Editorial

Retinal glia and NF-κB in diabetic retinopathy pathogenesis

Susanna S. Park^

Department of Ophthalmology & Vision Science, University of California Davis Eye Center, Sacramento, CA, USA

Correspondence to: Susanna S. Park, MD, PhD. Department of Ophthalmology & Vision Science, University of California Davis Eye Center, Ernest E. Tschannen Eye Institute, 4860 Y St., Sacramento, CA 95817, USA. Email: sscpark@ucdavis.edu.

Comment on: Ding X, Sun Z, Guo Y, *et al.* Inhibition of NF-κB ameliorates aberrant retinal glia activation and inflammatory responses in streptozotocin-induced diabetic rats. Ann Transl Med 2023;11:197.

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Diabetic retinopathy (DR) is a leading cause of irreversible blindness in adults (1-3). Treatments available to limit vision loss from complications of DR include intravitreal injection of drugs that inhibit vascular endothelial growth factor (VEGF) or inflammation, surgery and retinal laser photocoagulation (3). Despite these interventions, blindness from DR persists since the retinal vasculopathy and neuronal degeneration cannot be reversed.

Extensive research has been conducted to decipher the molecular pathways involved in the development of DR in the hopes of finding a cure. Oxidative stress and inflammation are important pathways activated in DR (3). Recent studies indicate that neurodegeneration of retinal ganglion cells and glial cell activation occur before development of retinal vasculopathy and are important early steps involved in the pathogenesis of DR (4). Glial cell activation triggers inflammation and oxidative stress, which in turn worsens DR.

In the publication by Ding *et al.*, retinal glia was targeted to limit retinal neuronal degeneration from DR (5). Muller cells are the principal retinal glial cells that stretch across the thickness of the retina and provide homeostatic and metabolic support to neurons by mediating transcellular ion, water and bicarbonate transport (6). They are components of the neurovascular unit in the retina, regulating the blood-retinal barrier and synaptic activity of retinal neurons. Microglia are resident immune cells contributing to immune surveillance. Microglia, activated by retinal injury, produce proinflammatory mediators and kill degenerating retinal neurons (7). Targeting the retinal glia to limit retinal damage from DR is a novel, logical approach.

Ding *et al.* used a rat model of DR to study the effect of inhibition of nuclear factor-κB (NF-κB) activation via systemic administration of IMD-0354 (5) since NF-κB is a transcription factor that regulates the activation of microglia and Muller cells (8). In addition, *in vitro* studies were conducted using cultured retinal glial cells to evaluate the effects of IMD-0354. The authors found that the increase in nuclear NF-κB-p65 associated with DR was reduced by IMD-0354 administration. IMD-0354 also inhibited microglia and Muller cell activation and oxidative damage and apoptosis of the retinal neurons associated with DR. Decreased retinal production of VEGF and inflammatory cytokines was also observed. *In vitro* studies similarly showed that IMD-0354 inhibited the molecular changes associated with high glucose in cultured Muller cells and microglia.

The study findings are compelling although many questions remain unanswered. What are long-term effects of inhibiting NF-κB activation on retinal function and development of DR? Since NF-κB is ubiquitously expressed, is systemic inhibition of this factor well tolerated? Since the pathogenesis of DR is complex, further investigation is needed regarding the role of NF-κB and glia in the development of DR.

^ ORCID: 0000-0001-5911-6671.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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