melanocytes, as well as in the cytoplasm of choroidal vascular endothelial cells. Jalliffa and associates also reported that SIRT1 mRNA was detected in the outer nuclear layer (ONL), inner nuclear layer (INL), and ganglion cell layer (GCL) of the retina by in situ hybridization (Jaliffa et al., 2009). In the human eye, expression of SIRT1 was detected in the lens epithelium of patients with senile cataract (Zheng and Lu, 2011; Lin et al., 2011), and retinas (Maloney et al., 2012). For the normal human corneal epithelium, Alves et al. reported that 50% showed negative expression of SIRT1 and 30% weak expression, and 20% were considered significantly immunoreactive using 10 corneal specimens (Alves et al., 2012).

5. Neuroprotective effect of SIRT1 against Wallerian degeneration

The optic nerve is formed by the axons of retinal ganglion cells, which are the second neurons in the visual pathway. When experimental transection of the optic nerve is done, the ganglion cells are severed from their axons. Therefore, the ganglion cell axons (constituting the optic nerve, optic chiasm and optic tract up to the lateral geniculate nucleus) would be expected to undergo anterograde degeneration, since the transection of a peripheral nerve causes degeneration of the distal segment. This phenomenon is known as Wallerian degeneration. It is considered that SIRT1 contributes to preservation of neurons from Wallerian degeneration (Tang and Chua, 2008; Zhang et al., 2011).

The neuroprotective effect of SIRT1 against Wallerian degeneration was first observed in a study of slow Wallerian degeneration (WldS) mutant mice (Perry et al., 1990). WldS mutant mice exhibit a significant delay in the onset of axonal degeneration after physical or chemical injury (Coleman and Perry, 2002; Coleman, 2005). WldS protein is composed of the N-terminal 70 amino acids of ubiquitin fusion degradation protein 2a (Ufd2a), which is a ubiquitin assembly protein, plus the complete sequence of nicotinamide mononucleotide adenylyltransferase 1 (Nmnat1), an enzyme that directly catalyzes the synthesis of nicotinamide adenine dinucleotide (NAD) (Conforti et al., 2000; Mack et al., 2001; Coleman, 2005). Both Nmnat1 activity and the short N-terminal have been shown to make a contribution to WldS-mediated axonal protection (Hilliard, 2009; Conforti et al., 2009; Avery et al., 2009; Coleman and Freeman, 2010). The Nmnat-1 portion of the fusion protein is essential for the prevention of axonal damage (Araki et al., 2004; Conforti et al., 2007; Sasaki et al., 2009; Babetto et al., 2010). Axonal protection by WldS is mediated through overexpression of Nmnat-1 via activation of a SIRT1-dependent process, while neuroprotection is blocked by the SIRT1 inhibitor sirtinol and by SIRT1 silencing with siRNA (Araki et al., 2004; Sasaki et al., 2009; Babetto et al., 2010). However, other findings have suggested that increased Nmnat1 activity and SIRT1 do not fully account for the neuroprotective activity of the WldS gene (Wang et al., 2005; Conforti et al., 2007; Sasaki et al., 2009), suggesting that NAD delays axonal regeneration by a local protective effect. Thus, the role of SIRT1 in axonal degeneration remains controversial as to whether the axonal protection is mediated by SIRT1-dependent (Araki et al., 2004) or SIRT1–independent mechanisms (Wang et al., 2005).

6. Neuroprotective effect of SIRT1 in retinal damage

SIRT1 also appears to have a neuroprotective effect in retinal damage. The retina is part of the nervous system, but various factors (including aging, UV radiation, and oxidative stress) can induce permanent damage to its architecture (Fletcher, 2010). SIRT1 is localized in most layers (including the ONL, INL, GCL, and RPE) of the normal mouse retina (Jaliffa et al., 2009). In SIRT1-deficient adult mice, multiple retinal cell layers were significantly thinner than in normal eyes and the inner and outer nuclear layers were disorganized (Cheng et al., 2003). 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 (Cheng et al., 2003).

SIRT1 protects the retinal cells from DNA damage such as oxidative stress-related retinal damage (Peng et al., 2010, 2011), apoptotic retinal death (Anekonda and Adamus, 2008), and anti-inflammation (Shindler et al., 2007; Kubota et al., 2011). On the other hand, the breakdown of SIRT1 causes retinal damage through multiple mechanisms. First both Oct4 and SIRT1 expression is decreased in aged retinal pigment epithelium cells (RPEs) or light-injured rat retinas (Peng et al., 2011). Second, light exposure up-regulate retinal activator protein-1 and reduce retinal SIRT1 activity in mice (Kubota et al., 2010). Third, diabetes-induced retinal inflammation mediated by downregulation of the adenosine monophosphate (AMP)-activated protein kinase (AMPK) pathway, is responsible for SIRT1 deactivation and NF-κB activation (Kubota et al., 2011; Zheng and Lu, 2011).

Oxidative stress is a subproduct of dysfunctional energy homeostasis (Wu et al., 2006). SIRT1 maintain energy homeostasis and anti-apoptotic mechanisms essential for optimal normal brain function to balance oxidative stress in the normal adult central nervous system (Wu et al., 2006). Jaliffa et al. reported that SIRT1 maintain survival pathways, balanced energy homeostasis, and physiological DNA repair mechanisms in photoreceptor cells to treat inherited retinal degenerative diseases (Jaliffa et al., 2009).

Several experimental studies have demonstrated a neuroprotective effect of SIRT1 against retinal and optic nerve damage. For example, intravitreal injection of SIRT1 activators prevents RGC loss in a dose-dependent manner through stimulating SIRT1 enzymatic activity in mice with optic neuritis (Shindler et al., 2007). This neuroprotective effect is blocked by sirtinol, a SIRT1 inhibitor (Shindler et al., 2007). Absence of E2fs, the transcription factor for SIRT1, cause downregulation of the p53 deacetylase activity of SIRT1, resulting in p53 hyperacetylation and an increase of apoptosis in the mouse retina (Chen et al., 2009). Bhattacharya et al. reported that P53 acetylation Lys379 increases through the inhibition of SIRT1 and SIRT2 in primary RPE cultures from human donor eyes (Bhattacharya et al., 2012). They concluded that pharmacologic treatments to block p53 phosphorylation or acetylation may protect RPE cells from apoptosis. SIRT1 gene transfer accompanied by Oct 4 rescues retinal cell loss and improves electroretinographic responses in rats with retinal phototoxicity (Peng et al., 2011). Furthermore, upregulation of SIRT1 by resveratrol protects cultured retinal cells from antibody-induced apoptotic death (Anekonda and Adamus, 2008). Resveratrol is a natural polyphenol found in red grapes and red wine that has been shown to enhance SIRT1 activity (Howitz et al., 2003; Baur, 2010; Haigis and Sinclair, 2010) (Fig. 4). Resveratrol also has a protective effect against phototoxic degeneration of the mouse retina in vivo (Kubota et al., 2010). These results suggest that SIRT1 is able to protect against diseases caused by oxidative stress-induced retinal damage, such as AMD, while anti-aging therapy with resveratrol could be an alternative treatment for retinal damage.

7. Protective effect of SIRT1 against senile cataract

Lin et al. reported that the SIRT1 expression in lens opacity was lower in patients ≥51 years old than in those <51 years old and was negatively associated with age (Lin et al., 2011). This indicates that decreased SIRT1 expression in the lens epithelium is associated with the grade of cataract and with patient age. Interestingly, Zheng et al. reported that the SIRT1 expression in the lens epithelium

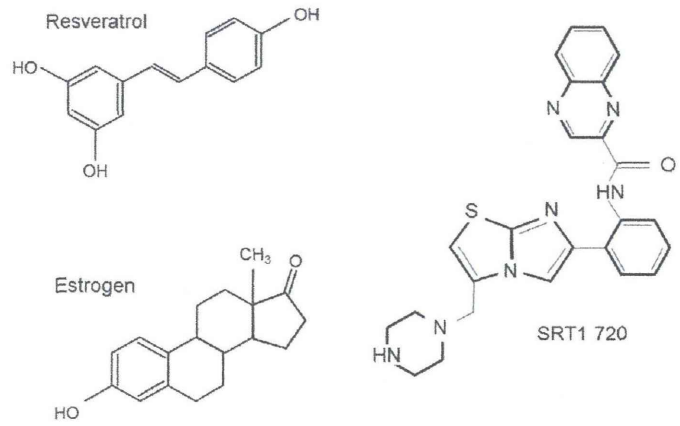

Fig. 4. Chemical structures of SIRT1 activators. Resveratrol is a polyphenolic compound found in grapes and wine and is a known activator of SIRT1. Resveratrol has a structure similar to that of an estrogen agonist and can bind to estrogen receptors. The experimental drugs SRT1720 is a low molecular weight activator of SIRT1 that is 1000 times more potent than resveratrol.

decreases with age, but there is an increase among patients older than 50 years who have senile cataract compared with persons older than 50 years without cataract (Zheng and Lu, 2011). Additionally, they reported that expression of both forkhead box class O (FOXO)3a and FOXO4 decreased with age, but expression in patients older than 50 years with age-related cataract was equivalent to that in persons younger than 40 years without cataract (Zheng and Lu, 2011). On the other hand, p53 downstream of SIRT1 is decreased in senile cataract (Zheng and Lu, 2011). Zheng et al. concluded that downstream p53 is inhibited, while the FOXO pathway is activated, in senile cataract, indicating that SIRT1 may have a protective effect against senile cataract formation (Zheng and Lu, 2011).

8. Protective effect of resveratrol and other SIRT1 activators against cataract formation

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a natural product occurring in grapes and various other plants (Fremont, 2000). The chemical structure of resveratrol is similar to that of the synthetic estrogen agonist, diethylstilbestrol (Gehm et al., 1997) (Fig. 4). Thus, resveratrol might acts as a mixed agonist/antagonist for estrogen receptors (Bowers et al., 2000). The effect of resveratrol on alternative splicing is dependent on SIRT1, SIRT3, and SIRT4 (Markus et al., 2011; Schirmer et al., 2012). Resveratrol has been reported to activate sirtuin (Costa Cdos et al., 2011), inducing the deacetylation of PGC-1α (Lagouge et al., 2006; Pallas et al., 2009), and resveratrol therefore has the ability to suppress cataract formation (Doganay et al., 2006; Barden et al., 2008; Pearson et al., 2008). Doganay et al. reported that resveratrol can prevent sodium selenite-induced oxidative stress and experimental cataract formation in rats (Doganay et al., 2006). This protective effect was supported by a higher level of glutathione and lower level of malondialdehyde in the lens and erythrocytes (Doganay et al., 2006). Pearson et al. reported that resveratrol-fed elderly mice showed a marked reduction of age-related diseases and cataract formation (Pearson et al., 2008). These results suggest that activation of SIRT1 by resveratrol has a protective effect against cataract formation. Barden et al. showed that grape seed proanthocyanidin extract reduced the production of reactive oxygen species in cultured canine lens epithelial cells by reducing tertiary butyl hydroperoxide-induced activity of the mitogen-activated protein kinase (MARK), which is a marker of stress-induced cell signaling, and phosphoinositide-3 kinase (PI3K) pathways, resulting in the prevention of cataract (Barden et al., 2008).

Recently, a series of experimental SRT drugs (SRT1720, SRT2183, and SRT1460) are reported to activate SIRT1 (Howitz et al., 2003; Milne et al., 2007; Dittenhafer-Reed et al., 2011). These small molecules are a potent activator of SIRT1 that is 1000 times more potent than resveratrol (Milne et al., 2007). However, the controversial mechanism of SIRT1 activation by SRT1720 has been reported (Pacholec et al., 2010) and several studies demonstrated that SRTs and resveratrol are not specific activator of SIRT1 (Beher et al., 2009; Zarse et al., 2010).

9. Summary

This review focused on the role of sirtuins in ocular aging. Many animal studies have shown that SIRT1 regulates ocular aging and the resistance of ocular tissues to oxidative stress by deacetylation of several proteins in an NAD+-dependent manner. Considering these data, SIRT1 is an attractive candidate for the development of therapeutic strategies to prevent ocular aging. However, it is unclear whether these animal data are applicable to ocular diseases in humans. Some clinical trials of SIRT1 activators have already been started for a variety of diseases, including cardiovascular disease, cancer, diabetes, and Alzheimer's disease. Future clinical trials should focus on further defining the role of SIRT1 in ocular aging. SIRT1 or SIRT1 activators may have the potential to prevent ocular aging, cataract, AMD, and glaucoma.

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