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Editorial

SIRT1 and Retinal Neovascular Diseases

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Editorial

There are two major retinal diseases, such as Diabetic Retinopathy (DR) and Oxygen-Induced Retinopathy (OIR), are associated with retinal neovascularization. The pathogenesis of DR and OIR is still under-investigation. SIRT1, a class III histone deacetylase, regulates development, cellular senescence, stress response, aging, inflammatory, tumor genesis and angiogenesis. Accumulating evidence shows that SIRT1 also play an important role in the pathogenesis of retinal neovascularization, activation of SIRT1 may be one of therapeutically approach for the treatment of DR and OIR.

SIRT1 and diabetic retinopathy

DR is one of the major microvascular complications of diabetes mellitus. Despite extensive research in the field, the exact mechanism of the pathogenesis of DR remains ambiguous. Biason-Lauber, et al. has identified a SIRT1 mutation in patients with type 1 diabetes [1]. SIRT1 was also demonstrated to be involved in the mechanisms of type 2 diabetes and manipulation of SIRT1 is suggested as a promising therapeutic target [2]. Retinal SIRT1 mRNA expressions were reduced in the type 1 and 2 diabetic mice models [3]. In the retinal endothelial cells, SIRT1 gene and protein expressions were also decreased when exposed to high glucose. This was accompanied by significant increased acetylation of NF-κB p65, the binding of p65 at MMP-9 promoter and the activity of MMP-9 [4]. Supplementation of high glucose with resveratrol ameliorated inhibition of SIRT1 activity and prevented increase in the acetylation of p65, binding of p65 with MMP-9 promoter and activation of MMP-9. Consistent with these, the same results were obtained from diabetic mice retina and donors with DR, confirming a role of SIRT1 in p65 acetylation and activation of MMP-9 in DR [4]. In the other study in the STZ-induced DR mice models, retinal SIRT1 activity was significantly lower, together with increased Phosphorylated-NF-κB and decreased phosphorylated-AMPK [5]. Systemic administration of resveratrol or AICAR (AMPK activator) to the diabetic animals led to significant increase in SIRT1 and AMPK activity [5]. Moreover, treatment with resveratrol suppressed leukocyte adhesion to the retinal vasculature and inhibited diabetes-induced expression of ICAM-1 and VEGF, both of which are known as pro-inflammatory and pro-angiogenic molecules responsible for the pathogenesis of DR [5]. Recent study showed that miR-195 upregulation was associated with SIRT1 mRNA downregulation and also reduced SIRT1 protein and enzyme level in the retina in diabetic rats [6]. Intravitreal injection of miR-195 antagomir normalised diabetes-induced SIRT1 reduction in the retinas of the rats. In addition, they measured antioxidant level in the retinas and found that diabetes-induced reduction of MnSOD levels were ameliorated by miR-195 antagomir injection [6]. These studies suggest that reduced SIRT1 expression mediated tissue damage in DR is modulated by specific miRNA.

SIRT1 and oxygen-induced retinopathy

In Oxygen-Induced Retinopathy (OIR) mice model mimicking some aspects of neovascularization of proliferative DR and Retinopathy of Prematurity (ROP), ischemic/nutrient deprived-induced upregulation of SIRT1 in retinal neurons from the avascular region may influence physiologic revascularization of ischemic areas via modulation of HIF signaling and secretion of pro-angiogenic and neuro-protective factors, such as VEGF and EPO, as well as through an altered inflammatory response and expression of anti-angiogenic factors [7]. This physiologic revascularization process is essential to repair vaso-obliterated retina and restore normal vessels. However, high levels of VEGF and EPO directly contribute to the proliferative stage of retinopathy. Disruption of SIRT1 may therefore dampen physiologic vascular regeneration and result in subsequent hypoxia-induced pathologic neovascularization [7]. However, the negative correlation of SIRT1 with some of pathological condition is also reported, a genetically overexpression of SIRT1 in either neurons or vessels within the mouse retina does not influence vaso-obliteration, pathologic neovascularization, or retinal neuron degeneration in OIR [8]. Furthermore, oral administration of SIRT1 activator, resveratrol or SRT1720, does not protect against vascular pathologies in OIR at the administrated dose [8].

Although the relevance of SIRT1 to the pathogenesis of DR and IOR is revealed, further investigation is needed to clarify the details of the role of SIRT1 in the regulation of the complex eye diseases and possible intervention of the disease process.

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