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Editorial

SIRT1 and Age-Related Macular Degeneration

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Editorial

Age-Related Macular Degeneration (AMD) is the leading cause of irreversible central vision loss in the elderly [1-3]. AMD is a complex disorder from the interaction of aging with multiple genetic and environmental risk factors. The late stage of AMD can manifest as either Geographic Atrophy (GA) or Choroidal Neo-Vascularization (CNV). The pathogenesis of AMD is still under-investigation. Recently, the abnormal of epigenetic factors such as DNA methylation and histone acetylation/deacetylation have been recognized as an important contributor for the development of AMD, and one of the hot topics in the study of the involvement of epigenetic factors is the histone deacetylase enzyme Mammalian Sirtuin1 (SIRT1) [4-9].

SIRT1 is a histone deacetylase converting enzyme, functioning as a NAD^+-dependent histone deacetylase [10]. SIRT1 regulates cell senescence, DNA damage repair, apoptosis [11] and longevity in response to caloric restriction in many organisms, including yeast, worms, flies, and possibly mammals [12]. SIRT1 plays an important role in normal and pathologic conditions [13]. Recently, SIRT1 has been shown not only to affect histone acetylation but also to target a variety of non-histone proteins, including p53 , nuclear factor-kappa B (NF-κB) , E2F1, peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α) and hypoxia-inducible transcription factors (HIF) [14,15].

SIRT1 is probably involved in the pathogenesis of AMD from some of the recent reports. Peng C. et al. displayed that SIRT1 expression was down-regulated in both aged human retina and aged RPE cells from both AMD and non-AMD donors [16]. In addition, the SIRT1 mRNA expression level and self-renewal ability were significantly decreased with age in retinal stem cells, whatever from rats or humans. Although different SIRT1 expression levels were shown in these articles, at least the results suggest that SIRT1 plays a role in the pathogenesis of the disease. Dysfunction and apoptosis of RPE cells are well known major factors that contribute to the pathogenesis of AMD. In young RPE cells, basal levels of p53 were low. By contrast, aged RPE showed increased expression of P53, which is a pro-apoptotic factor as a downstream of SIRT1 [17]. Further study revealed that aging robustly increased p53 phosphorylation and acetylation, which disrupt the interactions of P53 with Mdm2, leading to P53 stabilization [17]. On the other side, pretreatment of cells with resveratrol (a SIRT1 activator) significantly prevented increases of P53 acetylation and phosphorylation and eventually inhibited caspase-3-dependent RPE apoptosis.

Inflammation plays a major role in the pathogenesis of AMD. Amyloid beta (Aβ), a known constituent of drusen, can induce chronic inflammation [18]. Interesting, SIRT1 is also an inflammatory inhibitor. Treatment with SRT1720, a potent SIRT1 agonist, significantly attenuated Aβ-induced up regulation of Interleukin (IL)-6, IL-8, and matrix metalloproteinase-9 (MMP-9), whereas the inhibitory effects of SRT1720 on Aβ-induced up regulation of IL-6, IL-8, and MMP-9 were attenuated in the cells in which SIRT1 expression was knocked down [18]. In addition, pretreatment with SRT1720 inhibited the deleterious effects of Aβ on morphology and barrier function of RPE mono layers. Knockdown of SIRT1 significantly abolished the protective effect of SRT1720 on Aβ-induced barrier disruption [18]. The nuclear factor-kappa B (NF-κB) has been recognized as a key inflammation switch. SIRT1 inhibits NF-κB activation and in contrast, NF-κB signaling and inflammatory response can suppress the SIRT1 activity [19]. SIRT1 activation attenuated Aβ-induced inflammation by suppressing NF-κB activation, the transcription of which regulates expression of IL-6, IL-8, and MMP-9. These results demonstrated that Aβ-induced inflammation and RPE barrier disruption are regulated by the SIRT1/NF-κB pathway [18]

CNV causes more serious and rapid vision loss than other forms of AMD. Previous studies described the key role of SIRT1 as a critical regulator of angiogenesis [20,21]. The expression of SIRT1 is more frequent in human CNV membranes than non-AMD donor eyes [22]. Another study demonstrated that hypoxia initiates SIRT1 and augments HIF-2α, which in turn activates and releases VEGF [23]. Inhibiting the activity of SIRT1 properly is a promising method to cure retinal neovascular diseases. Interestingly, other reports showed different results, in vitro study, treatment ARPE-19 cells with SIRT1 inhibitor (nicotinamide) lead to decreased secretion of certain proangiogenic factors, such as VEGF-A, platelet-derived growth factor BB and angiogenin [22]. Further, resveratrol suppressed VEGF secretion induced by inflammatory cytokine (IFN-ɣ, TNF-a, IL-1β), TGF-β and hypoxia without influencing anti-angiogenic endostatin and PEDF secretion [24]. Another experiment revealed that SIRT1 pathway is involved in the mechanism of resveratrol inhibiting hypoxic-induced choroidal vascular endothelial cell proliferation through down-regulating the levels of HIF-1a, thus inhibiting VEGF secretion [25] as well as promoting apoptosis through the SAPK/JNK pathway. Khan A. et al. demonstrated that resveratrol can inhibit pathological angiogenesis both within and outside the eye in vivo and in vitro by a SIRT1-independent pathway [26]. The discrepancy of the effects of SIRT1 on angiogenesis may be due to the different activators or inhibitors used in different experiments and the other conditions used in the different experiments. Further studies should be performed to identify the accurate effect of SIRT1 on CNV formation.

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Taken together, SIRT1 may be important for maintaining RPE cell function and protecting them from apoptosis induced by oxidative stress or chronic inflammation damage. However, there are still some controversies regarding, the function of SIRT1 in the pathogenesis of AMD, for example, is SIRT1 an angiogenesis inducer or inhibitor in neovascularization in CNV and is the SIRT1 activators suitable for the application in the treatment of human AMD? Further research is needed for clarifying these questions.

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