PERSPECTIVE

Impacting dementia and cognitive loss with innovative strategies: mechanistic target of rapamycin, clock genes, circular non-coding ribonucleic acids, and Rho/Rock

A significant global impact from dementia: According to the World Health Organization (Dua et al., 2017), the current numbers for the prevalence and treatment costs for dementia worldwide are staggering. Almost 50 million individuals suffer from dementia. Dementia is now considered to be the 7th leading cause of death. Currently, at least five percent of the world's elderly population, equal to approximately 47 million individuals, have dementia. Moreover, at least sixty percent reside in low and middle income countries. Almost seventy-five percent of these new cases are to occur in these countries. The number of new cases each year throughout the globe is increasing at approximately 10 million per year. By the year 2030, 82 million people are expected to have dementia and by the year 2050, 152 million are expected to have the disease.

In regards to costs, it is estimated that greater than $800 billion United States dollars are spent to care for individuals with dementia on an annual basis. Such costs are greater than one percent of the global gross domestic product. By the year 2030, medical and social services could be overwhelmed with costs rising in the US alone to 2 trillion United States dollars annually. Furthermore, individual families encounter significant financial costs that involve social and adult living care as well as informal and companion care. In high-income countries, these costs for social care and informal care are almost shared in a fifty percent to fifty percent fashion but in low income countries, sufficient resources may only be available to provide fifteen percent of the expected costs.

In conjunction with the expected growing care needs to assist those with new onset as well as progressive dementia, the World Health Organization estimates the need for close to sixty million new health and social care workers. Implementing the need for these healthcare workers can sometimes be difficult since the onset and progression of dementia in individuals is not always well recognized. Dementia and cognitive loss is considered to be under diagnosed throughout the world. Once diagnosis is correctly performed, it can be in the late stages of the disease and care can become disjointed over time. Furthermore, the desires of those with dementia may not be respected or poorly understood which can further complicate care for affected individuals.

Implementing innovative strategies for dementia and cognitive loss: Dementia is a disorder that has multiple etiologies. Risk factors for cognitive loss include tobacco use, diabetes mellitus, low education in early life, and hypertension. Current treatments are limited and are geared to reduce symptoms but do not affect the course of the disease. Most available treatments that are directed to treat Alzheimer's disease (AD) involve the use of cholinesterase inhibitors (Ruhal and Dhingra, 2018). Dementia that may be caused by vascular disease may be treated with therapies that focus on vascular and metabolic disorders, such as diabetes mellitus (Maiese, 2018). Despite these limitations with current strategies, a number of new, innovative, and exciting treatment avenues are being developed that include pathways for the mechanistic target of rapamycin (mTOR), circadian clock genes, circular ribonucleic acids (CircRNAs), and rho-associated protein kinases (ROCKs) (**Figure 1**).

The mechanistic target of rapamycin: mTOR, also known as the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1 (FRAP1), oversees the transcription of genes and translation of proteins, proliferation of cells, cellular metabolism, and cellular longevity (Maiese, 2018). mTOR forms part of the complexes mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 has a number components that include Raptor, the proline rich Akt substrate 40 kDa, DEP-domain-containing mTOR-interacting protein, and mammalian lethal with Sec13 protein 8, termed mammalian lethal with SEC13 protein 8 (mLST8). mTORC2 has different components from mTORC1 and includes Rictor, mLST8, DEP-domain-containing mTOR-interacting protein, the mammalian stress-activated protein kinase interacting protein 1, and the protein observed with Rictor-1 (Protor-1) (**Figure 1**).

mTOR affects neurodegenerative disorders through apoptosis and autophagy (Maiese, 2018). mTOR activation blocks apoptotic cell death in the nervous system and can prevent β-amyloid (Aβ) toxicity that occurs during AD. Interestingly, mTOR may play a different role during autophagy. It is the inhibition of mTOR with subsequent autophagy activation that can lead to neural tissue protection and functional improvement. Autophagy activation that coincides with mTOR inhibition can be protective during neurodegenerative disorders to remove toxic cellular inclusions. Reduction in Aβ and tau production through autophagy induction and mTOR inhibition can lead to improved memory function in animal models of AD (Cheng et al., 2018). mTOR activation also may be associated with microglial activation and inflammation of the nervous system that may alter the onset and progression of cognitive loss (Morris et al., 2018).

It is important to recognize that dementia with cognitive loss represents a complex biological process that requires a fine modulation of the induction of autophagy. Autophagy inhibition with the activation of mTOR is sometimes necessary to protect neurons during oxidative stress exposure. In experimental models with neurons, astrocytes, and microglia that are exposed to inflammatory stressors and Aβ, cell injury rises during autophagy induction. In addition, cortical interneuron development has been shown to rely upon mTOR with a reduction in autophagy activity.

Circadian clock genes: Circadian rhythm clock genes are becoming increasingly recognized as important components that can affect dementia and cognitive loss (Maiese, 2017). Receiving light input from photosensitive ganglion cells in the retina, the mammalian circadian clock is in the suprachiasmatic nucleus located above the optic chiasm. The suprachiasmatic nucleus depends upon the pineal gland, hypothalamic nuclei, and vasoactive intestinal peptide to control the release of cortisol and melatonin, response to oxidative stress, and body temperature. Members of the basic helix-loop-helix-PAS (Period-Arnt-Single-minded) transcription factor family, that include CLOCK and BMAL1, oversee the expression of the genes *Cryptochrome* (*Cry1 and Cry2*) and *Period* (*Per1*, *Per2,* and *Per3*) in the clock gene family (**Figure 1**).

The clock gene pathway appears to be altered during dementia disorders. Rhythmic methylation of BMAL1 is changed in the brains of patients with AD, suggesting that modifications in the DNA methylation of clock genes may contribute to cognitive loss and behavior changes. In murine models of AD, there also exists marked changes in the expression of clock gene ribonucleic acid (RNA) that may indicate a dysfunction in the clock pathways during cognitive loss (Bellanti et al., 2017). Circadian rhythm dysfunction during cognitive loss also involves the induction of autophagy. It has been suggested that in animal models of AD a basal circadian rhythm that controls macroautophagy may be required to prevent cognitive decline and Aβ deposition. Loss in cognition and memory can occur if circadian rhythm function is impaired. For example, chronic sleep fragmentation has been shown to affect autophagy proteins in the hippocampus that ultimately leads to memory and cognitive loss.

In addition to their reliance upon autophagy, circadian pathways are linked to mTOR. Melatonin, a pineal hormone that controls circadian rhythm, employs autophagy pathways and mTOR to control aging and neurodegenerative processes. If mTOR activity is lost such as during microgravity studies, circadian rhythm becomes dysfunctional and leads to cognitive decline (Wu et al., 2017).

Circular RNAs: Small non-coding RNAs, termed microRNAs (miRNAs) have recently been identified as innovative strategies for a number of disorders that include dementia (Maiese, 2016). MiRNAs consist of 19–25 nucleotides and control gene expression by silencing targeted messenger RNAs translated by specific genes. Non-coding ribonucleic acids play an important role in numerous processes such as stem cell development and differentiated cell survival, vascular cell maintenance, tumorigenesis, angiogenesis, aging, and oxidative stress.

In the family of non-coding RNAs, circRNAs are non-coding RNAs of approximately 100 nucleotides in length that were initially identified as being circular in nature. CircRNAs have covalent bonds that maintain their circular structure. These non-coding RNAs have both *cis* and *trans* regulation, regulate gene expression through the sponging of miRNAs, control apoptotic pathways, modulate cancer growth, and may even function as biomarkers (Maiese, 2016). In regards to the onset of cerebral vascular disease that can lead to cognitive loss, it has been shown that circular antisense non-coding RNA in the INK4 locus in vascular smooth muscle

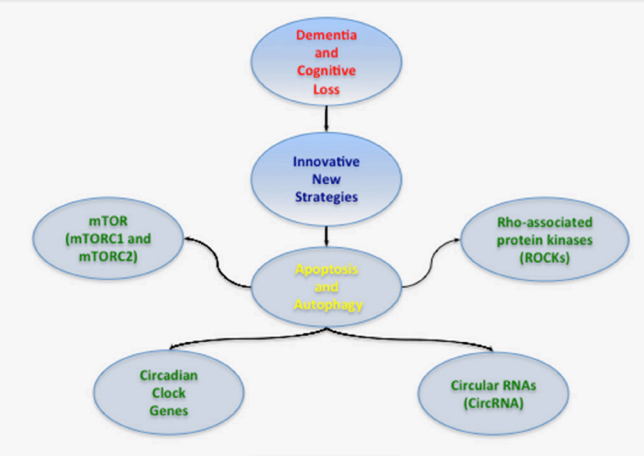

Figure 1 Novel pathways for dementia treatment.
Novel and innovative new strategies are needed to offer treatment for individuals with dementia. Dementia and cognitive loss are now considered to be the 7th leading cause of death in the world and only limited symptomatic treatments exist for the treatment of dementia. Exciting new work has highlighted innovative strategies with mechanistic target of rapamycin (mTOR), circadian clock genes, circular RNAs (CircRNAs), and rho-associated protein kinases (ROCKs). Each of these pathways interfaces with programmed death pathways of apoptosis and autopahgy and offer exciting prospects for treatments to prevent either the onset or progression of dementia and cognitive loss. mTORC1: mTOR complex 1; mTORC2: mTOR complex 2.

cells and macrophages can block exonuclease-mediated pre-ribosomal RNA processing, ribosome biogenesis, and the proliferation of cells that may lead to atherosclerosis and lead to dementia. CircRNAs also can serve as endogenous miRNA sponges to block carotid atherosclerotic disease, diabetes mellitus, and coronary artery disease that also may result in cognitive loss (**Figure 1**).

However, as with many biological systems, circRNAs are not consistent in offering protection against disease and may, at times, require target inhibition to prevent further disease progression. For example, up-regulation of some circRNAs may lead to apoptotic cell death during ischemia-reperfusion injury. CircRNAs may serve as a sponge for protective miRNAs, such as miR-7a, and promote myocardial and vascular injury.

ROCKs: ROCKs form part of the protein kinase A (PKA)/protein kinase G (PKG)/protein kinase C (PKC) family of serine-threonine kinases. In the mammalian population, ROCKs consist of a kinase domain with a coiled-coil region and a Pleckstrin homology domain. In regards to the ROCK sub-family in mammals, rho-associated, coiled-coil containing protein kinase 1 (ROCK1) and rho-associated, coiled-coil containing protein kinase 2 (ROCK2) control cell migration through actin organization. Yet, new work has revealed multiple functions for these kinases that can involve neurite growth oversight, tumor growth control through phosphatase and tensin homologue, insulin signaling, and endothelial cell tight junction maintenance. ROCKs also work in conjunction with a number of signal transduction pathways. In addition to mTOR signaling tied to ROCK pathways, ROCKs, such as ROCK1, can be activated by circRNAs that sponge the inhibitor miRNA-124 to lead to cellular proliferation (**Figure 1**).

In the nervous system, ROCKs also have recently been highlighted as important targets for cognitive loss and disorders that disrupt the native cerebral architecture. Both ROCK1 and ROCK2 appear to play a role in regulating neuronal dendritic structure. Activation of the Rho/ROCK signaling pathway during cerebral ischemic events promotes the Eph/Ephrin signaling pathway that results in blood-brain barrier disruption (Chen et al., 2018). Animal models of diabetic induced dementia have shown that reduction in ROCK2 expression can lead to improved cognitive ability (Mehla et al., 2013). Additional studies also performed in models of diabetic induced dementia suggested that reductions in ROCK2 expression are associated with increased cholinesterase inhibition. Yet, the overall function of the ROCK pathway in the brain during dementia is not entirely clear at this time since ROCKs appear to have both beneficial and detrimental functions. As an example, recent work has shown that ROCK1 can decrease Aβ secretion and increase autophagy-related substances, but ultimately ROCKs lead to increased intracellular accumulation of Aβ and do not assist with autophagic clearance of Aβ (Hu et al., 2016).

Future considerations: Novel and innovative new strategies are desperately required to provide treatment for individuals with dementia. Dementia and cognitive loss are now considered to be the 7th leading cause of death in the world. Loss of cognitive function presents a significant financial burden that is greater than one percent of the global gross domestic product and significantly impacts the ability of families and caretakers to adequately care for the increasing population of affected individuals. Furthermore, at present only limited symptomatic treatments exist for the treatment of dementia. Recent work has identified innovative strategies with mTOR, circadian clock genes, circRNAs, and ROCKs. Each of these pathways offer exciting prospects for future treatment strategies directed against cognitive loss, but further work is required to gain greater appreciation of the complexity of each of these pathways to ensure maximum treatment benefit and limit potentially detrimental outcomes.

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