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Novel Treatment Strategies for the Nervous System: Circadian Clock Genes, Non-coding RNAs, and Forkhead Transcription Factors

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Abstract

BACKGROUND—With the global increase in life span expectancy, neurodegenerative disorders continue to affect an ever increasing number of individuals throughout the world. New treatment strategies for neurodegenerative diseases are desperately required given the lack of current treatment modalities.

METHODS—Here we examine novel strategies for neurodegenerative disorders that include circadian clock genes, non-coding ribonucleic acids (RNAs), and the mammalian forkhead transcription factors of the O class (FoxOs).

RESULTS—Circadian clock genes, non-coding RNAs, and FoxOs offer exciting prospects to potentially limit or remove the significant disability and death associated with neurodegenerative disorders. Each of these pathways have an intimate relationship with the programmed death pathways of autophagy and apoptosis and share a common link to the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1) and the mechanistic target of rapamycin (mTOR). Circadian clock genes are necessary to modulate autophagy, limit cognitive loss, and prevent neuronal injury. Non-coding RNAs can control neuronal stem cell development and neuronal differentiation and offer protection against vascular disease such as atherosclerosis. FoxOs provide exciting prospects to block neuronal apoptotic death and to activate pathways of autophagy to remove toxic accumulations in neurons that can lead to neurodegenerative disorders.

CONCLUSIONS—Continued work with circadian clock genes, non-coding RNAs, and FoxOs can offer new prospects and hope for the development of vital strategies for the treatment of neurodegenerative diseases. These innovative investigative avenues have the potential to significantly limit disability and death from these devastating disorders.

Keywords

aging; aging-related disorders; Alzheimer's disease; apoptosis; autophagy; BMAL1; cell longevity; circadian rhythm; circular RNA; CLOCK; clock genes; Cryptochrome; deoxyribonucleic acid; diabetes mellitus; erythropoietin; forkhead; FoxO; Huntington's disease;

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metabolism; microRNA; mitochondria; mechanistic target of rapamycin (mTOR); non-coding RNA; oxidative stress; Parkinson's disease; period (PER); programmed cell death; REV-ERBα; RORα; RORE; silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1); sirtuin; stem cells; transcription factors; vascular disease

1. Introduction

According to the World Health Organization, non-communicable diseases (NCDs) are on the rise and can be attributed to more than sixty percent of the annual fifty-seven million global deaths (1). The rise in NCDs parallels an observed increase in life expectancy of the world's population. The age of the global population continues to increase with life expectancy approaching eighty years of age (2). In addition, the number of individuals over the age of sixty-five has doubled during the previous fifty years (3). It is expected that the number of elderly individuals in large developing countries such as India and China also will increase from five percent to ten percent over the next several decades (4, 5). There are a number of reasons that may account for the increased lifespan, but improvements in effective treatments for multiple disorders (6–10) and broader access to preventive care are believed to have contributed to the increased life span of the world's population. For NCDs, greater than ten percent of the population under sixty years of age is affected in high-income countries (1). In contrast, NCDs affect a much larger proportion of the population in in low and middle-income countries with at least one-third of the population under the age of 60 suffering from NCDs.

Interestingly, neurodegenerative disorders form a significant component of NCDs (11). Neurodegenerative disorders include more than six hundred disease entities and progressively lead to nervous system dysfunction (12). Acute and chronic neurodegenerative disorders lead to disability and death for greater than thirty million individuals worldwide (13). Improvements in clinical care that have fostered an increased life span of the global population are also believed to have produced a continual rise in the presentation of neurodegenerative disorders. Neurodegenerative disorders also may be on the rise as a result of other disorders that can severely impair the peripheral and central nervous system (CNS) (14). One example is the contribution of other NCDs such as diabetes mellitus (DM) (15). DM affects the global population (16, 17) such that approximately three hundred and fifty million individuals suffer from DM (18–22). Another eight million individuals also have metabolic disorders but remain undiagnosed at present (23–25). Impaired glucose tolerance in the young (5, 26) and the presence of obesity increases the risk of developing DM in these individuals (19).

DM is a multi-system disease that results in progressive deterioration of the body (16, 24, 27, 28) and the nervous system (29). In the nervous system, it leads to visual impairment (24, 30–32), stroke (4, 33–37), peripheral nerve disease (28, 38), and cognitive loss that may be associated with Alzheimer's disease (AD) (4, 39–43).

In addition to DM, vascular disease also contributes significantly to the onset and progression of disorders within the nervous system. Vascular disorders rank high among NCDs and fall within the five leading causes of death that include cardiac disease, cancer,

chronic lower respiratory disease, stroke, and traumatic accidents (44). Within vascular disorders, hypertension and associated elevated serum lipids are significant risk factors for stroke. Ischemic and hemorrhagic disorders of the brain affect at least fifteen million individuals every year and lead to an annual cost of seventy-five billion dollars in the United States (2, 13, 45–47).

2. Novel Nervous System Strategies

As noted, it is estimated that the incidence of neurodegenerative disorders will continue to increase as a result of the advancing age of the global population and the progressive increase in life span. On example of a nervous system disorder that is expected to increase is AD. The incidence of sporadic cases of AD is expected to significantly increase throughout the globe (13, 48, 49). Healthcare resources will be impacted to a large extent (29, 50). In the United States (US) alone, more than five million individuals are diagnosed with sporadic AD and at least four million are under treatment at an annual cost of four billion US dollars. AD is not the result of a single etiology (42). Multiple mechanisms may lead to cognitive impairment and involve cellular injury from β-amyloid (Aβ), tau, excitotoxicity, mitochondrial damage, acetylcholine loss, astrocytic cell injury, oxidative stress, and cellular metabolic dysfunction with DM (14, 51–57). Yet, there is a growing arsenal of novel therapeutic strategies directed against AD and other neurodegenerative disorders that include circadian rhythm clock genes (9), non-coding ribonucleic acids (RNAs), and the mammalian forkhead transcription factors of the O class (FoxOs) (56, 58, 59). These pathways share common signal transduction mechanisms with the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1) and the mechanistic target of rapamycin (mTOR). Each of these pathways can influence the onset and progression of neurodegenerative disorders and oversee critical pathways of programmed cell death that involve apoptosis and autophagy.

3. Autophagy and Apoptosis

Programmed cell death includes two vital pathways that involve apoptosis and autophagy (60–62) (Figure 1). Although apoptosis and autophagy are involved in programmed cell death, each pathway has unique characteristics that can differentiate apoptosis from autophagy (63). Apoptosis has two distinct phases that consist of an early phase that involves the loss of plasma membrane phosphatidylserine (PS) asymmetry and a subsequent later phase that leads to genomic DNA degradation (64–66). Apoptosis is the result of a series of cascade activation of nucleases and proteases that involve caspases (67, 68). These processes impact both the early phase of apoptosis with the loss of plasma membrane PS asymmetry and a later phase that leads to genomic DNA degradation. Loss of membrane PS asymmetry activates inflammatory cells to target, engulf, and remove injured cells (69–72). However, 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 (24, 73–75). In contrast, once the destruction of cellular DNA occurs, it is usually not considered to be completely reversible (59). Apoptosis in the nervous system can be involved in retinal degeneration (24, 76), pain sensitivity and neuronal injury (77), Aβ injury

(13, 78–82), epilepsy (83, 84), Parkinson's disease (11, 41, 85–87), diabetic injury (14, 17, 26, 88–90), traumatic brain injury (41, 91–93), and autism (94).

Autophagy recycles components of the cytoplasm in cells for tissue remodeling and seeks to eliminate non-functional organelles (60, 62, 89, 95, 96). Macroautophagy is a classification of autophagy that recycles organelles and consists of the sequestration of cytoplasmic proteins and organelles into autophagosomes. Autophagosomes then combine with lysosomes for degradation and recycling (13, 97). Microautophagy is the invagination of the lysosomal membranes for the sequestration and digestion of cytoplasmic components (5). Chaperone-mediated autophagy (58) relies upon cytosolic chaperones to transport cytoplasmic components across lysosomal membranes (98). Autophagy can be linked to 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 (99). In addition, autophagy is involved in a number of degenerative disorders such as cognitive decline (14, 56, 100), AD (40, 48, 83, 101, 102), Parkinson's disease (11, 87, 98, 103), Huntington's disease (59, 104, 105), DM (14, 17, 40, 89, 106, 107), and aging processes (8, 40, 85, 91, 108–111). Autophagy also may be required to preserve metabolic homeostasis with mTOR (112).

4. Circadian Clock Genes

Circadian rhythm clock genes have a significant role in the nervous system and with programmed cell death (9, 113) (Figure 1). The mammalian circadian clock resides in the suprachiasmatic nucleus (SCN) located above the optic chiasm and receives light input from photosensitive ganglion cells in the retina. The SCN depends upon the pineal gland, hypothalamic nuclei, and vasoactive intestinal peptide to control a number of processes that involve the release of hormones cortisol and melatonin, oxidative stress responses (114), and the regulation of body temperature (115).

In the clock gene family, members of the basic helix-loop-helix -PAS (Period-Arnt-Single-minded) transcription factor family, such as CLOCK and BMAL1 (116), oversee the expression of the genes *Cryptochrome (Cry1 and Cry2)* and *Period (Per1, Per2, and Per3).* Feedback is provided by PER:CRY heterodimers that can translocate to the nucleus to inhibit and block the transcription of CLOCK:BMAL1 complexes. Additional regulatory loops consist of retinoic acid-related orphan nuclear receptors REV-ERBα, also known as NR1D1 (nuclear receptor subfamily 1, group D, member 1), and RORα that are activated by CLOCK:BMAL1 heterodimers. The REV-ERBα and RORα receptors bind retinoic acid-related orphan receptor response elements (ROREs) present in the BMAL1 promoter to control transcription with RORs that can promote transcription and REV-ERBs that can repress transcription to result in circadian oscillation of BMAL1 (117, 118).

In the nervous system, rhythmic methylation of BMAL1 has been found to be changed in the brains of patients with AD, suggesting that alterations in the DNA methylation of clock genes may contribute to cognitive loss and behavior changes (53). Animal models of Parkinson's disease with 6-hydroxydopamine (6-OHDA) have shown decreased BMAL1

and RORα persisted with levodopa treatment, indicating that long-term levodopa treatment may impair circadian rhythm function (119). Interestingly, clock genes also impact lifespan that is related to neurodegeneration. In studies with *Drosophila melanogaster*, lifespan was reduced in three arrhythmic mutants involving ClkAR, cyc0 and tim0. ClkAR mutants had significant faster age-related locomotor deficits. Restoring Clk function was able to rescue *Drosophila* from the locomotor deficits. An increase in oxidative stress was noted with the mutant phenotypes, but deficits appeared to correlate best with loss of dopaminergic neurons rather than directly to the presence of oxidative stress in this case (120).

Circadian rhythm dysfunction during cognitive loss and aging can be associated with autophagy induction (121). In animal models of AD, a basal circadian rhythm that controls macroautophagy may be necessary to limit cognitive decline and Aβ deposition (122). It has been noted that mild changes in the external environment that affect circadian rhythm may alter cognition. Chronic sleep fragmentation has been shown to affect autophagy proteins in the hippocampus (123) that may affect memory and cognition (48, 56, 102, 124, 125). Autophagy in the hippocampus also is depressed during the absence of the PER1 circadian clock protein that may worsen the pathology of cerebral ischemia (126).

Circadian pathways are intimately linked to not only autophagy, but also the mechanistic target of rapamycin (mTOR) (127, 128). mTOR also is known as the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1. mTOR controls multiple functions that determine the transcription of genes, proliferation and senescence of cells, protein formation, cellular metabolism, and cellular longevity (9, 57, 77, 129, 130). Melatonin, a pineal hormone that controls circadian rhythm, relies upon autophagy pathways and mTOR to control processes of aging and neurodegeneration (131). Loss of mTOR activation can be involved with altered circadian rhythm and cognitive decline during prolonged space flight (130). Furthermore, cerebral ischemic infarction may be influenced by an alteration in circadian rhythm genes and fluctuations in mTOR activity (126, 132).

Circadian rhythm and mTOR pathways are also dependent upon SIRT1 (14, 133, 134). SIRT1, a member of the sirtuin family, is a histone deacetylase (4, 56, 59, 67, 135–138) that can transfer acetyl groups from ε-N-acetyl lysine amino acids on the histones of DNA to control transcription. Seven identified mammalian homologues of Sir2 exist that include SIRT1 through SIRT7. These histone deacetylases control post-translational changes of proteins and oversee cellular proliferation, survival, and senescence. SIRT1 is dependent upon nicotinamide adenine dinucleotide (NAD^+) as a substrate (138–142). SIRT1 is involved in neurodegenerative disorders (4, 143, 144) that require the modulation of autophagy and apoptosis (14, 58, 145, 146). SIRT1 can control stem cell survival by modulating autophagic flux (147). SIRT1 also can have an inverse relationship with mTOR in embryonic stem cells (20, 110) and block mTOR to promote autophagy and protect embryonic stem cells during oxidative stress (148). In regards to apoptotic pathways, SIRT1 activation can block external membrane PS exposure during the early phases of apoptosis in mature cells (70, 149–151). SIRT1 also can counteract apoptosis initiated by tumor necrosis factor-α (TNF-α) in endothelial progenitor cells (152). Loss of SIRT1 expression in

endothelial progenitor cells leads to apoptotic cell death that can occur in smokers and chronic obstructive disease patients (153).

SIRT1 has been associated with altered circadian rhythm function that affects the development of disorders such as AD (113). SIRT1 control of circadian rhythm and melatonin also may affect glucose tolerance and DM (115) as well as inflammation during obesity (154). Increased SIRT1 activity with a disruption in circadian rhythm also leads to additional disorders such as increased susceptibility to mammary carcinogenesis (155). Yet, SIRT1 may be beneficial under specific circumstances to regulate circadian rhythm gene expression that can foster hepatocellular proliferation and liver regeneration following liver resection (156). More recent work also suggests an important role for SIRT1 targets with aging and circadian gene expression in the liver (157).

5. SIRT1 and Non-coding RNAs

Given the critical importance of vascular disease in affecting the nervous system, SIRT1 and its ability to oversee small non-coding ribonucleic acids (RNAs), termed microRNAs (miRNAs) (134, 158–160), have become exciting targets for vascular disease and the nervous system (Figure 1). SIRT1 pathways are involved in vascular survival and senescence (88, 152, 161), atherosclerosis (162–166), lifespan extension (4, 167–169), diabetic retinopathy (170), cellular metabolism and DM (14, 17, 20, 115, 145, 171, 172), oxidative stress pathways (58, 148, 173–179), and neuronal survival and cognition (11, 113, 180–183).

MiRNAs are composed of 19-25 nucleotides and can control gene expression by silencing targeted messenger RNAs (mRNAs) translated by specific genes. Non-coding ribonucleic acids play an important role with SIRT1 to control stem cell development and differentiated cell survival. Under some conditions, increased SIRT1 activity is beneficial. Silencing of miR-195 in old mesenchymal stem cells promotes stem cell proliferation by increasing SIRT1 activity to restore anti-aging factors expression that include telomerase reverse transcriptase, the forkhead transcription factor FOXO1 (59), and protein kinase B (Akt) (160). Stem cell proliferation also may require increased SIRT1 activity in combination with the inhibition or dysfunction of mTOR signaling that is controlled by miRNAs (184). Vascular cell maintenance during DM appears to need SIRT1 activity controlled by miRNAs. Diabetic endothelial vascular dysfunction that occurs during hyperglycemia with the release of elevated free fatty acids can occur during the up-regulation of miR-34a that depresses the expression of SIRT1. During periods of hyperglycemia, angiogenesis is impaired as a result of suppressed SIRT1 expression and the up-regulation of miR-34a expression (185). The retinal microvasculature also can be impacted by miRNAs. Studies in rats demonstrate that an up-regulation of senescence-associated markers that include miR-34a depress SIRT1 expression and accelerate aging and oxidative stress injury in the retinal vasculature (176). Despite these studies, it should be noted that a reduction in SIRT1 activity controlled by miRNAs may at times offer a benefit to neuronal stem cell populations. Neuronal differentiation can occur through miR-34a that leads to decreased SIRT1 expression and DNA-binding of p53 in mouse neural stem cells (186).

Other forms of non-coding RNAs also impact vascular disease. Circular ribonucleic acids (circRNAs) are non-coding RNAs of approximately 100 nucleotides in length that were initially identified as being circular in nature (187–189). CircRNAs have covalent bonds that maintain their circular structure, have both *cis* and *trans* regulation, regulate gene expression through the sponging of microRNAs (miRNAs) (190), function as biomarkers, and control apoptotic pathways (60, 62). Circular antisense non-coding RNA in the INK4 locus (circANRIL) in vascular smooth muscle cells and macrophages prevents exonuclease-mediated pre-ribosomal RNA processing, ribosome biogenesis, and proliferation of cells that may lead to atherosclerosis through the onset of apoptosis (191). However, circRNAs may not always be protective against programmed cell death and apoptosis. Up-regulation of specific circRNAs may foster apoptotic cell injury during cell models of ischemic-reperfusion injury (192).

6. FoxO Transcription Factors

Given the scope of the world's population affected by neurodegenerative disorders, it is of particular concern that cognitive disorders such as AD can affect greater than 5 million individuals in the US alone (48, 193). Furthermore, approximately fifty million million people suffer from some form of dementia with approximately sixty percent of these cases resulting from AD (4, 12, 48, 194). Unfortunately, the availability of definitive treatments to resolve or prevent the onset of cognitive loss is limited and to the most extent such definitive treatments are non-existent (9, 50).

Mammalian forkhead transcription factors are a novel strategy to consider for neurodegenerative disorders, especially those that involve dementia and cognitive loss (59, 83, 195, 196) (Figure 1). Greater than one hundred forkhead genes and nineteen human subgroups that range from *FOXA* to *FOXS* have been identified since the original discovery of the *Drosophila melanogaster gene forkhead* (197). For neurodegenerative disorders, the mammalian FOXO proteins of the O class have significant relevance and have the members FOXO1, FOXO3, FOXO4, and FOXO6 (198). Previous terminology for forkhead proteins included forkhead in rhabdomyosarcoma (FKHR) (FOXO1), FKHRL1 (forkhead in rhabdomyosarcoma like protein 1) (FOXO3a), the *Drosophila* gene fork head (*fkh*), Forkhead RElated ACtivator (FREAC)-1 and -2, and the acute leukemia fusion gene located in chromosome X (*AFX*) (*FOXO4*) (199, 200). With the current nomenclature, an Arabic number is provided with the designation of "Fox", then a subclass or subgroup letter is provided, and finally the member number is listed within the subclasses of the Fox proteins (201). All letters are capitalized for human Fox proteins. For the mouse, only the initial letter is listed as uppercase and for all other chordates the initial and subclass letters are in uppercase (200, 202, 203).

FoxO proteins are transcription factors that bind to deoxyribonucleic acid (DNA) through the FoxO-recognized element in the C-terminal basic region of the forkhead DNA binding domain (204, 205). Following forkhead binding to DNA, target gene expression is repressed or activated through fourteen protein-DNA contacts with the primary recognition site located at α-helix H3 (206). Phosphorylation or acetylation that can block FoxO activity may alter the binding of the C-terminal basic region to DNA to prevent transcriptional activity (207).

FoxO transcription factors may impact neurodegenerative disorders through apoptosis and autophagy (60, 62). Inhibition or loss of FoxO activity usually improves cell survival during apoptotic cell injury. Blockade of FoxO transcription factor activity can protect against microglial cell demise during oxidative stress (71) and Aβ exposure (208), foster the protective effects of metabotropic glutamate receptors (209), increase neuronal cell survival through nicotinamide adenine dinucleotide (NAD^+) precursors (210), raise survival with growth factors (211), such as erythropoietin (EPO) (150, 212–214) and neurotrophins (215–217), and lessen metabolic and vascular disease (218). Antipsychotics, such as clozapine, may function through FoxO inhibition to protect against apoptotic neuronal cell loss (219). Pathways involving SIRT1 also can affect FoxO modulation of apoptotic cell death. SIRT1 can increase neuronal survival through modulation of FoxO activity (67, 140, 142, 220, 221). In addition, under some conditions, sirtuins and FoxO transcription factors may function synergistically to increase neuronal cell survival (4, 142). FoxO proteins in conjunction with SIRT1 pathways may offer protection against Aβ toxicity (181) and forkhead transcription factors, such as FoxO3a, may be dependent upon SIRT1 to reduce oxidative stress and cell injury during exposure to Aβ (222).

FoxO proteins may offer protection with neurons during autophagy induction. Increased FoxO activity, such as with FoxO1, can function to increase basal autophagy and reduce atherogenesis (56, 223). Ectopic expression of FoxO1 enhances autophagy and increases toxic Huntington's disease Huntingtin (mHtt) protein clearance in neuronal cell cultures (224). In addition, loss of FoxO and SIRT1 activity with a reduction in autophagy activity in models with *Drosophila* can lead to neuronal accumulation of Aβ (225).

Given the close ties of mammalian forkhead transcription factors with the programmed death pathways of apoptosis and autophagy, FoxOs are considered as vital targets to treat neurodegenerative disorders. For example, FoxO transcription factors play a significant role in inflammation and can affect vascular inflammatory pathways (203) and cardiac injury (201). Calcineurin and FoxO3 can interact in astrocytes during Aβ exposure that results in pro-inflammatory cytokines and injury to neurons (226). Since nuclear translocation of FoxO3 is tied to apoptotic neuronal DNA damage (59, 227, 228), FoxO transcription factors could be considered a therapeutic strategy to prevent excessive Aβ production and suppress the onset of AD. Under some conditions, Aβ exposure can result in the dephosphorylation and mitochondrial translocation of FoxO3a that leads to mitochondrial dysfunction (196). Furthermore, increased FoxO activity can function in concert with tribbles pseudokinase 3 to result in apoptotic and autophagic Aβ induced neuronal cell death (79). Inhibition of FoxO activity under such conditions can protect against oxidative stress and Aβ toxicity (208, 229).

7. Considerations for the Future

NCDs are increasing in prevalence throughout the world that parallels a rise in life expectancy in the global population. As a result, the prevalence of neurodegenerative disorders also has been impacted by acute and chronic neurodegenerative disorders resulting in disability and death for greater than thirty million individuals worldwide. Neurodegenerative disorders also may be on the rise as a result of other disorders that can

impair the peripheral and CNS that include DM and vascular disease. Present strategies to treat neurodegenerative disorders as well as associated disorders are extremely limited and warrant novel investigative pathways. In this respect, great enthusiasm is present for new therapies for neurodegenerative disorders that include circadian clock genes, non-coding RNAs, and FoxOs. Each of these pathways is able to modulate critical pathways of programmed cell death that involve autophagy and apoptosis. An intact circadian rhythm and expression of clock genes appear necessary to modulate autophagy, limit cognitive loss, and prevent neuronal injury. Non-coding RNAs can oversee neuronal stem cell development and differentiation, but also may be protective against vascular diseases, such as atherosclerosis. Mammalian forkhead transcription factors of the O class also offer exciting prospects for new therapies to prevent neuronal apoptotic death and to also employ pathways of autophagy to remove toxic accumulations in neurons that can lead to neurodegenerative disorders. Interestingly, the pathways of circadian clock genes, non-coding RNAs, and FoxOs are intimately dependent upon SIRT1 as well as mTOR pathways. Further investigation into each of these novel pathways should provide necessary insight into not only the treatment of neurodegenerative disorders, but also the ability to prevent the onset of disease in the nervous system.

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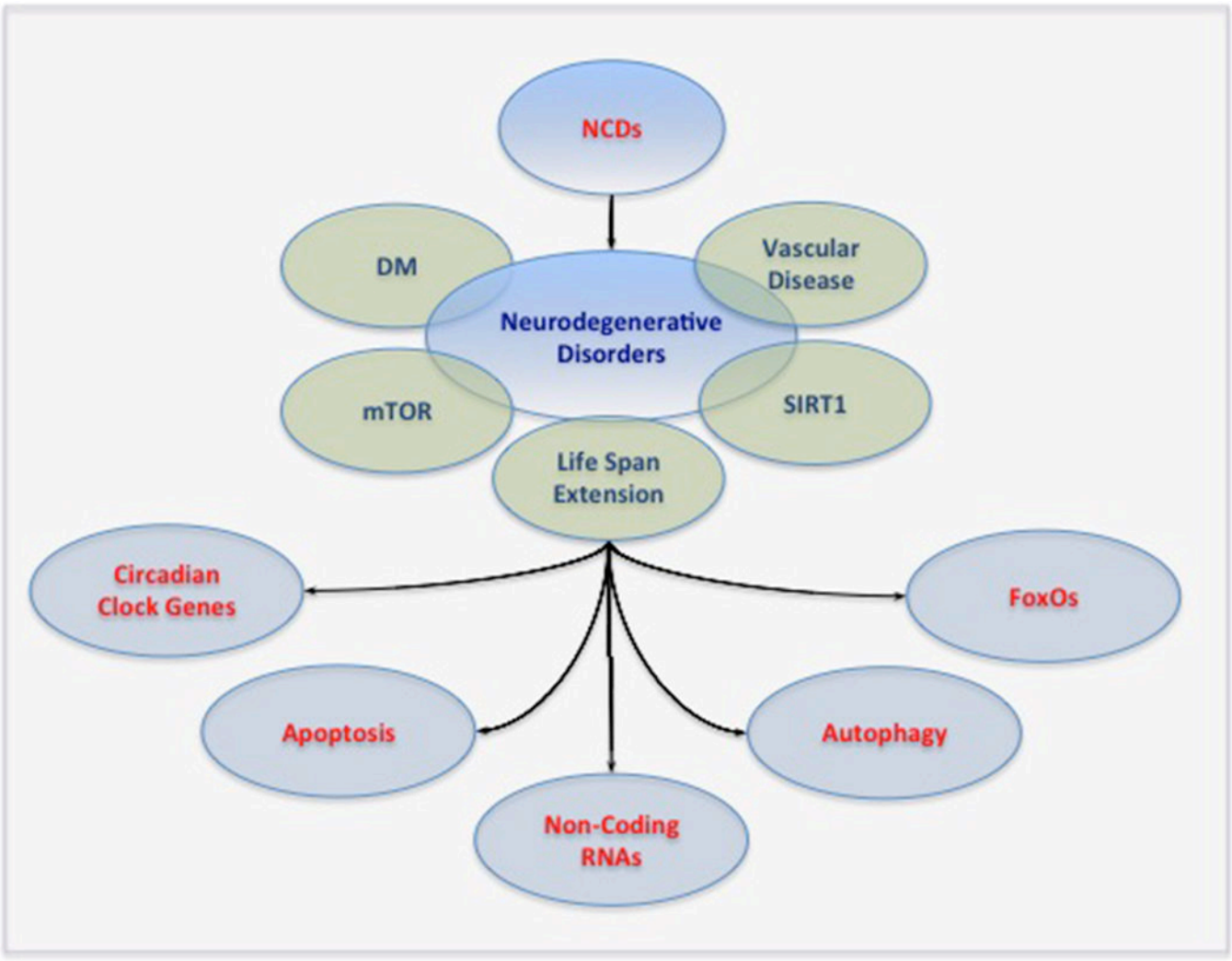

Figure 1. Innovative Strategies for Neurodegenerative Disorders

As global life span expectancy increases, non-communicable diseases (NCDs) and neurodegenerative disorders will impact a greater number of individuals throughout the world. New treatment strategies for neurodegenerative diseases are desperately warranted especially with the lack of current treatment modalities. Circadian clock genes, non-coding ribonucleic acids (RNAs), and the mammalian forkhead transcription factors of the O class (FoxOs) offer the potential to eliminate the disability and death associated with neurodegenerative disorders as well as address related disorders such as diabetes mellitus (DM) and vascular disease. These pathways have a close relationship with autophagy and apoptosis and share common links to the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1) and the mechanistic target of rapamycin (mTOR).