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JOBDI special edition—introduction

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It gives me great pleasure to introduce this special edition of the journal JOBDI, focusing on current experimental approaches investigating the mechanisms of diabetic retinopathy. Just as with any other subject of active scientific enquiry, there exist many reviews and books illustrating the state of the art and current thinking in the field. But it is always difficult, if not impossible, to create such publications in a way as to be entirely comprehensive. This is certainly true of the investigative field of diabetic retinopathy, which is often discussed as having a plethora of theories and approaches that can seem confusing and controversial to the novice and the experienced investigator alike.

Here we have made no attempt to be entirely comprehensive or to focus on one specific theory. Current theories involve glucose-induced free radical formation, oxidative stress, inflammation, activation by advanced glycosylation end products, neurodegeneration, vascular cell apoptosis, and protein kinase activation and offer many possible explanations for the disease. In time these phenomena may become part of a unified, although probably complex, mechanism.

It was rewarding to find that nearly every investigator invited to submit an article actually did so. The authors of the papers in this special edition are established experts in a variety of diverse areas of diabetic retinopathy research, representing a broad range of different hypotheses. They represent a sample of some of the less well-explored, but no less valid, approaches as well as the more established theories.

Our special edition begins with primary data from Dr. Renu Kowluru and colleagues. Dr. Kowluru, more than any other investigator, has contributed to the hypothesis that diabetes increases oxidative stress in the vascular cells of the retina. In her paper, Dr. Kowluru employs an IL-1β receptor knockout mouse to show that inflammation of the retina in diabetes requires the IL-1β receptor, and in its absence, there is a reduction in vascular cell apoptosis, which also appears to be induced through a mitochondria-regulated pathway.

We follow with a review from Drs. Stitt and Curtis, showing how part of the inflammatory signaling pathway includes, or may be triggered by, the formation of advanced glycation end products. Dr. Greg Liou et al. also focus on retinal inflammation, offering the hypothesis that vascular and neural dysfunction are due to cytokines released from microglia, and that signaling through the adenosine receptor has anti-inflammatory properties.

A review by Dr. Steven Abcouwer focuses on the role that retinal microglia plays in inflammation due to diabetic retinopathy and contemplates what function these little understood cells may have in disease. It is still unclear if activation of microglia should be considered compensatory or if their chronic activation may be detrimental to the long-term survival of retinal tissue.

Drs. Prathiba Jayaguru and Susanne Mohr also focus on glial cells, in this case the Müller glia. They review evidence that apoptosis of Müller glia in the retina is regulated by nuclear translocation of glyceraldehyde-3-phosphate dehydrogenase, an unusual function that may occur in response to inflammatory signals.

A primary data paper from the electrophysiology group headed by Dr. Algis Vingrys establishes that the slow P3 contribution to the electrophysiological response (ERG) wave is derived from Müller glial cells. Furthermore, there is a striking reduction in amplitude of the scotopic threshold response in 1-month streptozotocin diabetic rats. The scotopic threshold response (STR) can only be measured by stimulating

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the retinas of dark adapted animals (and humans) using very low-energy light flashes. The STR is considered to be derived primarily from the retinal ganglion cells and, to a lesser extent, the amacrine cells of the inner retina. The 32.7 % reduction in this response indicates malfunction of the inner retinal neurons, especially retinal ganglion cells.

Dr. Sarah Zhang and colleagues present a review of new evidence that the retinal ER stress response is invoked by diabetes. It becomes apparent that the ER stress may occur in response to inflammatory signaling, but again, it is unclear whether or not this is a compensatory mechanism or contributes to the pathology of the disease.

Drs. Heise and Fort offer a comprehensive review of recent evidence on the expression of crystallins and heat shock proteins in ocular tissues during development and various diseases. Ultimately the review focuses on the effects of diabetes on crystallin expression in the retina, which again may be interpreted as another protective or compensatory mechanism in diabetic retinopathy.

Unique work by Dr. William Eldred and colleagues shows evidence that the peptide adrenomedullin increases the neuronal nitric oxide signaling pathway in the retina and that this stimulus is elevated by diabetes. They show that inhibiting this adrenomedullin/nNOS pathway can alleviate some of the effects of diabetes on the ERG and suggest that a potential mechanism of action of ruboxistaurin is to inhibit the adrenomedullin/nNOS pathway in the retina.

Finally, a paper by Yun-Zheng Li and collaborators reviews the evidence that the permeability barrier of the retinal pigment epithelial layer becomes compromised in diabetic animal models in a similar fashion to the retinal vasculature. This study further emphasizes the complexity of diabetic retinopathy and the need to contemplate the effect of diabetes on all the different cellular components of the retina.

Collating these papers and reviews has been a fascinating task. They illustrate the diversity of approaches to the field and emphasize that there are no simple answers to the puzzle of diabetic retinopathy. While we can claim progress in the field, we should also remind ourselves of the most important reason to perform this research. Diabetic retinopathy causes some form of visual impairment in at least 3.8 million American adults (Center for Disease Control statistics for 2009) and accounted for more than 5 % of the cases of blindness worldwide (World Health Organization statistics 2002). With the alarming increase in the incidence of diabetes in many countries, it is not surprising that the World Health Organization has named diabetic retinopathy as a "priority eye disease."