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Understanding diabetic retinopathy

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A recent survey shows that diabetes affect 92.4 million people in mainland China [1], among which 16.9 million have diabetic retinopathy (DR) [2]. DR is one of the major causes of blindness in the working age population in both developing and developed countries. Although the exact mechanism by which diabetes causes retinopathy remains elusive, several hypotheses have been postulated to explain pathogenies of the disease. Here we invited five groups of scientists and clinicians to share their recent discoveries and expert opinions in molecular biology, pathophysiology, genetics, and epigenetics of DR.

Retinal angiogenesis is a hallmark of ischemic retinopathy in DR. Exchange proteins directly activated by cAMP (Epacs, namely Epac1 and Epac2) are important cAMP mediators that play crucial roles in maintenance of endothelial barrier and neuronal functions. However, functional roles of *Epac1* and *Epac2* remain to be determined. By transient occlusion of middle cerebral artery on *Epac1*- and *Epac2*-deficient mice, Liu and colleagues [3] demonstrated that $Epac2^{-/-}$ ipsilateral retinas showed more neuronal cell loss in ganglion cell layer, increased retinal thickness and stronger immunostaining of AQP4, GFAP, and Prx6 than those of $Epac2^{+/+}$. Whereas $Epac1^{-/-}$ ipsilateral retinae displayed similar pathology as those in $Epac1^{+/+}$ mice. Together, they demonstrated that *Epac2*-deficiency led to more severe ischemic retinopathy after the injury. On the other hand, the apelin and apelin receptor (APJ) system is known to cause endothelium-dependent vasodilatation and to be involved in angiogenesis. Microglial cells are major components of the immune system in the retina. Diabetic injury triggers these cells to release inflammatory cytotoxins that lead to neuronal and vascular cell death and develop diabetic retinopathy. However, it remains to be demonstrated if the activation of the inflammatory cytokines could be stimulated by apelin. Chen and colleagues [4] demonstrated that inflammatory cytokines secretion can be regulated by apelin stimulation. DR has a complex pathology that involves the vasculature of the inner retina and breakdown of the blood-retinal barrier. Barber [5] provided extensive evidence that DR is not only a vascular disease but also has a neurodegenerative component and that essentially all types of cells in the retina are affected, leading to chronic loss of visual function. Barber summarized recent developments in research towards understanding the complexities of retinal neurodegeneration occurring in DR, with neuronal loss, edema, glial cell reactivity and oxidative stress often observed. Indeed, in agreement with Barber's postulation, Zhu and coworkers [6] provided clinical evidence that type 2 diabetic patients without clinical evidence of diabetic retinopathy showed significantly decreased superior macular ganglion cell complex thicknesses in diabetic cases but no significant peripapillary retinal nerve fiber layer thickness changes were observed. The contrast sensitivities at all space frequencies were significantly different between diabetic patients and controls. In the diabetic group, average superior ganglion cell complex thicknesses positively correlated with both contrast sensitivities at high spatial frequencies and P50 amplitudes. These results suggest that ganglion cell complex thickness and visual function changes could be observed in diabetic subjects before the onset of any significant diabetic retinopathy. Despite cutting edge research in the field, how retina and its vasculature are damaged by the diabetic milieu remains to be explored.

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Kowluru and Mishra [7] suggested that the environmental factors, life style or disease process can also bring in modifications in the DNA, and these epigenetic modifications either silence or activate a gene without altering the DNA sequence. They discussed that diabetic environment regulates a number of genes in the retina, and a large body of evidence has shown that it also facilitates epigenetic modifications. Together, with epigenetic modifications taking an important place in diabetic retinopathy, they emphasize that it is now critical to investigate these epigenetic modifications, and understand their impact on this slowly progressed retinal disease.

Together, these results of laboratory and clinical investigations and expert opinions help us to better understand pathogenesis of DR.

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Biographical Sketch

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