

● PERSPECTIVE

Metabolism, neurodegeneration and epigenetics: emerging role of Sirtuins

Along with the progressive aging of the population, the prevalence of obesity, metabolic diseases and neurodegenerative disorders continues to grow. Moreover, increasing evidence suggests that metabolic alterations strongly influence the initiation and progression of neurodegenerative disorders. Accordingly, brain aging is accompanied by metabolic, morphological and neurophysiological changes leading to the development of neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and multiple sclerosis (Procaccini et al., 2016). Since each of these disorders involve impaired energy metabolism and/or adverse changes in the cerebral vasculature, a reduction in energy availability to neurons may contribute to increased vulnerability of the brain to develop neurodegenerative processes (Camandola and Mattson, 2017).

As part of the central nervous system (CNS), the retina shares the typical characteristic high metabolism of the brain and is susceptible to damage when subjected to metabolic impairment. Diabetic retinopathy (DR) is one of the common complications associated to diabetes mellitus (DM) and the leading cause of blindness worldwide. DR was classically considered a microvascular disease but it is currently accepted that may be a result of neurodegenerative processes. Abundant data suggest that most retinal neurons and glial cells are altered shortly after the onset of diabetes, even before clinical symptoms are observed, making the disease hard to diagnose at early stages (Lieth et al., 2000; Abcouwer and Gardner, 2014). Although considerable advances have been made in the field, the mechanisms involved in the initial phases of DR remain elusive. In this context, the emerging role of epigenetic mechanisms in the function and homeostasis of the CNS and its regulation of diseases has caught the attention of current investigations.

Acetylation is one of the most common epigenetic modifications. This process relaxes the chromatin structure allowing the recruitment and binding of transcription factors and RNA polymerase II. Acetylation is dynamically modulated by a fine balance between histone acetyltransferases (HATs) and histone deacetylases (HDAC) that are grouped in different classes. Class III HDACs are NAD⁺-dependent histone deacetylases, known as Sirtuins (SIRT). This family of proteins consists of seven members, SIRT1–SIRT7, ubiquitously expressed. A growing number of non-histone substrates, including cytoplasmic and mitochondrial targets, have also been shown to be deacetylated by Sirtuin family members, greatly expanding the potential biological roles of these enzymes. Sirtuins have been implicated in a spectrum of diseases like cancer, diabetes, obesity and neurodegenerative diseases (Poulose and Raju, 2015) generating a lot of interest.

Among the Sirtuin family, SIRT6 is a chromatin-bound enzyme that was described as a critical modulator of metabolism (Zhong et al., 2010) and plays a unique role in the retinal physiology (Silberman et al., 2014). In a previous work, we found that retinas from SIRT6 deficient mice showed major retinal neurotransmission impairment accompanied by changes in the expression of glycolytic genes and glutamate receptors and increased levels of apoptosis in the inner retinal layers (Silberman et al., 2014). Current investigations point to the role of HATs and HDACs in Diabetes and its complications as regulators of several key genes linked to the disease. Given the importance of glucose availability for retinal function and the critical role of

SIRT6 in modulating glycolysis, in our recent work we aimed to analyze SIRT6 involvement in the molecular machinery that regulates early neurodegenerative events during the development of experimental DR. Understanding the role of epigenetic processes in neurodegenerative events and the identification of cell-specific and tissue-specific epigenetic markers would provide a reference for designing targeted therapies and would help to elucidate the pathogenesis of neurodegenerative brain.

DR as a study case: Current treatments of DR focus on reducing vision loss related to neovascularization and diabetic macular edema (DME), while little consideration is given to the role of the neural retina in these processes. Different early events may contribute to a retinal neurodegenerative process such as the loss of neuroprotective factors or the release of neovascularization promoting factors. In a recent work, Zorrilla-Zubilete et al. (2018) found a time lapse in which non-obese diabetic (NOD) mice, that spontaneously develop type 1 diabetes, showed retinal increase of the vascular endothelial growth factor (VEGF) and the loss of the brain derived neurotrophic factor (BDNF) only two weeks after the onset of the disease when there is no evidence of vascular abnormalities. Given the importance of glucose availability for retinal function and the critical role of histone deacetylase SIRT6 in modulating glucose metabolism, they analyzed SIRT6 retinal levels and found a significant reduction both in protein and mRNA levels associated with increased acetylation levels of its substrates (H3K9 and H3K56). SIRT6 participation was further explored by studying the effect of its absence in mice with conditional deletion of sirt6 in the nervous system (Nes-Cre-SIRT6^{-/-}). Remarkably, retinas from Nes-Cre-SIRT6^{-/-} animals showed a molecular resemblance to diabetic retinas, exhibiting lower levels of BDNF and increased levels of VEGF. Moreover, acetylation levels of H3K56 were mostly increased in the retina inner nuclear layer where Müller cells nuclei reside.

Müller cells, the main glial cell of the retina, are among the first cells to demonstrate metabolic changes during retinal stress or disease. Activation of Müller cells, a process known as reactive gliosis, is associated with virtually any disease of the retina. This process promotes the survival of retinal neurons,

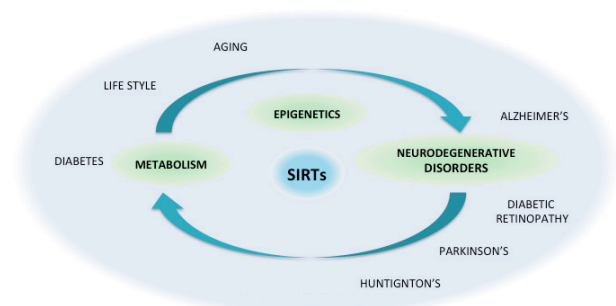


Figure 1 Novel role for Sirtuins (SIRT) as modulators of neurodegenerative processes.

As population ages, metabolic alterations increase and may influence the initiation and progression of neurodegenerative disorders. Impaired energy metabolism and/or adverse changes in the cerebral vasculature may contribute to increased vulnerability of the brain to develop neurodegenerative processes. Although Alzheimer's disease, Huntington's disease, Parkinson's disease and diabetic retinopathy differ in their underlying causes and pathophysiologies, deregulation of epigenetic mechanisms is becoming the focus of current investigations. How environmental factors can challenge the establishment and maintenance of epigenetic modifications would contribute to our further understanding of the origin and/or progression of neurodegenerative diseases.

but may also accelerate neuronal degeneration since the loss of glial support or its pathological transformation compromises neuronal functionality and viability. Thus, manipulating neuroprotective functions of retinal glia would be an important strategy to enhance neuronal survival. By using Müller cells enriched primary cultures subjected to a high glucose concentration, Zorrilla-Zubilete et al. (2018) found a significant decrease of SIRT6 levels and increased acetylation levels of H3K56 suggesting that SIRT6 may be downregulated in this cell type as a response to hyperglycemia. This observation was reverted by the overexpression of SIRT6. Additionally, in SIRT6 silenced Müller cells, VEGF levels increased which is consistent with the overexpression data. The most well-known regulator of VEGF transcription is hypoxia-inducible factor 1-alpha (HIF-1 α , and SIRT6 was described to co-repress HIF-1 α by deacetylating H3K9 at HIF-1 α target gene promoters (Zhong et al., 2010). Therefore, the VEGF increment observed in high glucose treated glial cells could be the result of a direct regulation exerted by SIRT6 at the promoter region of the gene or, most likely, the consequence of the de-repression of HIF1 α due to the decrease of SIRT6 levels. Although further studies will be necessary to confirm our observations, these findings suggest that neurodegenerative events epigenetically regulated may occur early during diabetes development, preceding proliferative and haemorrhagic vascular changes observed later in a diabetic retina.

Sirtuins and neurodegeneration: Epigenetic regulation involves several levels of gene expression ranging from direct modifications of the DNA and histone tails that modulate the level of transcription, to interactions with messenger RNAs that regulate the level of translation. Notably, epigenetic deregulation is currently drawing much attention as a key player in aging and age-related neurodegenerative disorders, such as AD, PD, and HD, where it may mediate interactions between genetic and environmental risk factors, or directly interact with disease-specific pathological factors.

In this context, several members of the Sirtuin family have been involved in the modulation of neurodegenerative disorders. For instance, recent findings demonstrate that SIRT3 overexpression could prevent neuronal disorganization in certain *in vivo* and *in vitro* aging models and neurodegenerative brain disorders like AD, HD and stroke (Anamika et al., 2017). Moreover, SIRT1 was described to display neuroprotective properties in experimental PD models (Albani et al. 2016). Furthermore, in accordance with our findings, Kabuski et al. (2017) showed that SIRT6 is critical to maintain genomic stability in the brain and that its loss leads to toxic Tau stability and phosphorylation suggesting that this enzyme could be targeted in AD.

In order to modulate the activity of sirtuins, several pharmacological agents are currently under study. Recent evidence supporting the potential use of SIRT inhibitors for the treatment of cancer, human immunodeficiency virus (HIV) infection, and muscular diseases, and of SIRT activators for age-related disorders has led to the identification of several SIRT modulators. Both chemical and biomedical characterization of SIRT modulators would motivate new alternative therapies and would represent a promising area that might provide the basis for designing new selective molecules.

Concluding remarks: In light of the increasing population aging neurodegenerative disorders are among the greatest challenges that need to be tackled. The study of the underlying mechanisms that lead to neurodegeneration is essential for identifying new therapeutic targets. Since epigenetic modifications are reversible events, regulating these processes is there-

fore a very promising method from a therapeutic perspective (**Figure 1**). Epigenomic studies coordinated with transcriptomic studies (genome-wide gene expression profiling) will be useful to validate functional effects of epigenetic changes on gene expression.

Noteworthy, while the focus of research so far has been on epigenetic regulation of neuronal function, the glial cell compartment has received less attention as to how epigenetics develop their differentiation and function. Given the paramount role of glial cells as CNS' first responders, epigenetic changes in this cell type occurring during CNS injury, neuroinflammatory conditions and neurodegenerative disease should be taken into account in future studies.

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