



Review

The role of SIRT1 in ocular aging



Tatsuya Mimura^{a,*}, Yuichi Kaji^b, Hidetaka Noma^c, Hideharu Funatsu^c,
Shinseiro Okamoto^d

^a Department of Ophthalmology, Tokyo Women's Medical University Medical Center East, 2-1-10 Nishiogu, Arakawa-ku, 116-8567 Tokyo, Japan

^b Department of Ophthalmology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan

^c Department of Ophthalmology, Yachiyo Medical Center, Tokyo Women's Medical University, Yachiyo, Chiba, Japan

^d Okamoto Eye Clinic, Yamato, Kanagawa, Japan

ARTICLE INFO

Article history:

Received 7 August 2012

Accepted in revised form 16 July 2013

Available online 26 July 2013

Keywords:

review

SIRT1

eye

ABSTRACT

The sirtuins are a highly conserved family of nicotinamide adenine dinucleotide (NAD⁺)-dependent histone deacetylases that helps regulate the lifespan of diverse organisms. The human genome encodes seven different sirtuins (SIRT1–7), which share a common catalytic core domain but possess distinct N- and C-terminal extensions. Dysfunction of some sirtuins have been associated with age-related diseases, such as cancer, type II diabetes, obesity-associated metabolic diseases, neurodegeneration, and cardiac aging, as well as the response to environmental stress. SIRT1 is one of the targets of resveratrol, a polyphenolic SIRT1 activator that has been shown to increase the lifespan and to protect various organs against aging. A number of animal studies have been conducted to examine the role of sirtuins in ocular aging. Here we review current knowledge about SIRT1 and ocular aging. The available data indicate that SIRT1 is localized in the nucleus and cytoplasm of cells forming all normal ocular structures, including the cornea, lens, iris, ciliary body, and retina. Upregulation of SIRT1 has been shown to have an important protective effect against various ocular diseases, such as cataract, retinal degeneration, optic neuritis, and uveitis, in animal models. These results suggest that SIRT1 may provide protection against diseases related to oxidative stress-induced ocular damage, including cataract, age-related macular degeneration, and optic nerve degeneration in glaucoma patients.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

The recognition of homeostasis and homeostatic mechanisms dates back to the 19th century French physiologist Claude Bernard, who established the concept of homeostasis or internal environment in the body. Walter Bradford Cannon expanded on Claude Bernard's concept of homeostasis (Cannon, 1932). Epigenetic mechanisms have recently been recognized for their essential contribution in maintaining homeostasis by regulating gene expression and chromatin structure. In part, gene expression is regulated by the reversible methylation of DNA and acetylation of histones, thus controlling a wide variety of cellular functions. Histone deacetylases (HDACs) are enzymes that deacetylate histones, and non-histone proteins, such as the p53 tumor suppressor protein, α -tubulin and forkhead transcription factors (Luo et al., 2001; Vaziri et al., 2001). 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. In addition to deacetylase activity, sirtuins also possess ADP-ribosyl transferase activity. They control energy homeostasis in response to stress but promote cellular aging when homeostasis fails thereby avoiding genomic instability (Rodriguez and Fraga, 2010). Thus, the sirtuins play an essential role in helping maintain cell homeostasis via regulation of both epigenetic and non-epigenetic mechanisms.

Silent information regulator 2 (Sir2), first described in yeast, was the first gene discovered in the sirtuin family (Shore et al., 1984; Gottlieb and Esposito, 1989). Sir2 shows a high level of evolutionary conservation and is an important regulator of senescence (Langley et al., 2002; van der Veer et al., 2007), cell differentiation (Takata and Ishikawa, 2003; Blander and Guarente, 2004; Anastasiou and Krek, 2006; Prozorovski et al., 2008; Wojcik et al., 2009), stress tolerance (Blander and Guarente, 2004; Anastasiou and Krek, 2006; Wojcik et al., 2009), metabolism (Blander and Guarente, 2004; Anastasiou and Krek, 2006; Wojcik et al., 2009), and cancer (Pruitt et al., 2006; Oberdoerffer et al., 2008; Han et al., 2013). Sirtuins have been suggested to have a role in aging (Gotta et al., 1997; Guarente and Kenyon, 2000), calorie restriction (Cohen et al., 2004; Nemoto et al., 2004;

* Corresponding author. Tel.: +81 33810 1111x7765, fax: +81 33894 0282.

E-mail address: mimurat-ky@umin.ac.jp (T. Mimura).

Rodgers et al., 2005; Nisoli et al., 2005; Corton and Brown-Borg, 2005; Civitarese et al., 2007; Milne et al., 2007; Bordone et al., 2007; Mulligan et al., 2008; Coppari et al., 2009; Satoh et al., 2010; Baur et al., 2010; Qiu et al., 2010; Gesing et al., 2011; Takemori et al., 2011; Radak et al., 2013), and inflammation (Yeung et al., 2004; Qiu et al., 2010), and apoptosis (Bhattacharya et al., 2012; Liu et al., 2012). Overexpression of Sir2 prolongs the lifespan of various organisms, whereas deletion or mutations of Sir2 leads to a shorter lifespan (Kaeberlein et al., 1999; Tissenbaum and Guarente, 2001; Rogina and Helfand, 2004). Seven human Sir2 homologues, generally known as sirtuins, have been identified to date, and these are designated as SIRT1 to SIRT7 (Frye, 1999, 2000).

There have been numerous reports suggesting that sirtuins are important anti-aging molecules and may have a role in preventing several age-related ocular diseases. These age-related changes of the eye are listed in Table 1. The process of ocular aging may be influenced by various factors, which include aging itself, ultraviolet (UV) radiation, oxidative stress (Fletcher, 2010), systemic diseases (such as diabetes, hypertension (DellaCroce and Vitale, 2008), or metabolic syndrome), and lifestyle factors (Fig. 1). Interaction of these various etiological and environmental factors during the aging process causes or exacerbates various age-related ocular diseases, such as pinguecula (Panchapakesan et al., 1998; Pham et al., 2005a, 2005b; Fotouhi et al., 2009; Mimura et al., 2011, 2012b), conjunctivochalasis (Di Pascuale et al., 2004; Mimura et al., 2009, 2012a), cataract (Oliver, 1906), spheroid degeneration (Fraunfelder et al., 1972), age-related macular degeneration (AMD) (Vinding, 1989), and glaucoma (Segal and Skwierczynska, 1967).

This article reviews current knowledge about the mechanisms underlying the actions of sirtuins in ocular tissues, with an emphasis on Sirt1, which is the best characterized family member. Modulation of sirtuin-related signal transduction and downstream effects may have potential applications in managing ocular diseases associated with aging, such as cataract, AMD, and optic nerve degeneration in glaucoma patients.

2. The sirtuin family

Sirtuins belongs to a family of histone deacetylases (HDACs) that have been divided into four groups (Fremont, 2000; Frye, 2000; Bastianetto and Quirion, 2002; Borra et al., 2005; Sinclair et al., 2006; Baur and Sinclair, 2006). HDACs from classes I, II, and IV share common features, as all of these molecules are zinc-dependent and exhibit some sequence similarities, while class III HDACs are NAD⁺-dependent enzymes that show no homology with the other HDACs. Sirtuins are Class III HDACs, which are essential for maintaining the silence of chromatin during histone deacetylation (Frye, 2000; Borra et al., 2005; Denu, 2005; Kaeberlein et al., 2005).

The mammalian sirtuin family has seven members, designated as SIRT1–7 (Frye, 1999, 2000; Michan and Sinclair, 2007) (Fig. 2). Structurally, sirtuins share significant sequence homology, with all of them containing a conserved catalytic domain of 275 amino acids and a nicotinamide adenine dinucleotide (NAD⁺)-binding domain, as well as unique additional N-terminal and/or C-terminal sequences of variable length (Frye, 1999; Sherman et al., 1999; Imai et al., 2000; Finnin et al., 2001; Yamamoto et al., 2007).

Sirtuins differ in their cellular localization, activity, and function, and are subdivided into four classes (I–IV) (Table 2) (Frye, 2000; North and Verdin, 2004; Carafa et al., 2012). Class I contains human SIRT1, SIRT2, and SIRT3, as well as all yeast sirtuins. Class I is divided in three subclasses (a, b and c). SIRT1 is positioned in Class Ia with yeast Sir2 and Hst1, while SIRT2 and SIRT3 belong to Class Ib together with yeast Hst2. Class II contains human SIRT4 along with sirtuins from bacteria, insects, nematodes, moulds, fungi, and protozoa. Class III contains human SIRT5, while class IV contains SIRT6 and SIRT7 in two different subclasses (IVa and IVb, respectively) (Frye, 2000). The high conservation among species confirms the extreme importance of this protein family. Class U consists of all bacterial sirtuins.

Seven sirtuin members (SIRT1–7) have distinct subcellular localizations: SIRT1 protein is localized in both the nucleus and cytoplasm of cells (Langley et al., 2002; Michishita et al., 2005),

Table 1
Summary of changes associated with ocular aging.

	Changes
Eyelids	Blepharochalasis, Blepharoptosis, Ectropion/Entropion, Eyelid malposition, Orbital fat prolapse, and Meibomian gland dysfunction.
Tears	Lacrimal obstruction, Dry Eyes/Watery eyes.
Conjunctiva	Pinguecula, Pterygium, Conjunctivochalasis.
Cornea	Shape and structure: Change of corneal curvature (shift from with-the-rule to against-the-rule astigmatism), Decreased corneal luster, Increased corneal fragility, and Increased thickness of Descemet's membrane. Diseases: Deposits (Arcus senilis, Hudson-Stahli line Hassall-Henle bodies), Limbal epithelium stem cell deficiency, Reduced endothelial cell density (Guttata, Fuchs endothelial degeneration), and Decreased corneal sensitivity.
Iris	Smaller pupil, Decreased light reaction of the iris, and loss of iris pigment.
Trabecular meshwork	Increased pigmentation of the trabecular meshwork, Increased resistance to the outflow of aqueous humor.
Lens/accommodation	Decreased lens elasticity, Lens fiber differentiation, and Lens capsule deterioration. Cataract, Presbyopia.
Vitreous	Structure: Vitreous liquefaction, Condensation of the vitreous fluid, Enhanced fibrillary structure of the vitreous, Increased mobility of fibrillary structures, Formation of lacunae, and Posterior vitreous detachment (PVD). Diseases: Floating PVD, Flashes, Retinal tears, and Retinal detachment caused by traction on due to PVD, Epiretinal membrane, Macular hole, and Incidental vitreoretinal hemorrhage after PVD.
Retina	Structure: Changes of visual function (decreased visual field sensitivity, reduced contrast sensitivity, and increased dark adaptation threshold), Retinal vascular changes (dilatation, tortuosity, elongation, and neovascularization), Neurosensory retinal changes (loss of retinal pigment epithelial cells which is vital for integrity of the rods and cones, photoreceptors, and ganglion cell), Decreased melanin content, Increased lipofuscin content, and Decreased cytoplasmic volume. Diseases: Epiretinal membrane, Retinal tear, Retinal detachment, Senile tigroid fundus, Retinal degenerations, Drusen, Central/branch retinal vein occlusion, Central/branch retinal artery occlusion, and Diabetic retinopathy.
Macular region	Structure: Decrease in number of foveal ganglion cells, Decrease in retinal macular microcirculation (Retinal ischaemia) Diseases: Drusen, Age related macular degeneration, Subretinal neovascular membrane, Epiretinal membrane, Macular hole, Cystoid macular edema, Pigment epithelial detachment
Optic nerve	Structure: Decrease of axons, Axonal swelling at the lamina cribrosa, Thickening of the lamina cribrosa, and Increase of elastic fibers. Diseases: Glaucoma

Download English Version:

<https://daneshyari.com/en/article/6197185>

Download Persian Version:

<https://daneshyari.com/article/6197185>

[Daneshyari.com](https://daneshyari.com)