Molecular Mechanisms and Therapeutic Strategies for Retinal Degeneration

Retinal degeneration is characterized by the death of retinal neural cells, particularly the photoreceptors, and can be categorized into inherited disorders, such as retinitis pigmentosa (RP) and complex disorders, such as age-related macular degeneration (AMD), diabetic retinopathy and glaucoma. The inherited form is regarded as predominantly genetic inheritance and affects about 1 in 3000 people worldwide [1]. The complex form is closely associated with genetic and environmental factors. Neural cell death in retinal degeneration is a complex process that involves numerous factors and multiple signal pathways. Although the inherited and complex forms of retinal degeneration have their own distinctive features, they have some disease mechanisms in common, such as oxidative stress and inflammation. A significant understanding of disease mechanisms and new therapies has been developed in the last decade. This thematic issue aims to collect recent advances in the elucidation of mechanistic insights and the appraisal of new therapeutic strategies. We welcomed review articles concerning the molecular basis of retinal degeneration, gene and stem cell-associated therapies, and drug discovery.

Phosphodiesterase 6 (PDE6) is highly expressed in photoreceptors and plays a critical role in phototransduction. Mutations in PDE6 subunits cause RP, the most common form of inherited retinal degeneration [1]. A naturally occurring loss-of-function mutation in the Pde6b gene results in early retinal degeneration in rd1 mice. In this thematic issue, Zou et al. reported that PDE5 (encoded by Pde5a), a close member of PDE6, enhanced photoreceptor survival and facilitated rod outer segment formation [2]. The authors overexpressed mouse PDE5 in rd1 mouse retinas via neonatal electroporation. Rd1 mice with overexpression of PDE5 showed significantly increased thickness of the outer nuclear layer, compared to rd1 mice without PDE5 overexpression, suggesting PDE5 counteracted rod cell loss. Outer segments were present in PDE5-expressed rod cells, whereas outer segments in rod cells without PDE5 expression were barely developed. PDE5 also upregulated rhodopsin expression [2]. This study sheds new light on PDE-associated function in phototransduction and in the pathogenesis of RP.

Wu et al. contributed to this thematic issue by discussing the pathological mechanisms and therapeutic options in retinal degenerative diseases [3]. The authors review clinical phenotypes and genetic patterns of inherited retinal degeneration and discuss the underlying mechanisms. In particular, the authors review current gene therapy in inherited retinal disorders, including viral and nonviral gene delivery, and discuss stem cells' therapeutic potential in retinal disorders. In addition, the authors consider the association of gut microbiota with the pathogenesis of diabetic retinopathy and suggest that modulation of intestinal microbiota may be a therapeutic target for treating patients with this condition [3].

Cao et al. contributed to this issue by discussing the association of nutrients, dietary patterns and probiotics with AMD [4]. AMD is the most common cause of visual defects in the aged population, currently affecting over 196 million people globally [5]. There is no effective treatment for dry (geographic atrophy) AMD, which accounts for 90% of cases. The authors reviewed the effect of nutrients on AMD: clinical trials demonstrate that higher consumption of fish (higher intake of ω-3 fatty acids) is associated with decreased risk for AMD; antioxidative polyphenols, macular pigments and vitamins reduce the risk of development and progression of AMD. On the other hand, increased intake of carbohydrates is associated with a higher risk for AMD progression. The authors also discuss how special dietary patterns affect AMD: the Mediterranean diet shows protection against advanced AMD, whereas the Western diet is associated with advanced AMD in several cohort studies. Additionally, the authors review the association of gut dysbiosis with AMD. Obesity-related gut microbiota is linked to AMD pathology (e.g. retinal angiogenesis); a high-glucose diet also induces a wide range of AMD pathological features in mice. High-fat or high-glucose diet changes the composition and diversity of intestinal bacterial populations, affects liver metabolism and induces systemic inflammation [4]. These findings suggest the functional role of the ‘gut-liver-retina axis’ in the pathogenesis of AMD.

There are a great many studies related to retinal degeneration. This thematic issue represents a small collection of recent developments in molecular mechanisms and therapeutic strategies in retinal degeneration. We have set up a platform for Current Medicinal Chemistry readers to explore further in this field.
REFERENCES


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