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Review Article

Retinal Neuroprotective Effect of Sirtuins

Tatsuya Mimura[1]*, Hidetaka Noma[2], Hideharu Funatsu[3], Aki Kondo[1] and Masao Matsubara[1]

[1]*Department of Ophthalmology, Tokyo Women's Medical University Medical Center, Japan*
[2]*Department of Ophthalmology, Hachioji Medical Center, Tokyo Medical University, Japan*
[3]*Department of Ophthalmology, Yachiyo Medical Center, Tokyo Women's Medical University, Japan*

***Corresponding author**
Tatsuya Mimura, Department of Ophthalmology, Tokyo Women's Medical University Medical Center East, 2-1-10 Nishiogu, Arakawa-ku, Tokyo, 116-8567 Japan. Tel: 81 33810-1111 (Ex7765); Fax: 81 33894-0282; E-mail: mimurat-tky@umin.ac.jp

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Abstract

In this paper, we review current knowledge about the retinal neuroprotective effect of sirtuins. The sirtuins are highly conserved nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylases that are involved in mammalian diseases of aging. The human genome encodes seven different sirtuins (SIRT1-7). SIRT1 is localized in the nucleus and cytoplasm of the cells making up all normal ocular structures, including the retina. Age-related macular degeneration (AMD) is a typical age-related condition due to the lifelong accumulation of molecular damage caused by reactive oxygen species (ROS). SIRT1 can decrease ROS levels and promotes cell survival under oxidative stress. Upregulation of SIRT1 has a protective effect against retinal degeneration in animal models. Resveratrol is a polyphenolic SIRT1 activator that has been shown to increase the lifespan and to protect various organs against aging, including oxidative stress-induced retinal damage. Anti-aging therapy with resveratrol could be an attractive treatment option for age-related macular degeneration.

INTRODUCTION

istone deacetylases (HDACs) are enzymes that deacetylate histones, but also act on certain non-histone substrates. Class III HDACs, which are known as sirtuins, catalyze deacetylation of the acetyl-lysine residues of histones using nicotinamide adenine dinucleotide (NAD+) as a cofactor. Silent information regulator 2 (Sir2) was the first gene of the sirtuin family to be discovered. Sir2 shows a high level of evolutionary conservation and is an important regulator of senescence, cell differentiation, stress tolerance, metabolism, and cancer in several organisms. Sirtuins have been suggested to have a role in aging [1,2], calorie restriction [1-10], and inflammation. Overexpression of Sir2 prolongs the lifespan of various organisms, whereas deletion or mutation of Sir2 leads to a shorter lifespan [11-13]. Seven human Sir2 homologues (sirtuins) have been identified to date, and these are designated as SIRT1 to SIRT7 [14-15]. Sirtuins are also important in preventing age-related ocular diseases [16]. In this review, we focus on the retinal neuroprotective effect of sirtuins.

ENZYMATIC ACTIVITY OF SIRTUINS

Sirtuins carry out deacetylation via a two-step reaction that consumes NAD+ and releases nicotinamide (NAM), O-acetyl-adenosine diphosphate (ADP) -ribose (AADPR), and the deacetylated substrate [17-21]. Sirtuin activity is regulated by the intracellular [NAD]/[NADH] ratio and responds to changes of cellular metabolism [22-25]. NAD+ is an activator of sirtuins, while nicotinamide and NADH are inhibitors. Sirtuins can catalyze deacetylation or ADP-ribosylation reactions, with both of these reactions involving cleavage of NAD+ as a cofactor and the production of nicotinamide (NAM). Five sirtuins (SIRT1, SIRT2, SIRT3, SIRT5, and SIRT7) catalyze deacetylation of the lysine residues of their target proteins, using NAD+ as cofactor and releasing nicotinamide along with the production of 2'-O-acetyl-ADP ribose [25-27]. In contrast, SirT4 and SirT6 catalyze ADP-ribosylation which involves transfer of an ADP-ribosyl moiety to the substrate [26,28].

Sirtuins have a highly conserved core domain that contains a catalytic domain and an NAD+-binding site [29]. Human SirT2 is composed of two globular domains, one of which is large, while the other is small. The large domain contains an inverted classical open α/β Rossmann-fold, six β-strands that form a parallel β-sheet, and six -helices, while the small domain is composed of a helical module and a zinc-binding module. The active site is located at the interface between the large and small domains, along with a binding site for NAD+. The NAD+-binding pocket can be divided into three spatially distinct regions, which are the A site showing affinity for adenine–ribose, the B site with affinity for nicotinamide–ribose, and the C site that binds NAD+. In the presence of an acetyl-lysine substrate, the NAD+-bound B site undergoes a conformational change that brings nicotinamide into proximity with the C site so that it can be cleaved. The ADP

ribose product then returns to the B site, allowing deacetylation to occur. The C site is the binding site for free nicotinamide. At high concentrations, nicotinamide can occupy the site and block the conformational change of NAD+ [30].

RETINAL DISTRIBUTION AND ROLE OF SIRTUINS

Jaliffa and associates investigated the localization of SIRT1 in adult mouse eyes by in situ hybridization They found SIRT1 in the nucleus and cytoplasm of cells from all normal ocular structures, including the cornea, lens, iris, ciliary body, and retina. They reported that SIRT1 mRNA was detected in the outer nuclear layer (ONL), inner nuclear layer (INL), and ganglion cell layer (GCL) of the mouse retina by *in situ* hybridization (Figure 1) [31]. However, there has been no report about detection of SIRT1 in the human eye.

SIRT1-deficient mice are smaller than normal at birth and usually die during the early postnatal period [32]. Even if these mice survive, they exhibit infertility and often have a shorter snout than normal mice [32]. Additionally, all SIRT1-deficient mice fail to open one or both eyes [32]. To date, only a few studies have assessed the ocular role of SIRT1, including its relationship with the development of cataract [33,34], retinal degeneration [31,35-41], optic neuritis [42], and uveitis [43]. The most important ocular role of SIRT1 may be protecting the retina and optic nerve against degeneration.

AMD AND OXIDATIVE STRESS

Free radicals are atoms or molecules with at least one unpaired electron in an outer shell and these radicals are known to play an important role in the pathogenesis of cellular aging. In most biological structures, free radical damage is closely associated with oxidative damage, with antioxidants being particularly important for diminishing the cumulative effect of oxidative damage over the long lifespan of humans by passivating free radicals. AMD is a typical age-related condition, which is considered to arise from aging and the lifelong accumulation of molecular damage caused by reactive oxygen species (ROS) [44]. In the retina, ROS (including free radicals) cause damage that leads to apoptotic cell death, dysfunction of the retinal pigment epithelial cells, accumulation of lipofuscin, formation of drusen, and impairment of Bruch's membrane, and ROS-related damage is considered to be responsible for the pathological changes of AMD [45].

The Age-Related Eye Disease Study demonstrated that oxidative stress can promote the development of AMD, while antioxidants and zinc supplements delay the progression of AMD and loss of vision [46]. Oxidatively modified proteins have been detected in drusen by proteomic analysis [47]. SIRT1 decreases ROS levels and promotes cell survival under oxidative stress [48]. Thus, SIRT1 may prevent ROS-dependent apoptosis of retinal neurons under oxidative stress [49]

NEUROPROTECTIVE EFFECT OF SIRT1 IN THE RETINA

The retina is part of the nervous system. Various factors (including aging, UV radiation, and oxidative stress) can induce permanent damage to the retinal architecture [44], while SIRT1

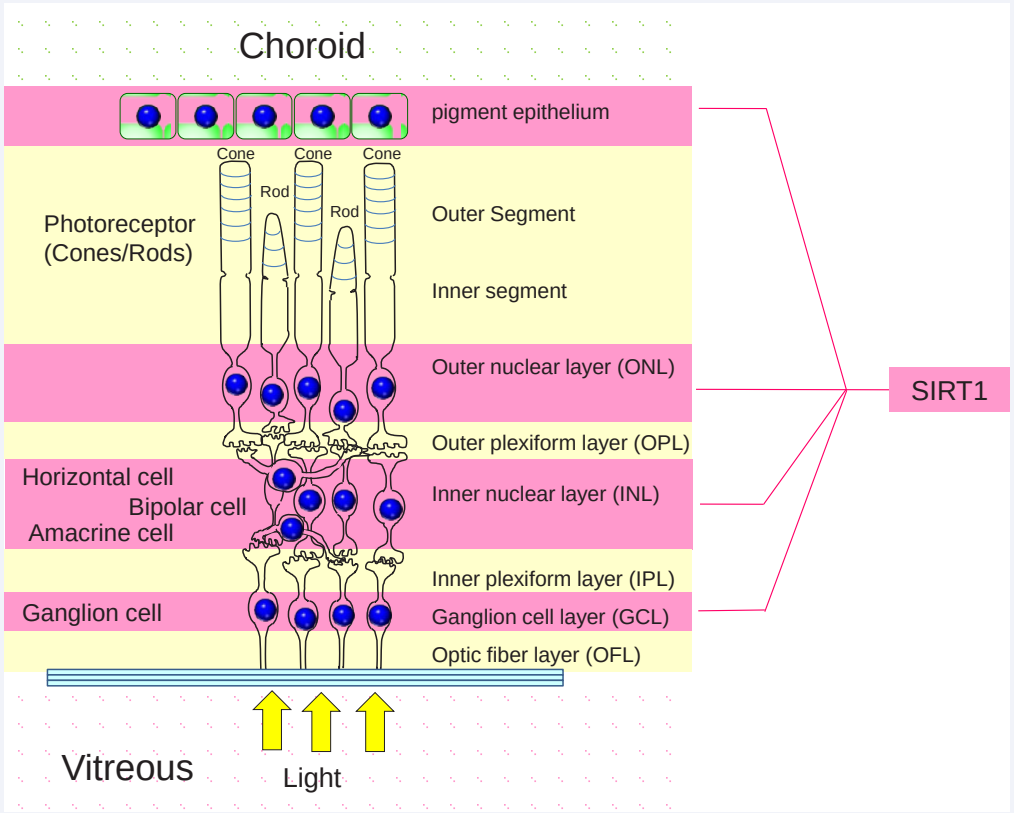

Figure 1 Localization of SIRT1 in the mouse retina (Jaliffa 2009). SIRT1 is expressed in the retinal pigment epithelium (RPE), outer nuclear layer (ONL), inner nuclear layer (INL), and ganglion cell layer (GCL).

appears to have a neuroprotective effect on the retina. SIRT1 is localized in most layers of the normal mouse retina (including the ONL, INL, GCL, and RPE) [31]. In SIRT1-deficient adult mice, multiple retinal cell layers are significantly thinner than in normal mouse eyes, while the inner and outer nuclear layers are disorganized [35]. The inner and outer photoreceptor cell segments are also difficult to detect in SIRT1-deficient adult mice, indicating that SIRT1 has an important role in ocular morphogenesis [35].

Several experimental studies have demonstrated a protective effect of SIRT1 against retinal and optic nerve damage. For example, intravitreal injection of SIRT1 activators prevents RGC loss in a dose-dependent manner by stimulating SIRT1 enzymatic activity in mice with optic neuritis [42]. This neuroprotective effect is blocked by sirtinol, a SIRT1 inhibitor [42]. Absence of E2fs, the transcription factor for SIRT1, causes downregulation of the p53 deacetylase activity of SIRT1, resulting in p53 hyperacetylation and an increase of apoptosis in the mouse retina [37]. Transfer of the SIRT1 gene with Oct 4 prevents retinal cell loss and improves electroretinographic responses in rats with retinal phototoxicity [40]. Furthermore, upregulation of SIRT1 by resveratrol protects cultured retinal cells from antibody-induced apoptotic death [36]. Resveratrol is a natural polyphenol found in red grapes and red wine that has been shown to enhance SIRT1 activity [10,25,50] (Figure 2), and it also has a protective effect against phototoxic degeneration of the mouse retina *in vivo* [38]. These findings suggest that SIRT1 can provide protection against diseases caused by oxidative stress-induced retinal damage, such as AMD, while anti-aging therapy with resveratrol could be a potential treatment for retinal damage.

SUMMARY

We reviewed the influence of sirtuins on retinal aging and degeneration. Some clinical trials of SIRT1 activators have already been started for a variety of diseases, including cardiovascular disease, cancer, diabetes, and Alzheimer's disease. However, many uncertainties remain, especially concerning the preventative effect of SIRT1 on AMD. SIRT1 activators such as resveratrol, rather than SIRT1 itself, may be candidate drugs for AMD.

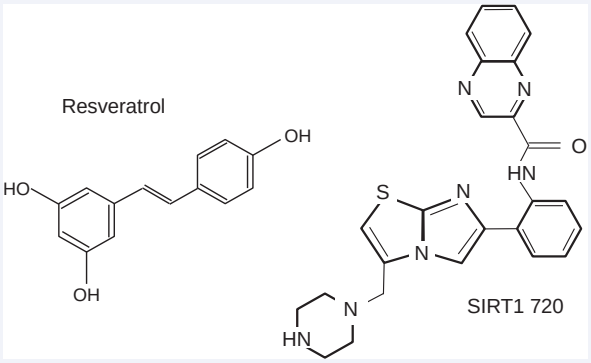

Figure 2 Chemical structure of two SIRT1 activators. Resveratrol is a polyphenolic compound found in grapes and wine, which is known as an activator of SIRT1. The experimental drug SIRT1720 is low molecular weight SIRT1 activator that is 1,000 times more potent than resveratrol.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and for writing this paper.

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