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Sirtuins: Developing Innovative Treatments for Aged-Related Memory Loss and Alzheimer's Disease

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Abstract

The world's population continues to age at a rapid pace. By the year 2050, individuals over the age of 65 will account for sixteen percent of the world's population and life expectancy will increase well over eighty years of age. Accompanied with the aging of the global population is a significant rise in non-communicable diseases (NCDs). Neurodegenerative disorders will form a significant component for NCDs. Currently, dementia is the 7th leading cause of death and can be the result of multiple causes that include diabetes mellitus, vascular disease, and Alzheimer's disease (AD). AD may represent at least sixty percent of these cases. Current treatment for these disorders is extremely limited to provide only some symptomatic relief at present. Sirtuins and in particular, the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1), represent innovative strategies for the treatment of cognitive loss. New work has revealed that SIRT1 provides protection against memory loss through mechanisms that involve oxidative stress, Aβ toxicity, neurofibrillary degeneration, vascular injury, mitochondrial dysfunction, and neuronal loss. In addition, SIRT1 relies upon other avenues that can include trophic factors, such as erythropoietin, and signaling pathways, such as Wnt1 inducible signaling pathway protein 1 (WISP1/CCN4). Yet, SIRT1 can have detrimental effects as well that involve tumorigenesis and blockade of stem cell differentiation and maturation that can limit reparative processes for cognitive loss. Further investigations with sirtuins and SIRT1 should be able to capitalize upon these novel targets for dementia and cognitive loss.

Keywords

aging; aging-related disorders; Alzheimer's disease; apoptosis; autophagy; CCN4; erythropoietin; diabetes mellitus; histone deacetylases; metabolism; oxidative stress; programmed cell death; stem cells; SIRT1; sirtuins; transcription factors; vascular disease; WISP1; Wnt1 inducible signaling pathway protein 1

The Global Aging of the World's Population

It is expected that the number of individuals age 65 or older will increase from 524 million to over 1.5 billion by the year 2050. This number would represent sixteen percent of the

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world's population. The age of the global population will increase with life expectancy well over eighty years of age (1). Of further interest, it has been observed that the number of individuals over the age of sixty-five has doubled during the previous fifty years (2). 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 (3, 4). For developed nations, the development of new and effective strategies for multiple disorders that include cardiovascular disease (5–9), glucose regulation (10–15), and metabolic disease (15–19) as well as access to preventive care measures have contributed to the increased life span of the world's population.

Accompanying the increasing age of the world's population is a rise in non-communicable diseases (NCDs). NCDs cause more than sixty percent of the annual fifty-seven million global deaths (20). Interestingly, neurodegenerative disorders form a significant component for NCDs (21). Neurodegenerative disorders include more than six hundred disease entities and progressively lead to nervous system dysfunction (22). Acute and chronic neurodegenerative disorders lead to disability and death for greater than thirty million individuals worldwide (23). Improvements in clinical care that have fostered an increased life span for the global population are also believed to have produced a continual rise in the presentation of neurodegenerative disorders that can result in memory loss (24). According to the World Health Organization (25), tens of millions of individuals worldwide suffer from dementia and memory loss. Currently, at least fifty million individuals in the world have dementia and dementia is now considered to be the 7th leading cause of death (26). The number of new cases of memory loss 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.

Memory Loss with Advanced Aging

Multiple etiologies can result in memory and cognitive loss, such as diabetes mellitus (DM), vascular disease, and Alzheimer's disease (AD). DM affects multiple systems of the body and results in progressive functional loss, such as in cardiac tissue (7, 27, 28), renal disease (11, 29, 30), and the nervous system (14, 31–34). In the nervous system, DM can lead to visual impairment (32, 35–37), stroke (3, 38–42), memory loss (24, 43, 44), and may also be a component of AD (3, 31, 44–46).

Vascular disease as well contributes significantly to the onset and progression of memory impairment. Dementia caused by vascular disease may be treated with therapies that focus on hypertension and metabolic disorders (47). 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 (48). Vascular disease through a number of cellular mechanisms can present significant risk for stroke and memory loss (49–54). In addition, cerebral ischemic and hemorrhagic disorders affect over fifteen million individuals every year and lead to an annual cost of seventy-five billion dollars in the United States (1, 23, 55–57).

If one considers AD during cognitive loss, this disorder affects greater than 5 million individuals in the United States alone (58, 59). Worldwide, over fifty million million people suffer from some form of dementia with approximately sixty percent of these cases resulting from AD (3, 22, 59, 60). Multiple pathways may lead to AD such as cellular injury from β-amyloid (Aβ), tau, excitotoxicity, mitochondrial damage, acetylcholine loss, astrocytic cell injury, oxidative stress, mechanistic target of rapamycin, microRNAs, and iron regulation (45, 47, 61–65). Most available treatments that are directed to treat AD involve the use of cholinesterase inhibitors (66) while newer therapies focus on trophic pathways such as erythropoietin (EPO) (61, 67–72).

Innovative Pathways for Cognitive Loss with Sirtuins

An innovative pathway to tackle the challenges of cognitive loss and Alzheimer's disease involves sirtuins. Sirtuins are histone deacetylases (59, 73–80) that 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 the family members of the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1) through SIRT7. These histone deacetylases oversee post-translational changes of proteins and control cellular growth, metabolism, stem cells, and neuronal and vascular function as well as cell death through apoptosis and autophagy (14, 47, 81–85).

SIRT1 may have particular value as a target against memory loss and AD. Several studies suggest that SIRT1 activation can decrease oxidative stress and prevent cell injury that would lead to memory loss and neurodegenerative disorders such as AD (77, 80, 86–91). Oxidative stress may incite aberrant cell cycle re-entry that can lead to neuronal death during AD (92, 93). Reduction in reactive oxygen species in models of AD has led to reduced toxicity of Aβ, further suggesting that oxidative stress is a critical component in the pathology of AD (59). In other models of AD, agents that reduce levels of oxidative stress with reduction in Aβ expression led to improved cognitive function (94).

SIRT1 also may function to directly prevent Aβ and tau toxicity as well as mitochondrial dysfunction. SIRT1 may be active against Aβ to decrease the toxicity of this protein (95–98). Additional studies suggest that dysregulation of tau exon 10 splicing could be prevented by SIRT1 to block neurofibrillary degeneration (99). Work also has demonstrated that SIRT1 can preserve mitochondrial function and reduce oxidative stress and the generation of reactive oxygen species to preserve cellular function (4, 14, 50, 75, 81, 100–103). Overall, through these processes with SIRT1 activation, memory function is improved (82, 99).

Vascular and neuronal protection in the brain that would be relevant for ischemic mediated dementia as well as AD also may be modulated by SIRT1 activation (3, 73, 77, 87, 104–111). New studies have demonstrated that other agents, such as EPO, may rely upon SIRT1, to protect neuronal (17, 112), vascular (113, 114), and cardiac cells (75). Pathways such as Wnt1 inducible signaling pathway protein 1 (WISP1/CCN4) also can be dependent upon SIRT1 for neuronal cell protection (24, 115).

Future Considerations

Given that the number of individuals age 65 or older will increase from over 524 million to over 1.5 billion by the year 2050, it is clear that NCDs also will increase. Neurodegenerative disorders will form a significant component for NCDs that result in cognitive impairment, memory loss, and an increase in the incidence of AD. New and innovative treatment strategies are required to prevent the onset and development of disabilities tied to cognitive loss. SIRT1 is an attractive target for the treatment of cognitive loss. SIRT1 can provide protection against a number of central nervous insults that affect memory and cognitive impairment that include oxidative stress, Aβ toxicity, neurofibrillary degeneration, vascular injury, mitochondrial dysfunction, and neuronal loss. However, modulation of SIRT1 activity can have unwanted clinical effects if not precisely targeted. For example, SIRT1 can be associated with tumorigenesis (50, 116–118). However, examples exist that show that SIRT1 also may limit tumor growth (83). Although some reports note that SIRT1 can be beneficial against diabetic retinopathy (14), in other circumstances un-controlled vascular growth through SIRT1 could be detrimental (17, 119). In the nervous system, SIRT1 may be a negative modulator of neural precursors. Only a loss of SIRT1 may result in the differentiation and maturation of embryonic stem cells in the nervous system that may be required for reparative processes (3, 81, 118). Despite these concerns, sirtuins and especially SIRT1 offer new hope for the treatment of cognitive loss in conjunction with further investigation and understanding of these pathways.

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