The Expression of SIRT1 in Ocular Tissues

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Abstract

SIRT1 is a nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase which regulates many physiological and pathological processes. Over the past decade, increasing attention has been paid to the wide distribution of SIRT1 in the eye and its important role in eye development. The short review summarized the most recent research in the study of SIRT1 related to eye development and its distribution in eye.

Keywords: SIRT1; Eye; Epigenetic alterations; Histone Deacetylases (HDACs)

Introduction

Epigenetic alterations play important roles in a wide variety of physiological and pathological events [1]. As one of the most important epigenetic regulators, Histone Deacetylases (HDACs) are able to deacetylate lysine residues on histone and non-histone proteins [2], regulating chromatin structure, gene expression and protein function. Eighteen human HDACs have been identified and grouped into 4 classes based on their homology to respective yeast orthologues [3,4]. The human sirtuins family, homologs of the yeast silent information regulator 2(Sir2), belongs to class III HDACs. They are NAD+-dependent deacetylases and contain seven members (SIRT1-7) with varied functions, structures, and localizations [5]. Among them, SIRT1 is the most extensively studied, primarily because of its regulation of diverse cellular targets and functions as well as its therapeutic potential.

Human SIRT1 comprises 747 amino acids divided into three main regions: the central core, possessing the deacetylase domain, which consists of a large NAD+-binding subdomain with a Rossmann fold and a smaller subdomain composed of a helical module and a Zn2+-binding module, and the N- and C-terminal domains, containing regulatory elements and binding domains for SIRT1 co-activators or repressors [6]. For example, the C-terminal regulatory segment (CTR) has a stabilizing role on the SIRT1 catalytic domain and changes occur in the C-terminal extension of the CTR can inhibit the activity of the catalytic domain [7]. As a NAD+-dependent enzyme, the activity of SIRT1 is primarily regulated by the NAD+/NADH ratio which is affected by energy and redox status. In other words, all the enzymes involved in NAD+ biosynthesis could regulate SIRT1 activity. Indeed, fasting and caloric restriction were demonstrated to increase NAD+ levels, thereby enhancing SIRT1 activity. The product nicotinamide generated from NAD+ is an inhibitor of the deacetylation reaction and is used often as a general sirtuin inhibitor [8]. Besides influenced by the level of NAD+, SIRT1 is regulated through transcriptional level, post-transcriptional manner [9] and post-translational modifications, such as phosphorylation [10], Sumoylation [11], methylation [12], S-nitrosylation [13] and carboxylation [14], leading to alteration of SIRT1 level and activity. In addition, the activity of SIRT1 can be regulated by its nuclearcytoplasmic shuttling [15].

The proteins of Sir2s family have been found in a variety range of organisms and highly conserved from bacteria to humans [16]. From the finding an ability to maintain chromatin silencing and genome stability [17], SIRT1 has been linked to variety of physiological and pathological processes and diseases such as DNA repair, cell fate, metabolic regulation, apoptosis, cell survival, aging, inflammation, angiogenesis, oxidative stress, neurodegenerative diseases, cancer and cardiovascular dysfunction. As the extension of the nervous and vascular system, eye diseases associated with SIRT1 have been reported over the past decade. Previous reviews indicated the role of SIRT1 in retinal and ocular aging [18,19]. In this context, the aim of the current review is to present current understanding of the role of SIRT1 in eye development and its distribution of eye tissues.

Roles of SIRT1 in the eye development

Mice carrying two null alleles of sir2a were smaller than normal at birth, and most died during the early postnatal period. In an outbred background, the sir2a null animals often survived to adulthood, but both sexes were sterile. These results found by McBurney et al. suggest that the SIRT1 protein is essential for normal embryogenesis and for normal reproduction in both sexes [20]. In addition, they observed that in the SIRT1 deficiency animals, eyelids remained closed forever or for several months. In some animals, the eyes, although normal in size, had abnormalities of the cornea, lens, and retina; these may be attributed to be secondary to persistent eyelid closure [20]. Likewise, the similar eyelid defects in SIRT1-null mice also have been reported by Kamel et al. [21]. Almost at the same time, Cheng et al. [22] analysed eye abnormalities in SIRT1-deficient mice at all stages. For example, eyes from these mice were small, irregularly shaped with abnormal closure of the optic fissure. Moreover, multiple retinal cell layers were significantly thinner by histological analyses, and in some areas, the inner and outer nuclear layers were disorganized. Besides, the inner and outer segments of photoreceptor cells were difficult to discern. These eye defects were even observed in embryos as early as E12.5, so they believe that SIRT1 have an important role in eye morphogenesis and retinal development [22]. Further study showed that SIRT1 mRNA and protein were reduced in E28s knockout mice.
retina at E14 and P0, which correlated with p53 hyper acetylation and elevated retinal progenitor apoptosis [23]. Treatment of pregnant mice from E16 with resveratrol, an activator of SIRT1, blocked >70% of E2fs null retinal progenitor cells apoptosis at P0 [23]. Thus, activating E2fs induce SIRT1 to block p53 acetylation and apoptosis establishing a novel E2f-SIRT1-p53 pro-survival role in retinal development [23].

### Distribution of SIRT1 in the eye

Jaliffa et al. [24] provided evidences at the first time of the details of SIRT1 mRNA and protein levels and distributions in normal adult mouse eyes. They detected SIRT1 mRNA by RT-PCR in the neuroretina, Retinal Pigment Epithelium (RPE), ciliary body, and lens. The highest levels of SIRT1 mRNA were in the neuroretina. By performing in situ hybridization with radioactive probes, SIRT1 mRNA was detected in the Outer Nuclear Layer (ONL), Inner Nuclear Layer (INL), and Ganglion Cell Layer (GCL) of the retina. They also studied SIRT1 protein distribution in the normal mouse eye using immunohistochemical staining and shown that strong, specific SIRT1 immunoreactivity displayed in cell nuclei and cytoplasm of all ocular tissues, such as the cornea, lens, ciliary body, RPE, and retina. Only 20% of cases in 10 specimens are SIRT1 positive immunolabeling in human normal conjunctival epithelia [25]. Significant SIRT1 immunolabeling was observed in the nuclei and cytoplasm of corneal epithelial cells, and SIRT1 was also detected in the nuclei of flattened corneal endothelial cells and in keratocytes. However, no SIRT1 was detected in the acellular part of the corneal stroma [24]. In the ciliary body, SIRT1 was found mainly in the nuclei of ciliary process cells, also in the pigmented and nonpigmented ciliary epithelial cell layers. The adult mouse lens displayed SIRT1 principally in the nuclei of the epithelial and fiber cells. No SIRT1 was detected in the lens capsule.

SIRT1 immunolabeling was detected in the RPE and melanocyte nuclei, while mostly in the cytoplasm of choroidal vessels endothelial cells. The retinal distribution of SIRT1 was exclusively observed in the nuclei of the ONL, INL, and GCL and was never detected in the cytoplasm [24]. Another study reported by Maloney et al. [26] has shown different evidences of the SIRT1 expression in the retina. In contrast, they found that SIRT1 was predominantly expressed in the cytoplasm in the GCL, Inner Plexiform Layer (IPL), Outer Plexiform Layer (OPL), and photoreceptor inner segments in foetal and adult human’s eyes as well as in mouse retinas, although some nuclear localization was seen in a subset of mouse retinas. Moreover, SIRT1 expression was seen to be exclusively cytoplasmic in mouse retinal progenitor cells, while in both nuclei and cytoplasm in the human retinal progenitor cells [26]. Compared with our study, we revealed that SIRT1 was mainly located in the GCL, OPL, inner segments of photoreceptor and RPE in rat retina. Furthermore, both nuclei and cytoplasm were showed SIRT1 expression in GCL and RPE layers. Only cytoplasmic expression of SIRT1 was found in the ONL and INL. These very different SIRT1 distributions in nuclear and cytoplasm in different cell types or spices suggest that the SIRT1 expression may be variable in different period of time in retinal development and cell differentiation. Further researches need to confirm the conditions and time points which influence SIRT1 translocation between nuclear and cytoplasm that may be important in cell fate determination.

The expression of sirt1 in eye is extensive (Table 1) and the importance of sirt1 of the biological functions in eye is also gradually recognized including cell metabolism, cell survival, aging, cellular senescence, stress response, inflammatory signalling induced by infection and others [27]. Further investigation will offer a far clearer perspective as to the roles of sirt1 in normal eye function maintaining and common eye diseases.

### Table 1: The expression of SIRT1 in eye and its function.

| Tissues                | Functions                                      |
|-----------------------|------------------------------------------------|
| Corneal epithelium    | Inhibition of inflammation and promote healing  |
| stroma cells          | anti-oxidative stress, survival                |
| Endothelium           | Ciliary body                                   |
| Lens epithelium       | Maintaining epithelium normal function?        |
| Fibril cells          | Anti-oxidative stress, Cell survival           |
| RPE, outer nuclear layer | Anti-oxidative stress, prevention of cell apoptosis |
| Ganglion cell         | Anti-oxidative stress, prevention of aging and cell apoptosis, inhibition of angiogenesis |
| Optic nerve           | Promote wound healing                          |

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