Neurodegeneration in Diabetic Retinopathy: Current Concepts and Therapeutic Implications

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The prevalence of diabetes mellitus (DM) has increased significantly in recent decades in China. Recently, it has been reported that the estimated prevalence of DM among a representative sample of Chinese adults was 11.6% and the prevalence of prediabetes was 50.1%.[1] Furthermore, the awareness, treatment, and control rates of DM in the general Chinese population are disproportionately low, raising concerns for future high rates of diabetes-related morbidity and mortality.

Diabetic retinopathy (DR), a specific microvascular complication of DM, remains the leading cause of acquired vision loss worldwide in middle-aged and therefore economically active people.[2] With the increasing number of people with DM, the number of DR and vision-threatening DR, which includes severe non-proliferative DR (PDR), PDR, and diabetic macular edema (DME), has been estimated to rise to 191.0 million and 56.3 million, respectively, by 2030.[3]

Treatment of the classic risk factors (i.e., hyperglycemia and hypertension) is currently recommended for preventing or arresting the development of DR.[4] Intensive insulin therapy also has been found to lessen the progress of DR to some extent, while it has also been implicated to be responsible for decrease of DR.[5]

However, we are normally doing nothing specifically addressed to the eye until very advanced stages when laser photocoagulation, intravitreal injections of corticosteroids or anti-vascular endothelial growth factor agents, and vitreoretinal surgery are implemented. A better understanding of the pathogenesis of DR would permit the development of novel and more efficient preventional/interventional strategies against DR.

Metabolic changes in the diabetic retina result in altered expression pattern of a number of mediators including growth factors, neurotrophic factors, cytokines/chemokines, vasoactive agents, and inflammatory and adhesion molecules, resulting in vascular lesions and cell death.[6-8] DR has been considered a microcirculatory disease of the retina. However, there is emerging evidence to suggest that retinal neurodegeneration is an early event in the pathogenesis of DR which could participate in the development of microvascular abnormalities.[9,10] Therefore, the study of the underlying mechanisms leading to neurodegeneration and the identification of the mediators in the cross talk between neurodegeneration and microangiopathy is essential for the development of new therapeutic strategies.

Neuronal integrity is essential for vision. In the early stages of DM, a routine clinical evaluation of a patient's sensory capacity will, in a high proportion of patients, reveal deficiencies that they are commonly unaware of in daily life. These deficits include decreased hue discrimination and contrast sensitivity, delayed dark adaptation, and abnormal visual fields.[11] Neural apoptosis and reactive gliosis, the hallmarks of retinal neurodegeneration, have already been observed in diabetic donors without microcirculatory abnormalities when compared with the retinas from nondiabetic patients matched by age.[12,13] These findings

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suggest that, at least in some patients, neurodegeneration antedates the microcirculatory abnormalities that occur in DR, and in some respects, the early stages of DR could be considered a neuropathy rather than simply a microangiopathy. This concept has informed our understanding not only in the pathogenesis of DR but also in the design of new therapeutic approaches. In addition, it has been recently demonstrated that in the early stages of DR, an imbalance between proapoptotic and survival signaling exists in the neuroretinas of diabetic patients.[14]

Retinal ganglion cells (RGCs), located in the inner retina, are the retinal neurons in which the apoptotic process related to DM is first detected.[15] This loss of neural cells results in a reduction in the thickness of the retinal nerve fiber layer detected in diabetic patients without or with only minimal DR by using scanning laser polarimetry or optical coherence tomography (OCT).[16-18] Glutamate accumulation in the extracellular space, oxidative stress, an imbalance in the retinal production of neuroprotective factors, and inflammation are the main factors involved in the development of neurodegeneration in the setting of DR.[19]

The retinal neurodegenerative process can be assessed *in vivo* by using electroretinography and, in particular, multifocal electroretinography (mfERG) which permits us to explore the retinal function in terms of electrical response in different areas of the retina. The most consistent and widely reported aspect of the ERG that changes early in DR using animal models and patients is the oscillatory potential implicit time which reflects electrophysiological communication between the amacrine cells and the bipolar cells with interactions from ganglion cells to amacrine cells.[20] Such early indicators reflect retinal neural dysfunction and perhaps progression to neurodegenerative pathology in the later stages of disease. As such, the ERG has an important clinical value in DR while ERG is a very sensitive but is also a quite cumbersome and time-consuming examination in which corneal electrodes are necessary. Fundus autofluorescence (FAF) might reflect the damage of the retina and has a relationship with visual function as well as photoreceptor integrity. The integrity of the inner segment–outer segment junction and the external limiting membrane was disrupted. FAF gives new insight into the evaluation of DME. Dynamic FAF monitoring helps to better evaluate the disease progression of DME as well as visual function.[21] The spectral domain OCT is another very useful tool which complements mfERG because it provides anatomical images and enables measurement of thickness of the different retinal layers. This is more rapid than mfERG, and the most useful parameter in identifying diabetes-induced retinal neurodegeneration is the reduction of the thickness of RGC layer and the fiber nerve layer. There is evidence that neurodegeneration measured by either mfERG or OCT is present in patients with normal fundoscopic examination.[9] The question is whether the neurodegenerative process can be considered a predictor of microvascular disease or even an active mediator of the microvascular impairment. The proof of concept in the clinical setting that neurodegeneration participates in microangiopathy is based on an observational study in which neurodegeneration assessed by mfERG predicts that retinal locations will develop new retinopathy in the near future (that means in a period between 1 and 3 years).[22] Therefore, neurodegeneration could be a useful index to predict the development of microvascular disease in diabetic retina.

Therefore, it is reasonable to propose therapeutic strategies based on neuroprotection as a new and targeted approach for treating the early stages of DR. It will be of particular interest to evaluate changes in the nerve fiber layer, ganglion cell density, photoreceptor abnormalities, retinal thickness, and the quantification of the extracellular space of the retina. In fact, based on these two examinations, it should be possible to identify a phenotype of diabetic patients in which neurodegeneration has a key role in the development of DR and, therefore, those patients in whom neuroprotection should be more effective.

In conclusion, the central role of neurodegeneration in the pathogenesis of DR is a solid base for proposing neuroprotection as an effective strategy for preventing or arresting DR. However, clinical trials to determine not only the effectiveness and safety but also the compliance of a noninvasive route to administer these drugs, as well as a standardization of the methods for monitoring neurodegeneration such as mfERG and frequency domain-OCT, are needed.

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Conflicts of interest
There are no conflicts of interest.

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