# The Expression of SIRT1 in Ocular Tissues

**Ruihong Su[1]\* and Shikun He[2]**

[1]Medical University Eye Hospital and Eye Institute, Tianjin, China

[2]Department of Pathology and Ophthalmology, University of Southern California, Los Angeles, California, USA

\*Corresponding author: Ruihong Su, Tianjin Medical University Eye Hospital and Eye Institute, 251 Fukang Road, Xiqing Qu, Tianjin Shi, 300381, China, Tel: 0086 22 23346430; Fax: 0086 22 23346434; E-mail: sulove36@hotmail.com

## 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 orthologous [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 $Zn^{2+}$-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 primary 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 nucleocytoplasmic shuttling [15].

The proteins of Sirtuins families 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 E2fs knockout mouse

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 nuclear 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 nucleus 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 contract, 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 which 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.

| Ocular tissues | Functions |
|---|---|
| Corneal epithelium stoma cells endothelium | Inhibition of inflammation and promote healing anti-oxidative stress, survival |
| Ciliary body | Maintaining epithelium normal function? |
| Trabecular meshwork | Anti-oxidative stress? Cell survival |
| Lens epithelium and Lens fibril cells | Anti-oxidative stress, prevention of cell apoptosis |
| Retina RPE, outer nuclear layer Inner nuclear layer Ganglion cell | Anti-oxidative stress, prevention of aging and cell apoptosis, inhibition of angiogenesis |
| Optic nerve | Promote wound healing |

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

## References

1. Portela A, Esteller M (2010) Epigenetic modifications and human disease. Nat Chem Biol 28: 1057-1068.

2. Glozak MA, Sengupta N, Zhang X, Seto E (2005) Acetylation and deacetylation of non-histone proteins. Gene 363: 15-23.

3. Gray SG, Ekstrom TJ (2001) The human histone deacetylase family. Exp Cell Res 262: 75-83.

4. Gao L, Cueto MA, Asselbergs F, Atadja P (2002) Cloning and functional characterization of HDAC11, a novel member of the human histone deacetylase family. J Biol Chem 277: 25748-25755.

5. Feldman JL, Dittenhafer-Reed KE, Denu JM (2012) Sirtuin catalysis and regulation. J Biol Chem 287: 42419-42427.

6. Sauve AA, Wolberger C, Schramm VL, Boeke JD (2006) The biochemistry of sirtuins. Ann Rev Biochem 75: 435-465.

7. Davenport AM, Huber FM, Hoelz A (2013) Structural and Functional Analysis of Human SIRT1. J Mol Biol 426: 526-541.

8. Jackson MD, Schmidt MT, Oppenheimer NJ, Denu JM (2003) Mechanism of nicotinamide inhibition and transglycosidation by Sir2 histone/protein deacetylases. J Biol Chem 278: 50985-50998.

9. Yamakuchi M (2012) MicroRNA Regulation of SIRT1. Front Physiol 3: 68.

10. Sasaki T, Maier B, Koclega KD, Chruszcz M, Gluba W, et al. (2008) Phosphorylation regulates SIRT1 function. PloS ONE 3: e4020.

11. Yang Y, Fu W, Chen J, Olashaw N, Zhang X, et al. (2007) SIRT1 sumoylation regulates its deacetylase activity and cellular response to genotoxic stress. Nat Cell Biol 9: 1253-1262.

12. Liu X, Wang D, Zhao Y, Tu B, Zheng Z, et al. (2011) Methyltransferase Set7/9 regulates p53 activity by interacting with Sirtuin 1 (SIRT1). P Natl Acad Sci USA 108: 1925-1930.

13. Kornberg MD, Sen N, Hara MR, Juluri KR, Nguyen JV, et al. (2010) GAPDH mediates nitrosylation of nuclear proteins. Nat Cell Biol 12: 1094-1100.

14. Caito S, Rajendrasozhan S, Cook S, Chung S, Yao H, et al. (2010) SIRT1 is a redox-sensitive deacetylase that is post-translationally modified by oxidants and carbonyl stress. FASEB Biol 24: 3145-3159.

15. Tanno M, Sakamoto J, Miura T, Shimamoto K, Horio Y (2007) Nucleocytoplasmic shuttling of the NAD+-dependent histone deacetylase SIRT1. J Biol Chem 282: 6823-6832.

16. Brachmann CB, Sherman JM, Devine SE, Cameron EE, Pillus L, et al. (1995) The SIR2 gene family, conserved from bacteria to humans,

functions in silencing, cell cycle progression, and chromosome stability. Gene Dev 9: 2888-2902.

17. Guarente L (2000) Sir2 links chromatin silencing, metabolism, and aging. Gene Dev 14: 1021-1026.

18. Ozawa Y, Kubota S, Narimatsu T, Yuki K, Koto T, et al. (2010) Retinal aging and sirtuins. Ophthal Res 44: 199-203.

19. Mimura T, Kaji Y, Noma H, Funatsu H, Okamoto S (2013) The role of SIRT1 in ocular aging. Exp Eye Res 116: 17-26.

20. McBurney MW, Yang X, Jardine K, Hixon M, Boekelheide K, et al. (2003) The Mammalian SIR2 Protein Has a Role in Embryogenesis and Gametogenesis. Mol Cell Biol 23: 38-54.

21. Kamel C, Abrol M, Jardine K, He X, McBurney MW (2006) SirT1 fails to affect p53-mediated biological functions. Aging Cell 5: 81-88.

22. Cheng HL, Mostoslavsky R, Saito S, Manis JP, Gu Y, et al. (2003) Developmental defects and p53 hyperacetylation in Sir2 homolog (SIRT1)-deficient mice. P Natl Acad Sci USA 100: 10794-10799.

23. Chen D, Pacal M, Wenzel P, Knoepfler PS, Leone G, et al. (2009) Division and apoptosis of E2f-deficient retinal progenitors. Nature 462: 925-929.

24. Jaliffa C, Ameqrane I, Dansault A, Leemput J, Vieira V, et al. (2009) Sirt1 involvement in rd10 mouse retinal degeneration. Invest Ophthalmol Vis Sci 50: 3562-3572.

25. Alves LF, Fernandes BF, Burnier JV, Mansure JJ, Maloney S, et al. (2012) Expression of SIRT1 in ocular surface squamous neoplasia. Cornea 31: 817-819.

26. Maloney SC, Antecka E, Odashiro AN, Fernandes BF, Doyle M, et al. (2012) Expression of SIRT1 and DBC1 in Developing and Adult Retinas. Stem Cell Int 2012: 1-8.

27. Song L, Kang C, Sun Y, Huang W, Liu W, et al. (2016) Crocetin Inhibits Lipopolysaccharide-Induced Inflammatory Response in Human Umbilical Vein Endothelial Cells. Cell Physiol Biochem 40: 443-452.