy [31,75], autism [76], diabetic injury [15,23,42,77–79], and traumatic brain injury [66,80–82].

The mechanistic target of rapamycin

The mTOR is an important pathway during neurodegeneration [83,84] (Figure 1). mTOR is also known as the mammalian target of rapamycin and the FK506-binding protein 12–rapamycin complex-associated protein 1. mTOR governs the transcription of genes, protein formation, proliferation and senescence of cells, cellular metabolism, and cellular longevity [8,17,69,85,86]. mTOR forms the complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) [1,31,87,88]. mTORC1 consists of Raptor, the proline-rich Akt substrate 40 kDa (PRAS40), Deptor (DEP domain-containing mTOR-interacting protein), and mammalian lethal with Sec13 protein 8, termed mLST8 (mLST8/GβL) [7]. mTORC2 includes Rictor, mLST8, Deptor, the mammalian stress-activated protein kinase-interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) [89–94].

mTOR can modulate diabetes [24,32,66,95–97], neurodegenerative disorders [2,31,36,66,67,98–101], and dementia [11,15,17,102]. mTOR has a significant role in the modulation of autophagy induction [103]. Important in the signaling cascade of mTOR is AMP-activated protein kinase (AMPK). AMPK can prevent mTORC1 activity through the activation of the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex and can lead to the induction of autophagy [34,46,104–106].

mTOR affects neurodegenerative disorders through apoptosis and autophagy [8,18,20]. mTOR activation, in many cases, prevents apoptotic cell death in the nervous system [31,94]. Loss of mTOR activity leads to apoptotic neuronal cell death [107] and aggravation of oxidative stress pathways [108]. mTOR activation can protect against neuronal injury during ischemic preconditioning [109], loss of neurite outgrowth [110], permanent cerebral ischemia [111], cervical spinal cord injury [112], memory loss [113], and Aβ toxicity [11,72–74,114,115].

In contrast with apoptosis in the nervous system, activation of autophagy with the inhibition of mTOR activity can also be neuroprotective [116]. Inhibition of mTOR activity with the induction of autophagy increases cell survival in neonatal models of ischemia [117] and during excitotoxicity [118]. Inhibition of mTOR with autophagy activation results in neural tissue protection and functional improvement in models of spinal cord injury [119]. Autophagy is protective during prion protein disease [120] and as mentioned previously in models of Huntington's disease [7,121]. In experimental models of AD, disease progression and duration can be associated with dysfunctional autophagic processes as well as inhibition of mTOR activity [122]. Reduction in Aβ production and improved memory function in animal models of AD have been associated with autophagy activation [123].

In some cases, limitations with the induction of autophagy may be required for protection. A reduction in autophagy combined with the activation of mTOR in animal models of traumatic spinal cord injury improves function and increases survival of motor neurons [112]. During ischemic stroke in rodents, blockade of autophagy reduces infarct size and protects cerebral neurons [124]. Autophagy inhibition and activation of mTOR protects dopaminergic neurons during oxidative stress exposure [108]. In tri-cultures of neurons, astrocytes, and microglia that are exposed to inflammatory stressors and Aβ, cell injury rises

during autophagy [125]. Autophagy also can impair endothelial progenitor cells, lead to mitochondrial oxidative stress, and block new blood vessel formation during elevated glucose exposure [126]. Cortical interneurons rely upon mTOR activity with reductions in autophagic activity [85]. Trophic factors, such as erythropoietin (EPO), offer protection against hypoxia and oxidative stress in retinal progenitor cells by limiting the induction of autophagy [127]. EPO can prevent neonatal brain damage in the developing rodent during hyperoxia exposure and oxygen toxicity by inhibiting autophagy [128]. Insulin growth factor-1 prevents neuronal injury by preventing the induction of autophagy in Purkinje neurons [129].

Silent mating-type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*)

mTOR pathways are also dependent on SIRT1 [15,130,131] (Figure 1). SIRT1, a member of the sirtuin family (sirtuin 1), is a histone deacetylase [6,16,40,55,132–135] that can transfer acetyl groups from *N*-acetyl lysine amino acids onto the histones of DNA to control transcription. Seven identified mammalian homologs of Sir2 include SIRT1 through SIRT7. These histone deacetylases oversee post-translational changes of proteins, cellular proliferation, survival, and senescence. SIRT1 relies upon nicotinamide adenine dinucleotide (NAD⁺) as a substrate [135–139]. SIRT1 is vital for neurodegenerative disorders [6,140,141] that require the modulation of autophagy and apoptosis [15,27,142,143]. SIRT1 can control stem cell proliferation by modulating autophagic flux [144]. SIRT1 has an inverse relationship with mTOR in embryonic stem cells [46,145] and blocks mTOR to promote autophagy and protect embryonic stem cells during oxidative stress [146]. SIRT1 activation blocks external membrane PS exposure during the early phases of apoptosis in mature cells [58,147–149]. SIRT1 can counteract apoptosis initiated by tumor necrosis factor- α (TNF- α) in endothelial progenitor cells [150]. Loss of SIRT1 expression in endothelial progenitor cells results in apoptotic cell death that can occur in smokers and chronic obstructive disease patients [151]. SIRT1 also drives vascular survival and senescence [77,150,152], cellular metabolism [15,136,145,153–155], atherosclerosis [156–160], lifespan extension [6,161–163], oxidative stress pathways [27,146,155,164–169], neuronal survival and cognition [6,55,170–173], and retinopathy [174].

Future perspectives

Current treatments for neurodegenerative disorders are limited and require novel investigative pathways. Interestingly, mTOR and SIRT1 each offer new directions for the treatment of neurodegenerative disorders. mTOR and SIRT1 also are intimately associated with one another to control the pathways of autophagy and apoptosis. It is important to recognize that oversight of programmed cell death requires a degree of precision that can finely control the level of activation of these pathways such as with autophagy that will block the progression of neurodegenerative disorders rather than worsen these conditions. Additional insights into these pathways should offer effective and safe treatments for neurodegenerative disorders.

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Abbreviations

AD	Alzheimer's disease
AMPK	AMP-activated protein kinase
Aβ	β -amyloid
Deptor	DEP domain-containing mTOR-interacting protein
EPO	erythropoietin
mTOR	mechanistic target of rapamycin
mTORC1	mTOR Complex 1
mTORC2	mTOR Complex 2
PS	phosphatidylserine

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Figure 1. Novel treatments for the nervous system

New treatments for neurodegenerative disorders involve the mTOR and the SIRT1. The pathways of mTOR and SIRT1 are closely aligned to control apoptosis and autophagy. mTOR forms the complexes mTORC1 and mTORC2 and together with SIRT1 can oversee multiple neurodegenerative disorders that include Alzheimer's disease, dementia, Huntington's disease, Parkinson's disease, vascular cell loss, and blockade of stem cell survival.