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Review Article

Distinct Forms of Photoreceptor Cell Death in Retinitis Pigmentosa

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Abstract

Photoreceptor degeneration is the ultimate cause of vision loss in many retinal disorders, such as retinal heredo-dystrophies, age-related macular degeneration, diabetic retinopathy, and retinal detachment. Apoptosis due to both cysteine proteases and alternative pathways is the most elucidated form of programmed cell death. However, there are other forms of cell death, such as autophagy and necrosis, both regulated by a finely-tuned network of biochemical signaling.

Retinitis pigmentosa is a heterogeneous group of inherited retinal disorders in which abnormalities of the photoreceptors or the retinal pigment epithelium lead to progressive visual loss. Initially, affected people experience defective dark adaptation with constriction of the peripheral visual field and, eventually, loss of the central vision. In this brief review, we are going to outline distinct forms of photoreceptor death in retinitis pigmentosa.

Keywords: *Photoreceptor; Retinitis Pigmentosa; Apoptosis; Autophagy; Necrosis*

An Overview of Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a clinically and genetically group of inherited retinal disorders. It is characterized by alterations of photoreceptors (PRs) and retinal pigment epithelium (RPE) resulting in progressive retinal degeneration. In 1857 Donders first described such a similar tapeto-retinal disorder as "retinitis pigmentosa". Nowadays, it is known that the inflammation is not the main process in heredo-dystrophic retinal pathologies but the term "retinitis" is still accepted worldwide [1]. On the other hand, the word 'pigmentosa' is consistent with the ocular fundus including typical pigmentary alterations in the retinal periphery.

The prevalence of RP is variably reported as one case for each 3500-5000 individuals [2-7]. With a total of more than 200.000 affected American people [8] and approximately two millions of affected individuals worldwide [9]. The heterogeneous group of RP is referred to as a rare disease according to the medical literature and the European Commission on Public Health.

Within the eye presentation, there are two main groups: typical RP or rod-cone dystrophy (RCD) (approximately 80-90%), in which the most injured PRs are the rods, and atypical RP or cone-rod dystrophy (CRD) (approximately 10-20%), in which the cones are the primarily damaged PRs [1]. In the majority of affected individuals (about 85% of cases), the inherited retinal dystrophies are an isolated disorder referred to as non-syndromic RP. However, in some patients (about 15% of cases) PR disorders are the epiphenomenon of a multi-systemic specific syndrome (i.e. Usher syndrome, Bardet-Biedl syndrome) referred to as syndromic RP [1,10].

Typical RP primarily involves the PRs responsible for peripheral vision and night vision causing progressive dysfunction and loss of rods which leads to defective dark adaptation, night blindness, and reduction of visual field [10]. For these reasons, affected patients experience the following symptoms: nyctalopia, glare aversion, tunnel vision with constricted visual field, and variable worsening of visual

acuity. The fundus examination reveals typical clinical signs: 'bone-spicule' pigment deposits in the mid periphery along with RPE atrophy, attenuation of retinal vessels, variable pallor of the optic disc, and a relatively spared macula surrounded by a peri-macular ring of depigmentation [11]. In some young adults with RP other clinical features are found, such as posterior sub capsular cataract, cystoid macular edema with partial tractional component, and intra-retinal deep white dots secondary to RPE degeneration. Moreover, some pathologic elements might be detected in the vitreous, for instance free melanin pigment granules, uveal melanocytes and/or macrophage-like cells [12], which suggest involvement of the entire ocular posterior segment. The age of onset, rate of progression, and the severity of the disease are extremely variable not only depending on the genetic background but also on other (still unknown) influencing factors [13]. Symptoms may start in childhood as well as in adulthood, more often in early adulthood and occasionally in mid-adulthood. Even though the progression of the disease is unpredictable, severe visual impairment typically occurs by the age of about 40-50 years. This large phenotypic heterogeneity can be partially explained by the huge genetic heterogeneity [10].

The Role of Vascular Dysregulation

To date, significant efforts are ongoing to make to assess the correlation between genetic mutations and the clinical manifestations in RP. However, most of the mutations occur in genes coding for proteins involved in the cycle of vision at the level of either rods and cones or RPE [14]. In the course of the disease, the PRs move towards apoptosis [15], so that the outer nuclear layer of the retina flattens. The pigment deposits, described as bone-spicule pigmentation, result from both RPE degeneration and migration into the neural retina as a consequence of the PRs' death [16]. Much is now known about the molecular and biochemical mechanisms involved in the degeneration and death of PRs. Nevertheless, there is evidence that oxidative stress and related conditions play an important role in this group of inherited retinal dystrophies [17]. Recent studies have observed reduced blood flow in both ocular and peripheral zones in patients suffering from RP [14]. Disturbed auto regulation of ocular perfusion provokes an irregular blood flow, which means an unstable retinal blood supply and an attenuation of retinal vessels with reduced neurovascular coupling [18]. As a consequence, free radicals as well as oxidative stress increase. Therefore, quite a large number of RP patients show a high prevalence of a vascular dysregulation syndrome as a primary manifestation of ocular blood flow dysfunction [19, 20].

Molecular Pathways for Photoreceptor Cell Death

RPE and choroid provide metabolic support for the PRs. When physically detached from the underlying RPE, the PRs are substantially injured and gradually go into degeneration. Furthermore due to changes of RPE cells or abnormalities of choroidal vessels as occurs in most inherited retinal diseases (such as RP or age-related macular degeneration), PRs progressively die [21]. Causes and clinical findings differ from one disease to another, but the underlying biochemical mechanisms involved in the PRs' death largely share common molecular pathways [22-24]. Originally defined on the basis of the morphological appearance obtained in ultrastructural studies, cell death has been classified in three main forms: apoptosis, autophagy and necrosis [25,26]. The term "apoptosis" can be translated as "falling off" from the ancient Greek and morphological characteristics are as follows: condensation of the nucleus and cytoplasm, rounding-up of the cell, reduction of cellular volume, and engulfment by resident phagocyte [27]. Biochemical evidence has highlighted the importance not only of caspase-dependent pathways [28,29] but also of caspase-independent pathways (apoptosis-inducing factor -AIF-, endonuclease G, cathepsins, calpains, polyADPribose polymerases-PARP). Apoptosis is a relatively slow process, requiring approximately from 6 to 18 hours [22,30]. Autophagy, meaning "self-eating", is the process by which cellular macromolecules (proteins, lipids and nucleic acids) and organelles (mitochondria) are digested by lysosomes [31, 32]. Transmission electron microscopy shows the formation of large inclusions (autophagosomes and autolysosomes) in the cytoplasm with lack of condensation and fragmentation of cells [27]. Necrosis, from the Greek term meaning "dead", is a biochemical process mediated by the activation of receptor-interacting protein 1 and 3 (RIP1 and RIP3) [33-35]. Indeed, recent studies revealed the importance of the "RIP kinase-dependent necrosis" in photoreceptor degeneration [36,37]. Ultrastructural studies have observed the following morphological changes in cells going to necrosis: swelling of the cytoplasm and organelles, a gain in cell volume, plasma membrane rupture, and connections with the extracellular cavity [27]. Necrosis is typically a rapid process which requires a few hours to be completed and involves the activation of the immune system which increases localized inflammation [22].

In different models of RP (naturally occurring or genetically manipulated), Chang and co-workers demonstrated that rods might undergo apoptosis when there are mutations in phosphodiesterase 6beta, peripherin, and rhodopsin [38]. Several subsequent studies investigated the role of caspase activation in PR death but results are conflicting [39-43]. Caspases are initially produced as catalytically inactive zymogens which are subsequently activated by proteolytic cleavage or allosteric conformational changes. Also, excessive exposure to light induces apoptosis in PRs because of overactivation of the phototransduction pathway and accumulation of 11-cis retinal, the chromophore of rod and cone opsins [44,45]. In addition to the caspase-dependent pathway, there is a caspase-independent pathway inducing apoptosis primarily by the activity of AIF [46], a flavoprotein located in the mitochondrial intermembrane space and involved in the respiratory chain and oxidative phosphorylation [47,48]. In models of RP, nuclear translocation of AIF following an increased activity of calpain and PARP has been observed in dying PRs [49,50]. In RP night vision loss is typically one of the initial symptoms due to rod dysfunction and death. Later even central vision drops due to cone degeneration and death. As Chang has observed, rod cell death occurs through apoptosis [51]. Conversely, cone cell death is mostly due to necrosis mediated by the RIP kinase pathway [52]. There are two members in the RIP kinase family, RIP1 and RIP3. They both are crucial mediators of necrosis [53] and they interact forming the "necrosome", a necrosis-inducing protein complex [54,55].

Conclusions

Recent studies have highlighted apoptosis as one of the primary actors in the pathogenesis and the development of the degeneration of PRs. Despite several pharmacological attempts aimed to slow, inhibit or block apoptosis, thus little has been achieved. Furthermore, novel investigations of the degeneration of PRs have demonstrated that even other patterns of cell death, such as autophagy and necrosis, are finely regulated active processes. The crosstalk among different pathways of cell death involves redundant mechanisms. The biochemical signaling between the PRs and the environment allows for the predominance of a certain form of cell death in a specific situation. For instance, starving PRs activate autophagy whereas caspases and RIP kinase trigger apoptosis. There is also RIP kinase-independent mechanisms to provoke necrosis of which little is known.

Further studies to better understand complex mechanisms underlying the PRs' death are needed to discover and develop novel treatments for protecting PRs from degeneration. The chance to apply regenerative therapeutic strategies to blinding disease is an ongoing goal of the scientific community. In the future, manipulations of endogenous stem cells (which should not stimulate an immune response with inflammatory cell infiltration) along with their deployment as therapy may represent a viable method to repair one or more types of photoreceptor degeneration.

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Competing Interests

The authors declare that there are no conflicts of interest.

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