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Opinion

Diabetic Retinopathy: Targeting BIGH3 to Develop Novel Molecular Therapies

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Abstract

Diabetic retinopathy (DR) is a complication of diabetes due to damage of blood vessels in the retina. Aside from being a major cause of blindness in the world, DR also has a significant impact on quality of life. Although there are methods to delay the progression of DR, there are no existing therapeutic regimens for early intervention. Thus, it is critical to develop cost-effective therapies towards preventing DR development.

Keywords: Diabetic retinopathy; Vision

Abbreviations: DR: Diabetic retinopathy; HRP: Human retinal pericytes; TGFβ: Transforming Growth Factor Beta; BIGH3: TGFβ-induced Gene Human Clone 3

Opinion

The worldwide prevalence of diabetes is reported as 463 million (substantially exceeding the US population) and it is projected to rise to 700 million by 2045 [1]. Specifically, in the United States, 1 in 5 diabetics remain undiagnosed, which can only increase the current estimate on number of cases and also the scope to its management [2]. It has been well established that a longstanding history of uncontrolled diabetes can lead to multi-organ dysfunction, such as nephropathy, peripheral vascular disease, and diabetic retinopathy (DR).

DR is a microvascular complication and a major cause of blindness in the world. The rapid formation of new blood vessels in the retina will lead to induce microaneurysms and a loss of vasculature integrity. DR not only affects the eye, but also has a detrimental impact on a person's quality of life. A cross-sectional, population-based study assessed the health-related quality of life and the impact of DR in 1,064 participants. The visual impairment related to DR was found to have a profound effect on social factors, such as mobility, independence, and mental health [3]. This study suggests that people with diabetes, who receive proper management of their disease, are living healthier and happier lives.

When it comes to preventing diabetes-related complications, patients are generally advised to have good control over one's blood sugar levels and blood pressure from an early standpoint. Making lifestyle modifications can delay the onset of DR, however, since this complication is initially asymptomatic, it's difficult to make an early prognosis. It is not until the later stages of DR that symptoms begin to manifest with various visual disturbances. Current treatments are focused to preserve vision with the use of vascular endothelial growth factor inhibitors to attenuate growth of new blood vessels or laser photocoagulation to seal leaking blood vessels in the retina.

However, these treatments often impose a financial burden on patients, given the need for frequent administration. This suggests a need for cost-effective therapeutic approaches aimed toward preventing DR, while encouraging continuity of care. A novel molecular pathway on the pathogenesis of DR may serve to identify potential therapeutic targets for early intervention.

One of the hallmarks of early DR is the loss of human retinal pericytes (HRP) through apoptosis. However, the exact mechanisms that promote pericyte dropout are unknown. Pericytes are contractile cells that envelop the endothelial cells of capillaries. They help maintain adequate blood flow, as well as the integrity of the blood-brain barrier [4,5]. There are several proposed signaling pathways on the pathogenesis of DR. One of them involve the inflammatory response to diabetes in which HRP apoptosis is caused by TGFβ secreted by macrophages of the immune system when they enter the retina. TGFβ results in an increase of TGFβ-

induced Gene Human Clone 3 (BIGH3) that binds to integrin receptors in HRP, leading to apoptosis [6].

BIGH3 is an extracellular pro-apoptotic protein that accumulates in the retinal vessels. BIGH3 mediates cellular adhesion, proliferation, and apoptosis through an autocrine signalling mechanism by interacting with HRP integrin receptors [7,8]. Previous studies have demonstrated that treatment of increased concentrations of TGFβ causes a rise in BIGH3 synthesis in mammalian pericytes and endothelial cells, followed by apoptosis [9,10]. This suggests BIGH3-mediated apoptosis in HRP may contribute to the progression of DR.

Although there is supporting evidence of an association between BIGH3 and DR, the complete molecular pathway of BIGH3-mediated apoptosis in HRP warrants further investigation. As HRP are vital to maintaining retinal vasculature, it is critical to find an innovative molecular pathway and therapy targets to inhibit the BIGH3-bound integrin. Overall, a molecular therapy from this pathway may not only prevent DR, but also improve the patients' quality of life.

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Conflict of Interest

Authors declare no conflicts of interest.

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