Role of Sirtuin 1 in the pathogenesis of ocular disease (Review)

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Abstract. Sirtuin (SIRT)1, a member of the SIRT family, is a highly conserved NAD^+-dependent histone deacetylase, which has a regulatory role in numerous physiological and pathological processes by removing acetyl groups from various proteins. SIRT1 controls the activity of numerous transcription factors and cofactors, which impacts the downstream gene expression, and eventually alleviates oxidative stress and associated damage. Numerous studies have revealed that dysfunction of SIRT1 is linked with ocular diseases, including cataract, age-associated macular degeneration, diabetic retinopathy and glaucoma, while ectopic upregulation of SIRT1 protects against various ocular diseases. In the present review, the significant role of SIRT1 and the potential therapeutic value of modulating SIRT1 expression in ocular development and eye diseases is summarized.

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1. Introduction

Epigenetic alterations have critical roles in various physiological and pathological processes (1). Histone deacetylases (HDACs) are among the most important epigenetic regulators, which deacetylate lysine residues on specific histone and non-histone proteins (2). According to the homologies of the respective yeast orthologues, human HDACs have been divided into four classes (3,4). The human sirtuin (SIRT) family, belonging to class-III HDACs, is a class of NAD^+-dependent deacetylases and contains seven members (SIRT1-7) (5). Among them, SIRT1 has been most widely studied. The human SIRT1 protein contains 747 amino acids and is composed of three major regions (Fig. 1) (6,7). The level and activity of SIRT1 is regulated at the transcriptional and post-transcriptional level (8), with post-translational modifications including phosphorylation (9), sumoylation (10), methylation (11), S-nitrosylation (12) and carboxylation (13). Besides, the activity of SIRT1 distinctly depends on the NAD^+/NADH ratio and may be affected by nucleocytoplasmic shuttling (14).

The SIRT family has been identified to be highly evolutionarily conserved in various organisms from bacteria to humans (15). SIRT1, maintaining the silenced chromatin state and genomic stability (16), has been associated with various physiological and pathological processes and conditions, including DNA repair, metabolic regulation, aging, oxidative stress, angiogenesis, inflammation, neurodegenerative diseases and cardiovascular dysfunction. Previous reviews have indicated the major roles of SIRT1 in retinal and ocular aging (17-19). Increasing evidence has demonstrated that SIRT1 is also involved in other eye diseases, which are not limited to aging. The present review focuses on the current understanding and the potential therapeutic value of SIRT1 in ocular disorders.

2. Developmental roles and distribution of SIRT1 in the eye

It has been reported that mice carrying two null alleles of SIRT1 (also known as SIR2a in lower organisms) are small, and most of them die shortly after birth. Outbred SIRT1-null animals usually survived until adulthood, but were sterile (20). In SIRT1-deficient mice, eyelids remained closed accompanied by abnormalities of the cornea, lens and retina (20,21), and eyes were smaller, with the optic fissure being abnormally closed (22). Furthermore, there were significantly thinner retinal cell layers and disordered inner and outer nuclear layers. In addition, it was difficult to identify the inner and outer segments of photoreceptor cells. These eye defects occurred in early embryos, which implied that SIRT1 regulated ocular morphogenesis and retinal development (22). In addition, SIRT1 was reduced in the retina of mice with knockout of E2fs, which are essential positive cell cycle regulators, resulting in

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hyperacetylation of p53, a pro-apoptotic factor downstream of SIRT1, and increased retinal progenitor cell apoptosis (23). Treatment of pregnant mice with resveratrol, an activator of SIRT1, significantly blocked the apoptosis at P0 (23). Thus, the pro-survival role of E2f/SIRT1/p53 in retinal development has been established.

SIRT1 was detected in the cornea, lens, ciliary body, retinal pigment epithelium (RPE) and neuroretina in mice and humans, and in human normal conjunctival epithelium (24-26). Jaliffa *et al* (24) firstly reported that SIRT1 was predominantly localized in the nuclei of ocular cell, including corneal epithelial cells, ciliary process cells and ciliary epithelial cells, the epithelial and fiber cells of the lens, RPE cells and melanocytes, and exclusively in the nuclei of cells of the outer nuclear layer (ONL), inner nuclear layer (INL) and ganglion cell layer (GCL) but never in the cytoplasm. They also detected SIRT1 in the cytoplasm of corneal epithelial cells and choroidal vessel endothelial cells (24). Another study reported that SIRT1 was mainly expressed in the cytoplasm in the GCL, inner plexiform layer (IPL), outer plexiform layer (OPL), and inner segments of photoreceptors (26). In addition, SIRT1 was identified to be exclusively expressed in the cytoplasm of mouse retinal progenitor cells (RPCs), while it was present in the nuclei and cytoplasm in human RPCs (26). These apparently different SIRT1 distributions in different cell types of different species suggest that SIRT1 expression may be variable during different periods of retinal development and cell differentiation.

3. SIRT1 and eye diseases

SIRT1 and corneal diseases. Under normal conditions, the corneal epithelium is important for the maintenance of the physiological corneal function, rendering the cornea highly resistant to microbial invasion. A high-glucose (HG) environment led to the downregulation of SIRT1 and upregulation of acetylated p53 (Ac-p53) and insulin-like growth factor binding protein-3 (IGFPB3) in primary human corneal epithelial cells as well as corneas from insulin (Ins)$2^{Akita/+}$ mice (27). Overexpression of SIRT1 in corneal epithelial cells and $Ins2^{Akita/+}$ mice significantly led to a downregulation of Ac-p53 and IGFPB3, and an upregulation of the levels of phosphorylated (p)-AKT and IGF-1 receptor precursor. In addition, SIRT1 overexpression in corneal epithelium promoted the wound healing process under HG conditions, which may involve reinforcement of the IGFBP3/IGF-1/AKT pathway with the decrease of Ac-p53 (27). With the progression of diabetic dry eye (DE) in a mouse model, SIRT1 expression in the cornea rose in the first stage and then decreased. Furthermore, the expression of forkhead box O3 (FOXO3), which ameliorated the response to oxidative stress as a substrate of SIRT1, and the antioxidant enzyme Mn-superoxide dismutase (MnSOD) protein had a similar tendency with SIRT1, which suggests a role of SIRT1 in the resistance to oxidative stress (28). In summary, SIRT1 activation may be an effective approach for treating diabetic keratopathy.

Recent studies have demonstrated that microRNAs (miRNAs) may regulate corneal development and diseases. miRNA-204 directly downregulated SIRT1 in the cornea, and overexpression of miRNA-204 in human corneal epithelial cells inhibited cell cycle progression, cell proliferation and cell migration during the healing of wounded corneal epithelium in mice (29,30). Furthermore, miR-204-5p antagomir promoted the wound healing process via SIRT1 regulation in type 1 diabetic $Ins2^{Akita/+}$ mice (30). Wang *et al* (31) reported that miRNA-182 was the downstream miRNA target of SIRT1 under HG conditions, and protected against peripheral damage of trigeminal ganglions and keratopathy in diabetic db/db mice by decreasing the expression of one of its target genes, NADPH oxidase 4. Therefore, SIRT1 may protect the cornea through the miRNA-mRNA regulatory network.

SIRT1 and cataract. Age-associated cataract (ARC) is a condition characterized by multiple mechanisms and has various risk factors, including genetic, metabolic, nutritional and environmental factors, as well as other ocular diseases (32). Previous studies have indicated that resveratrol is able to protect human lens epithelial cells from oxidative damage induced by H_2O_2 (33,34) and suppress experimental cataract formation in rats (35). The SIRT1 levels in the lens were identified to be significantly decreased in individuals aged ≥51 years, and to be negatively correlated with ARC in humans (36). Of note, SIRT1 was significantly increased in patients aged >50 years with ARC compared with that in age-matched subjects without ARC (37), and SIRT1 levels in the aqueous humor of ARC patients were positively correlated with the severity of nuclear cataract (38). Furthermore, while the expression of the downstream components of SIRT1, FOXO3a and FOXO4, was downregulated with age, it exhibited relative increases in ARC patients (37). By contrast, the expression of p53 increased with age, but active Ac-p53 was decreased in older patients with cataract compared with that in old individuals without cataract (37). These studies indicate that the increased SIRT1 may function as a compensation to alleviate ARC formation through inhibiting its downstream p53 acetylation and activating the FOXO pathway (37). Another study indicated that the enhanced interaction between SIRT1 and 8-oxoguanine (8-oxoG)-DNA glycosylase 1 (OGG1) and/or insufficient interaction between the histone acetyltransferase p300 and OGG1 may decrease the acetylation of OGG1 in the lens of patients with ARC, resulting in abnormal accumulation of 8-oxoG, a biomarker of oxidative damage, in the lens (39). Eventually, these changes accelerate the development of ARC, implying a destructive role of SIRT1 upregulation (39). These divergent results are possibly attributed to the difference in research methods and subjects. More comprehensive studies focusing on the precise mechanisms of SIRT1 in the pathogenesis of ARC are required.

SIRT1 and age-associated macular degeneration. Age-associated macular degeneration (AMD) manifests as either drusen/geographic atrophy or choroidal neovascularization (CNV). The pathophysiology and risk factors of AMD are complex (40). Chen *et al* (41) investigated three variants of the SIRT1 gene associated with AMD in Chinese Han individuals, and identified that the rs12778366 polymorphism within the promoter region of SIRT1 was significantly associated with AMD in recessive and codominant models. Expression of SIRT1 was more frequent in RPE and vascular endothelial cells (VECs) in human CNV membranes (42). By contrast,

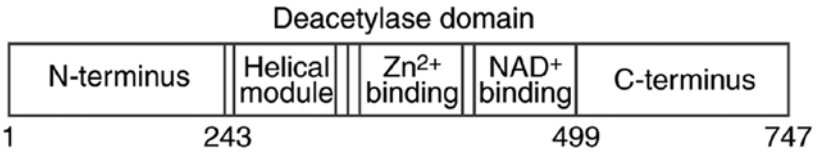

Figure 1. Schematic representation of the 1-dimensional structure of human SIRT1 protein. Human SIRT1 protein comprises 747 amino acids divided into three major regions: The central core, possessing the deacetylase domain, which consists of a large NAD^+-binding subdomain and a smaller subdomain composed 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. SIRT, sirtuin.

another study indicated that the expression and self-renewal ability of SIRT1 in retinal stem cells (RSCs) (43), human retina and RPE cells (44) obviously declined with age.

Dysfunction of RPE cells is a major risk factor for the development of AMD. In aged RPE cells, overexpression of SIRT1 and octamer binding transcription factor 4, a POU-domain transcription factor, reprogrammed the cells into retinal progenitor-like cells and enhanced their antioxidant enzymatic activities (44). The expression of p53 increased in aged RPE, and in young RPE cells, sirtinol (a SIRT1 inhibitor) increased p53 acetylation and phosphorylation, but only had a marginal effect on p53 expression and increased caspase-3 activation, which contributed to apoptosis of RPE cells (45). Furthermore, resveratrol obviously prevented p53 acetylation and phosphorylation, and eventually alleviated caspase-3-dependent RPE cell apoptosis (45). Recently, Golestaneh *et al* (46) developed an *in vitro* disease model of AMD through the generation of induced pluripotent stem cells (iPSCs) from RPE from patients with AMD and differentiation of these iPSCs into RPE (AMD RPE-iPSC-RPE), and observed the downregulation of SIRT1 and peroxisome proliferator activated receptor-γ co-activator-1α (PGC-1α) in AMD RPE-iPSC-RPE compared with that in normal RPE-iPSC-RPE. The study indicated that dysfunctional SIRT1/PGC-1α may decrease mitochondrial activity and increase reactive oxygen species (ROS) production in AMD RPE-iPSC-RPE, and contribute to the pathophysiology of AMD (46).

Oxidative stress accelerates the progression of AMD. Overexpression of SIRT1 or treatment with resveratrol protected against oxidative stress-induced RPE cell senescence through downregulation of p53 K382 acetylation and $p21^{Waf1/Cip1}$ accumulation (47), and increased the viability of H_2O_2-treated rat RSCs (43). On the contrary, knockdown of SIRT1 or application of SIRT1 inhibitors including nicotinamide (48) and sirtinol enhanced the toxicity of H_2O_2, making RPE cells hyper-sensitive to oxidative stress (47). Furthermore, SIRT1 rescued complement factor H (CFH) expression through increasing recruitment of signal transducer and activator of transcription 1 and decreasing the occupancy of the repressor FOXO3 in the CFH promoter of H_2O_2-treated ARPE-19 cells, which may prevent the oxidative stress-induced aging and cell damage and decrease the risk of AMD (49). A further experimental study indicated that SIRT1 levels were reduced in human RPE cells after treatment with amyloid β (Aβ), which is one of the constituents of drusen (50). Treatment with SRT1720, a potent SIRT1 agonist that suppresses the nuclear factor (NF)-κB signaling system, significantly decreased Aβ-mediated upregulation of inflammatory cytokines in RPE cells, and balanced the morphology and barrier function of RPE cell monolayers, which was obviously suppressed by knockdown of SIRT1 (50).

The expression of SIRT1 mRNA exhibited daily variations under the light-dark cycle conditions in the retina and was obviously upregulated in the dark phase (51). Considering that retinal cells consume more energy in the dark, the study linked SIRT1 regulation with the response to light stimuli and metabolic dysfunction in age-associated retinal diseases including AMD (51). In an *in vitro* study, ultraviolet B activated the phosphoinositide-3 kinase/AKT/extracellular signal-regulated kinase (ERK) pathway by reducing the expression of SIRT1 in a dose-dependent manner in ARPE-19 cells and suppressed the growth of the cells (52). In a mouse model of light-induced retinal degeneration, retinal SIRT1 activity was significantly reduced (53). Systemic administration of resveratrol not only significantly recovered retinal SIRT1 activity, but also restored histological and functional damage to the retina (53). Likewise, gene transfer of SIRT1 decreased retinal cell loss and improved the light-induced electroretinographic damage in rat retinas (44). In addition, the levels of activator protein (AP)-1 subunit c-fos were elevated in the retina of light-exposed mice and reduced by application of resveratrol (53). These studies suggest that SIRT1 activators or overexpression of SIRT1 protect the retina from light damage through inhibiting AP-1 bioactivity (53) and suppressing AKT and ERK phosphorylation (52).

CNV formation is a typical characteristic of wet AMD. Previous studies have indicated the regulative roles of SIRT1 in angiogenesis (54,55). Expression of SIRT1 was higher in human CNV membranes from AMD patients than in eyes from donors without AMD (42). *In vitro* studies demonstrated that hypoxia-induced upregulation of SIRT1 levels augmented hypoxia-inducible factor (HIF)-2α expression in choroidal endothelial cells, which in turn activated and released vascular endothelial growth factor (VEGF) (56). Thus, SIRT1 may promote CNV formation. However, other studies indicated that SIRT1 activation by resveratrol inhibited various inflammatory cytokines, transforming growth factor (TGF)-β-mediated VEGF secretion and hypoxia-mediated choroidal VEC proliferation through downregulation of HIF-1α (57,58). A study by our group indicated that resveratrol inhibited the HIF-1α/VEGF/VEGF receptor 2 signaling axis partly through SIRT1 (59). Khan *et al* (60) demonstrated that resveratrol inhibited the proliferation and migration of VECs and led to severely blunted neovascularization through activating eukaryotic elongation factor-2 kinase instead of the SIRT1-dependent pathway. The difference in drugs and experimental models may produce discrepant results regarding the function of SIRT1. The mechanisms of the effects of SIRT1 on CNV

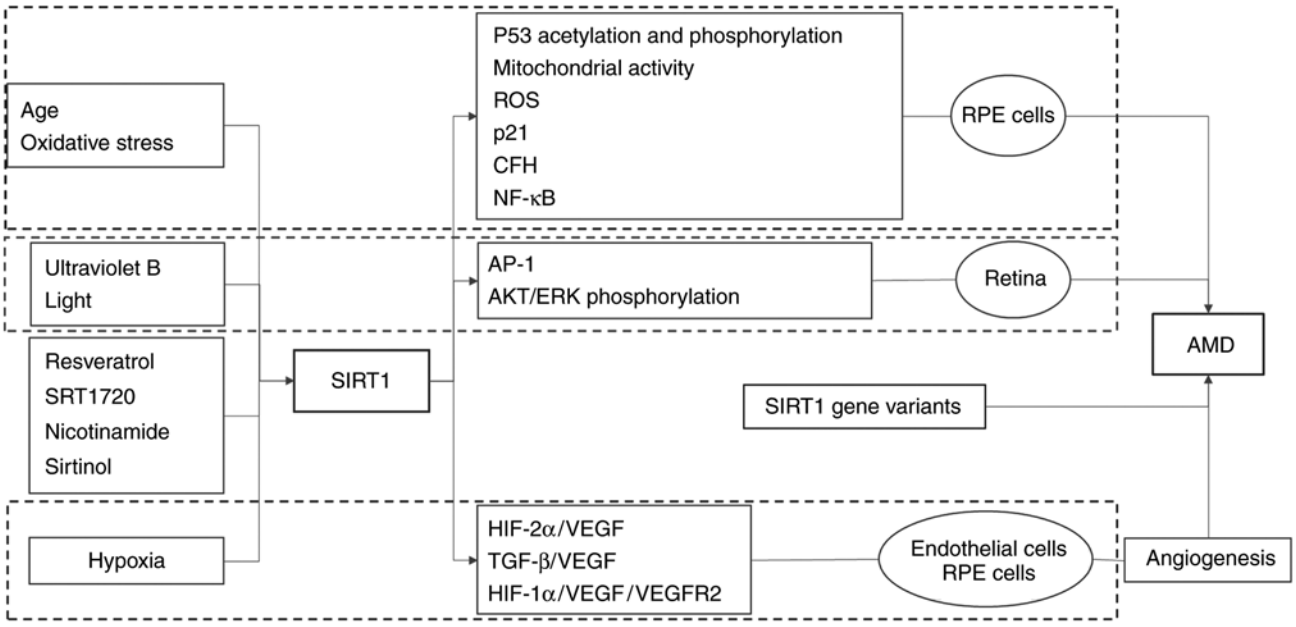

Figure 2. Role of SIRT1 in the pathogenesis of AMD. Factors and medicines (left) affected different cells and tissues function (right) through various pathways regulated by SIRT1 (middle), which ultimately induced the generation of AMD. SIRT, sirtuin; ROS, reactive oxygen species; RPE, retinal pigment epithelium; NF, nuclear factor; AP, activator protein; ERK, extracellular signal-regulated kinase; HIF, hypoxia-inducible factor; VEGFR, vascular endothelial growth factor receptor; TGF, transforming growth factor; AMD, age-associated macular degeneration; CFH, complement factor H.

formation require more comprehensive elucidation. The role of SIRT1 in the pathogenesis of AMD is summarised in Fig. 2.

SIRT1 and diabetic retinopathy (DR). DR is a severe complication of diabetes mellitus. Progression of diabetic blood glucose control suggests a 'metabolic memory' phenomenon (61,62). The expression of SIRT1 was reduced in the retinas of diabetic mice (63-66). Zheng *et al* (67) observed a decrease in SIRT1 and an increase of NF-κB, the pro-apoptotic gene B-cell lymphoma 2-associated X protein (Bax), poly ADP-ribose polymerase (PARP) and ROS in bovine retinal endothelial cells (RECs) cultured under HG after glucose normalization. SIRT1 overexpression mediated liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK) activity, which inhibited ROS pathway activation in HG in RECs, resulting in the suppression of NF-κB, Bax and PARP expression. In addition, ROS-induced PARP activity, at least in part, led to the downregulation of SIRT1 expression and amplified an auto-feedback loop regulating SIRT1 expression. These results implied that SIRT1 mediated a metabolic memory effect induced by HG through the SIRT1/LKB1/AMPK/ROS cascade (67). Another study reported that transient hyperglycemia caused persistent endothelial cell senescence through the imbalance between SIRT1, and that P300 induced the upregulation of Ac-p53 and its downstream p21 (68). Recently, Zhao *et al* (69) identified that increased expression of miR-23b-3p directly downregulated SIRT1, which increased Ac-NF-κB levels in human RECs with a metabolic memory effect induced by HG. Similar results were obtained in rats with streptozotocin-induced diabetic retinopathy as a metabolic memory model, in which vascular permeability was significantly suppressed by miR-23b-3p inhibitor (69). Furthermore, metformin, a blood glucose-lowering therapeutic, fenofibrate, a lipid-lowering therapeutic and resveratrol suppressed the memory of hyperglycemic stress via the SIRT1-dependent signaling pathway (67,68,70).

The overproduction of mitochondrial ROS and cytokines promotes the development of DR (71,72). Reduced SIRT1 in HG-cultured RECs obviously enhanced the acetylation of NF-κB p65 and AP-1, which binds to the promoter of matrix metalloproteinase (MMP)-9, which eventually activates MMP-9 (64,73). SIRT1 overexpression decreased the transcription of MMP-9 in REC (64,73) and ameliorated NF-κB/Rac1/NADPH oxidase-mediated mitochondrial damage in diabetic rat retina (65). SIRT1 overexpression suppressed the upregulation of endothelin 1, TGF-β1, collagen 1α and fibronectin, and prevented glucose-induced endothelial permeability and increases in total ROS/RNS levels in the retina of diabetic mice (74). In addition, systemic administration of resveratrol to the diabetic animals suppressed leukostasis and the upregulation of intercellular adhesion molecule-1 and VEGF (66). Exendin-4, a glucagon-like peptide 1 analogue, moderated ROS-mediated retinal cell death and recovered visual function by upregulating SIRT1 and SIRT3 expression in early-stage diabetic rats (75). Furthermore, SIRT1 may protect proliferative DR progression by inhibiting interleukin-17 (76). Another study indicated that miR-195 antagomir normalised tissue damage mediated by SIRT1 reduction in a rat model of DR (77).

Mice with oxygen-induced ischemic retinopathy (OIR) exhibit certain features of neovascularization that are characteristic of proliferative DR in humans (78). Increased SIRT1 in avascular retinal neurons of OIR mice mediated physiological revascularization of ischemic areas through modulating the HIF signaling pathway and secretion of pro-angiogenic and neuroprotective factors (79). However, ectopic overexpression of SIRT1 in mouse retinas or oral administration of SIRT1 activator did not alter the vaso-obliteration, pathologic

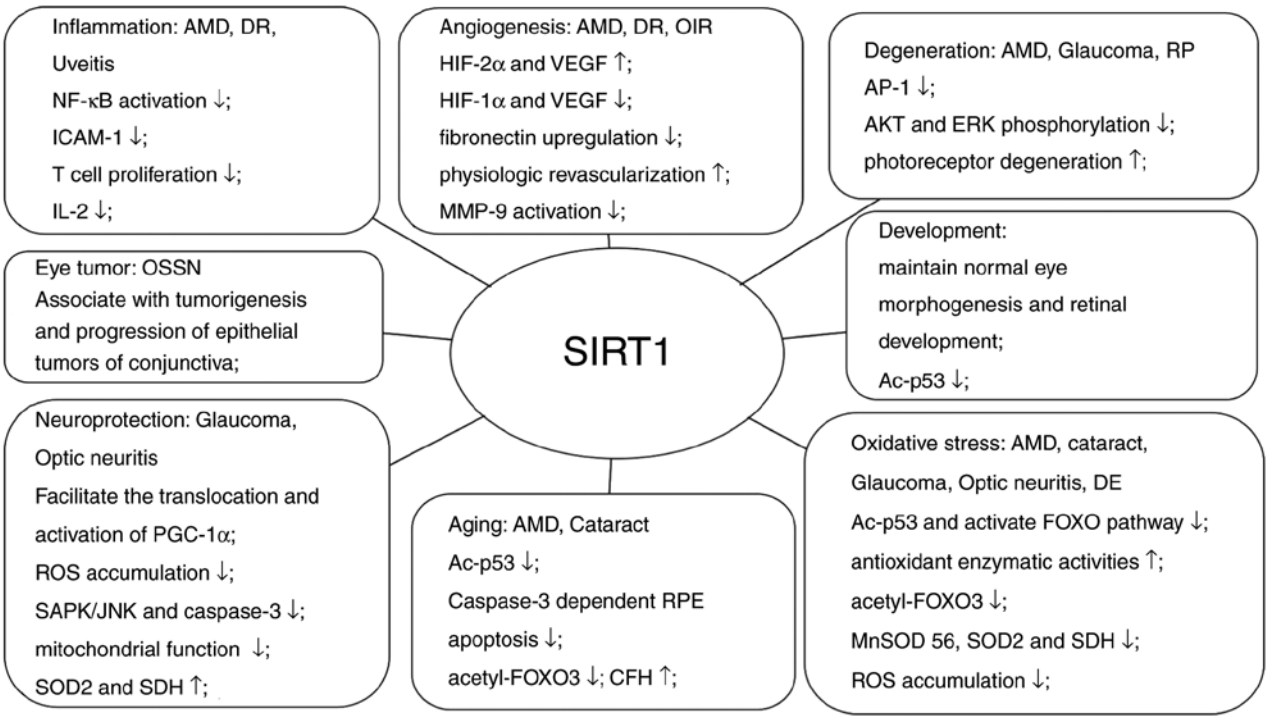

Figure 3. Roles of SIRT1 in eye diseases and development. The diagram depicts that SIRT1 plays significant role in ocular diseases by influencing various physiological and pathological processes such as inflammation, angiogenesis, aging, oxidative stress, neuroprotection and so on. ↓, suppression; ↑, enhancement. SIRT, sirtuin; AMD, age-associated macular degeneration; NF, nuclear factor; HIF, hypoxia-inducible factor; MMP, matrix metalloproteinase; SOD, superoxide dismutase; SDH, succinate dehydrogenase; JNK, c-Jun N-terminal kinase; ROS, reactive oxygen species; IL, interleukin; ICAM, intercellular adhesion molecule; AP, activator protein; ERK, extracellular signal-regulated kinase; Ac-p53, acetylated p53; CFH, complement factor H; FOXO, forkhead box O; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; OSSN, ocular surface squamous neoplasia; OIR, oxygen-induced ischemic retinopathy; PGC, peroxisome proliferator-activated receptor γ coactivator; SAPK, stress-activated protein kinase; DE, diabetic dry eye; DR, diabetic retinopathy.

neovascularization or retinal neuron degeneration in OIR (80). The protective role of SIRT1 in OIR requires more comprehensive study.

SIRT1 and glaucoma. Glaucoma is a group of chronic eye diseases ascribed to the irreversible death of retinal ganglion cells (RGCs) and progressive optic neuropathy, and results in serious vision loss and blindness. RGCs transmit light signals from the retina along their axons to the brain. Various types of stimuli, including trauma, ischemia, increased intraocular pressure, oxidative stress and inflammation, have been reported to lead to RGC death (81). SIRT1 has been linked with Alzheimer's and Huntington's disease in respective animal models and exerted a neuroprotective role in these diseases (82). Further studies have indicated the neuroprotective effects of SIRT1 on RGCs. For instance, resveratrol protected RGC-5 cells against serum deprivation-induced apoptosis by promoting the expression of SIRT1 and facilitating the translocation of PGC-1α from the cytoplasm to the nucleus (83,84). In addition, oral resveratrol administration or overexpression of SIRT1 following optic nerve crush injury in mice reduced RGC loss and ROS accumulation in the optic nerve (85). However, resveratrol was unable to prevent RGC loss after optic nerve crush injury in the eyes of SIRT1-knockout mice (85), which confirmed the necessity of SIRT1 expression for resveratrol-mediated neuroprotection. Furthermore, SIRT1 increased the viability of RGCs under hypoxic conditions through inhibiting stress-activated protein kinase/c-Jun N-terminal kinase and caspase-3 activation (86), in ischemic mouse retinas, mangiferin prevented RGC loss via SIRT1, which was suppressed by sirtinol (87), suggesting a neuroprotection role of SIRT1 on RGCs under hypoxic condition.

SIRT1 and optic neuritis. RGC loss also has been demonstrated in several experimental models of optic neuritis, including experimental autoimmune encephalomyelitis (EAE), which is an animal model of multiple sclerosis (MS). SIRT1 activator-associated suppression of RGCs loss delayed the onset of EAE and attenuated neuronal damage in EAE mice (88-90). The fact that the protective effect on RGCs by SIRT1 activators was blocked by sirtinol further suggests the neuroprotection role of SIRT1 activation (88,90). Pre-treatment with SIRT1 activators, resveratrol and SRTAW04, significantly reduced ROS and cell death caused by H_2O_2 in RGC-5 cells (91). Furthermore, SIRT1 activators induced a significant increase in SOD2 and succinate dehydrogenase expression in stressed RGC-5 cells and enhanced deacetylation and activation of PGC-1α (91). Similar protective mechanisms were observed in a mouse hepatitis virus A59-induced MS model (92). However, administration of SIRT1 activators neither suppressed the gross level of inflammation in the optic nerve nor attenuated the development of clinical EAE (88-90,92). During disease remission, EAE patients retain proper axonal density, suggesting that SIRT1 activator prevents permanent neurological dysfunction and neuronal damage in MS after acute spinal cord inflammation is resolved (90). In addition, resveratrol, through promoting SIRT1 expression and cholesterol synthesis, restored the number of surviving RGCs in the rats with optic nerve injury (93). Most

importantly, the neuroprotective effects of SIRT1 activators without immunosuppression may imply a potential benefit of combining anti-inflammatory therapies for optic neuritis as well as for non-inflammatory optic nerve diseases.

SIRT1 and uveitis. Uveitis is characterized by a process of intraocular inflammation resulting from multiple factors. Corticosteroids and immunosuppressive drugs are effective for relieving diverse uveitis, but have severe side effects, which limits their clinical application (94). Alternative, novel drugs or treatments are therefore required. Recent studies have applied SIRT1 activators in the treatment of uveitis animal models. For instance, oral application of resveratrol to mice with endotoxin-induced uveitis (EIU) led to inhibition of oxidative damage and significant increases in SIRT1 activity in the RPE-choroid, resulting in the suppression of NF-κB-mediated inflammation in the eye (95). Resolvin D1, a lipid-derived protein for intravitreal injection, prevented EIU in rats through increasing SIRT1-mediated downregulation of Ac-p53 and FOXO1 (96). Furthermore, treatment of mice with experimental autoimmune uveoretinitis (EAU) with SIRT1 activator SRT2379 alleviated inflammation through suppressing T cell proliferation, pro-inflammatory cytokine production and leukocyte infiltration (97). Gardner *et al* (98) reported that tumor necrosis factor (TNF)-α mediated the cleavage and inactivation of SIRT1 to drain lymph node effector cells in EAU, and that combined application of a suboptimal TNF-α blockade and SIRT1 activation had a synergistic suppressive effect on EAU. In addition, in an *in vitro* model of antibody-mediated autoimmune retinopathy, resveratrol treatment led to an upregulation of SIRT1 and Ku70 in retinal cells, blocked the influx of intracellular calcium and the entry of pro-apoptotic Bax from the cytoplasm to the mitochondria, to subsequently prevent caspase-3 activation and protect cells from apoptotic death induced by antibodies against recoverin and α-enolase (99). These studies demonstrated that activation of SIRT1 may be a potential treatment option for ocular uveitis.

3. Perspective

The present review mainly focused on the emerging evidence of the association between SIRT1 and the eyes. As summarized in Fig. 3, SIRT1 serves a significant role in ocular diseases by influencing various physiological and pathological processes such as inflammation, angiogenesis, aging, oxidative stress, neuroprotection. Although the potential protective role of SIRT1 has been demonstrated in numerous *in vitro* and *in vivo* models of ocular diseases, further studies are necessary to confirm the accurate mechanism and the most effective administration of SIRT1 activators and inhibitors in these diseases (100). In addition, it is required to determine whether the data obtained using animal models are applicable to human ocular diseases. In summary, SIRT1 may be considered as a valuable therapeutic target in ocular diseases.

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Availability of data and materials

The analysed data sets generated during the study are available from the corresponding author on reasonable request.

Authors' contributions

MZ and HZ drafted the article and revised it critically for important intellectual content. JL and HZ conceived and designed the present review.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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