Apoptosis and Other Cell Death Mechanisms after Retinal Detachment: Implications for Photoreceptor Rescue

Amy C.Y. Lo^{a, b} Tiffany T.Y. Woo^a Raymond L.M. Wong^{a, b} David Wong^{a, b}

^aEye Institute and ^bResearch Centre of Heart, Brain, Hormone and Healthy Ageing, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, SAR, China

Key Words

Programmed cell death • Caspase • Mitochondria • Necrosis • Neuroprotection

Abstract

Retinal detachment (RD) is one of the most common causes of blindness. This separation of the neurosensory retina from its underlying retinal pigment epithelium results in photoreceptor loss, which is the basis of permanent visual impairment. This review explores the various cell death mechanisms in photoreceptor death associated with RD. One of the major mechanisms is apoptosis, mediated by the intrinsic pathway, the Fas signalling pathway and/or the caspase-independent pathway. Other pathways of mechanisms include endoplasmic reticulum stress-mediated cell death, programmed necrosis and cytokine-related pathways. Understanding the mechanism of RD-associated photoreceptor death is likely to help us improve the current therapies or devise new strategies for this sight-threatening condition.

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Photoreceptor Apoptosis

Photoreceptor apoptosis forms an essential part of normal visual development, with evidence suggesting a critical period of development in which photoreceptors

are produced in excess and then culled to an appropriate level for adult usage [1]. These intrinsic programmes were argued to carry evolutionary advantages, in part contributing to the specificity of the adult neural circuitry [2].

Dysregulation of programmed cell death, however, has been held culprit in the pathogenesis of inborn errors, carcinogenesis and autoimmune diseases among many others. Multiple lines of evidence have shown that apoptosis is a major cause of neuronal loss after trauma, ischaemia and neurodegeneration in the central nervous system [3, 4]. Likewise, apoptosis is a major cause of photoreceptor degeneration and neuronal loss in diverse degenerative retinal diseases [5–11] as well as various retinal pathologies including retinal ischaemia/reperfusion injury [12–14], light-induced damage [15] and following retinal detachment (RD) [16–22].

Retinal Detachment

RD is one of the commonest sight-threatening eye diseases. It also occurs in a variety of retinal disorders such as age-related macular degeneration, diabetic retinopathy and retinopathy of prematurity. In RD, the outer retina (including the photoreceptors) is separated from the underlying retinal pigment epithelium, which provides the major metabolic and nutritional support for the pho-

toreceptors, leading to photoreceptor death and permanent visual loss. There are three main types of RD, including rhegmatogenous, tractional and exudative RD. Of these, rhegmatogenous RD is the commonest cause, affecting 6.3–17.9 per 100,000 persons per year [23]. The pathogenesis of rhegmatogenous RD involves the passage of liquefied vitreous under the neurosensory retina through a retinal break, which in turn separates the neurosensory retina from the underlying retinal pigment epithelium. Tractional RD is caused by proliferative retinopathy such as proliferative diabetic retinopathy; it can also be the consequence of penetrating trauma of the posterior segment. The resulting proliferative membranes of this condition contract and pull the neurosensory retina away from the underlying retinal pigment epithelium, causing a detachment. Exudative RD, on the other hand, is characterised by the accumulation of fluid in the subretinal space secondary to retinal or choroidal vascular, inflammatory or malignant diseases. RD of the exudative type is usually less extensive than the other two types.

Management of RD depends on the type and aetiology of the detachment. Standard methods of treatment include laser photocoagulation, pneumatic retinopexy, scleral buckling and primary vitrectomy. The treatment for rhegmatogenous RD would be surgery aiming to locate all retinal breaks, close the breaks by creating chorioretinal irritation around each break and eliminate the traction that caused the breaks. Most clinical trials have shown that there is no significant difference between the outcomes of different surgical options (pneumatic retinopexy, scleral buckling and primary vitrectomy) for rhegmatogenous RD, though some may show a preference towards primary vitrectomy [24–29]. Prognoses of tractional and exudative RD depend on the aetiology and extent of the underlying condition.

To date, there are no effective treatments for RD-induced permanent loss of vision. Although surgery can reattach the retina and the surgical outcome is greatly improved and associated with less complications [30], visual acuity is not always restored due to photoreceptor apoptosis that continues after RD. Some patients experience visual impairment despite successful surgical reattachment. Therefore, identification of the mechanisms that underlie photoreceptor death after RD is crucial to developing new treatment strategies for retinal disease in which RD is a clinical feature.

Apoptosis

Apoptosis is a highly complex process regulated by a wide range of cell signals and eventually leading to DNA fragmentation and cell demolition. Much insight has been gained in recent years concerning the signalling pathways and proteins involved, but current models tend to attribute effects to the few known complexes, and many key signalling players remain to be elucidated [31].

Two major signalling cascades have been identified, namely the extrinsic and intrinsic pathways [32]. Both centrally involve the caspase family of proteins as initiators and effectors of apoptosis propagation [33]. Initiator caspases are, by definition, the first to be activated in the apoptotic pathway in context. They in turn activate effector caspases, which trigger a series of proteolytic events that eventually lead to cell death [34].

The Extrinsic Pathway

The extrinsic pathway is initiated when certain death receptors (DR) on the cell surface are activated by death ligands (DL). DR mainly comprise the tumour necrosis factor (TNF) receptor family including FAS, TNFR1 and TRAIL (TNF-related apoptosis-inducing ligand) receptor (activated by their respective DL such as FAS ligand, TNF and TRAIL) [35]. Binding of a DL to a DR results in death-inducing signalling complex formation [36], which brings together the initiator caspases of the extrinsic pathway, i.e. procaspase-8 and procaspase-10 [37]. Cleavage of procaspase-8 releases caspase-8 into the cytosol to act on effector caspases.

The Intrinsic Pathway

The intrinsic pathway is triggered by a variety of factors including genotoxic stress, UV irradiation, certain hormones (e.g. glucocorticoids) and cytokine deprivation [37]. Exposure to these factors leads to mitochondrial outer membrane permeabilisation (MOMP) and eventually cytochrome c release from the mitochondria into the cytosol [38]. The release of cytochrome c from the mitochondria is also regulated by proteins of the B-cell lymphoma 2 (Bcl-2) family. The Bcl-2 family is divided into two classes of molecules that have opposing effects: anti-apoptotic members such as Bcl-2 and Bcl-xL that protect the cell against apoptosis, and proapoptotic members such as Bcl-2-associated X protein (Bax) and Bcl-2 homologous antagonist/killer (Bak) that trigger apoptosis.

The apoptosome formed between released cytochrome c, apoptosis-activating factor 1 and caspase-9 recruits and activates the initiator caspase of the intrinsic path-

way, procaspase-9. Cleavage of procaspase-9 liberates caspase-9, which in turn activates downstream effector caspases [39].

The Final Common Pathway

A final common pathway for both intrinsic and extrinsic cascades involves activation of the effector caspases (caspase-3, caspase-6 and caspase-7) by caspase-8 in the extrinsic pathway or caspase-9 in the intrinsic pathway. This then triggers cleavage of cellular proteins, nuclear shrinkage and DNA fragmentation [37].

RD-Associated Photoreceptor Apoptosis

Much progress has been made in our understanding of apoptosis and photoreceptor death. Photoreceptor apoptosis after RD was first described in humans after traumatic RD [16] and in cats after experimental RD [17]. Since then, photoreceptor apoptosis associated with RD has been extensively studied in a variety of experimental model systems [40–42] such as cats, rabbits, rodents, ground squirrels [43] and primates [44, 45]. Photoreceptor apoptosis has been correlated with retinal functional changes, and inhibition of apoptosis could limit the retinal functional loss [46].

Cellular Changes after RD

Histopathological changes following RD have been well documented in animal models [40–42, 47, 48] and human patients [48, 49]. During apoptosis after RD, photoreceptors initially develop the characteristic morphological features of apoptosis, followed by a clearance process where apoptotic bodies are engulfed and digested by phagocytes [50]. The chain of molecular and cellular processes that happens in the retina after RD is strictly regulated and related to the signalling cascades that have been identified.

Mitochondria and Intrinsic Pathway

When proapoptotic Bax and/or Bak are activated, MOMP is triggered and leads to the release of cytochrome c and hence apoptosis. In fact, increased expression of Bax has most often been implicated as a cause of cell death [51, 52], and the overexpression of Bax generally induces apoptosis. Similarly, overexpression of Bax leads to extensive rod photoreceptor death in the eye [53]. In contrast, the genetic deletion of Bax in Bax-deficient mice abolished cell loss after RD, suggesting a critical role of the Bax-mediated apoptotic pathway in RD-associated

photoreceptor death. Further evidence pointing to the involvement of the intrinsic pathway came from studies on caspases. Time-dependent activation of caspases-3, -7 and -9 was first shown in experimentally detached retina [19], indicating the involvement of caspases in photoreceptor death after RD. Yet, inhibition of caspases by the wide-range caspase inhibitor Z-VAD-fmk fails to block photoreceptor apoptosis [54], suggesting an involvement of other caspase-independent pathways.

Fas Signalling Pathway

The receptor-mediated extrinsic pathway also contributes to RD-associated photoreceptor apoptosis. Experimental RD resulted in activation of both the Fas proapoptotic pathway and the intrinsic pathway [20]. Injection of anti-FAS receptor antibody reduced caspase-9 activity [20] as well as the number of TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling)-positive photoreceptors, and preserved the outer nuclear layer (ONL) [21]. These results point to a beneficial effect of Fas signalling pathway inhibition in photoreceptor preservation after RD.

Caspase-Independent Pathway

It is evident that a caspase-independent pathway exists in apoptosis. MOMP causes cell death even if caspases are inhibited [55], and a wide-range caspase inhibitor, Z-VAD-fmk, fails to block photoreceptor apoptosis [54]. These findings that photoreceptor apoptosis still develops when the downstream caspases are inhibited suggest a mitochondria-mediated but caspase-independent pathway for photoreceptor apoptosis. Previous research showed that apoptosis-inducing factor (AIF) is a caspase-independent apoptotic factor. AIF is normally confined to the mitochondrial intermembrane space [56]. During apoptosis, AIF translocates to the cytosol and then to the nucleus, triggering peripheral chromatin condensation and, later, large-scale DNA degradation [56]. The mitochondrionuclear translocation of AIF was also observed after RD in experimental rats [54] and mice [22] as well as in human retinae [22], providing strong evidence of AIF contribution to RD-associated photoreceptor apoptosis.

Other Pathways of RD-Associated Photoreceptor Death Mechanism

Interestingly, recent research has shown that while apoptosis is believed to be the major cause of photoreceptor death after RD, it is not the only cause. The involve-

ment of the apoptotic pathway is well documented; yet, inhibitors of this pathway can only partly rescue photoreceptors, suggesting the existence of other pathways for RD-associated photoreceptor death.

Endoplasmic Reticulum Stress-Mediated Cell Death

In response to stress, disruption of endoplasmic reticulum (ER) homeostasis – often termed ‘ER stress’ – occurs in the cell and results in accumulation of unfolded proteins in the ER lumen [57, 58]. ER stress is initially a self-protection mechanism; yet, prolonged or excessive ER stress can lead to ER stress-mediated cell death [59]. ER stress has been shown to be important in neuronal death in neurodegenerative disorders [60–62] as well as retinal degenerations [63–66]. In experimental RD, elevation of two ER stress markers in association with retinal cell death suggested that ER stress-mediated apoptosis is one pathway for RD-associated photoreceptor death [67].

Programmed Necrosis

Besides apoptosis, Trichonas et al. [68] showed that there is a redundant mediator of photoreceptor death after experimental RD. When caspases are inhibited by the wide-range caspase inhibitor Z-VAD-fmk, necrosis mediated by receptor-interacting protein (RIP) kinase takes place and becomes the dominant form of photoreceptor death after RD. RIP1 is a serine/threonine kinase that forms a complex with Fas-associated death domain and caspase-8 upon death domain receptor stimulation [69]. Consistently, there is an increased level of high-mobility group box1 protein, a factor released from necrotic cells, but not apoptotic cells, in human eyes with RD [70], confirming the existence of necrotic photoreceptor death. As RIP-mediated programmed necrosis happens in addition to apoptosis after RD and both lead to photoreceptor death, it was postulated that simultaneous inhibition of RIP kinases and caspases may be one effective strategy for photoreceptor protection after RD.

Cytokines

Cytokines are secreted protein molecules that can regulate caspase activity and therefore cell apoptosis in response to injury. In the eye, higher levels of vitreous cytokines were observed after RD [71–78]. One particular cytokine, monocyte chemoattractant protein-1 (MCP-1), has been shown to be associated with photoreceptor cell death. Increased expression and release of MCP-1 was found in detached retina [70, 79], while injec-

tion of MCP-1-blocking antibody greatly reduced RD-induced photoreceptor apoptosis [80]. It was postulated that the chemotactic properties and possibly macrophage/microglion-generated oxidative stress might contribute to the cytotoxic effect of MCP-1 on photoreceptors after RD.

Photoreceptor Rescue and Neuroprotective Strategies

Understanding the mechanisms by which photoreceptors die may suggest strategies for rescuing the photoreceptors after RD. Several useful neuroprotective strategies including oxygen supplementation, delivery of neurotrophic factors and blockade of protein activity in the apoptotic signalling pathway have been postulated.

Oxygen Supplementation

Detachment of the outer retina from its underlying retinal pigment epithelium diminishes the source of its nutrient and oxygen. Presumably, the detached retina is hypoxic and hypoglycaemic. Indeed, oxygen supplementation (hyperoxia) was reported to reduce photoreceptor death in experimental RD, good evidence suggesting that oxygen supplementation between diagnosis and surgery will improve outcomes [1, 81–83].

Neurotrophic Factors

Neurotrophic factors have been shown to be important in photoreceptor rescue [18]. The first experimental success was the use of basic fibroblast growth factor in the Royal College of Surgeons rat [84]. Other neurotrophic factors such as brain-derived neurotrophic factor (BDNF) [85], nerve growth factor (NGF) [86, 87] and glial cell line-derived neurotrophic factor (GDNF) [88] have also been shown to be useful in experimental RD. Intravitreal injection of recombinant NGF increased the number of nuclei in the ONL while decreasing the number of TUNEL-positive cells [86, 87]. In general, long-term maintenance of high levels is desired for photoreceptor rescue and survival. Yet, the short half-life of these agents means repeated intravitreal injection, which is impractical and causes undesirable side effects. Alternatively, a transfection agent containing sequences coding for the desired protein can be used instead. Gene delivery of GDNF by recombinant adeno-associated virus was tested and resulted in a thicker ONL and less apoptotic cells in the photoreceptor layer [88].

Table 1. Agents which reduced the extent of photoreceptor apoptosis in animal models after RD

Potential therapeutic agent	Mechanism of neuroprotection	Model system
BDNF [85]	Maintain surviving photoreceptors; reduce Müller gliosis; promote outer segment regeneration (?)	Cat
BDNF [54]	–	Brown Norway rats
BDNF and bFGF [46]	–	Brown Norway rats
Recombinant adeno-associated virus expressing GDNF [88]	–	Lewis rats
Fas receptor-neutralising antibody [20, 21]	–	Brown Norway rats
NGF [86, 87]	Prevent apoptosis	Sprague-Dawley rats
MCP-1 [80]	Chemotactic effect on macrophages/ microglia and macrophage/ microglion-generated oxidative stress	MCP-1 ^{-/-} mice; Mac-1 ^{-/-} mice; C57BL/6 mice
HIV protease inhibitors [22]	Inhibit mitochondrial release of AIF and cytochrome c	GFP transgenic mice
Recombinant adeno-associated virus vector expressing heme oxygenase 1 [91]	–	Sprague-Dawley rats
Interleukin-6 [92]	–	Wild-type C57BL mice; IL-6 ^{-/-} mice; Brown Norway rats
Recombinant adeno-associated virus encoding X-linked inhibitor of apoptosis [93]	–	Brown Norway rats
Palomid 529 [94]	Inhibit Akt/mammalian target of rapamycin pathway	New Zealand red pigmented rabbits
Minocycline [95]	–	C57BL/6J mice
Met12 (small peptide inhibitor of Fas receptor) [90]	Inhibition of Fas signalling	Brown Norway rats
Stromal cell-derived factor 1 [96]	–	Mice
Necrostatin-1 [68]	RIP1 kinase inhibitor	Brown Norway rats; C57BL/6 mice

bFGF = Basic fibroblast growth factor; GFP = green fluorescent protein.

Apoptosis-Based Therapies

Interfering directly with the apoptotic pathway is appealing, given the extensive research showing that apoptosis is ubiquitous and occurs virtually in every cell type. Apoptotic cell death is the main cause of photoreceptor death after RD. Manipulation of the various signalling pathways in apoptosis is neuroprotective; it can decrease the number of dead retinal cells and may therefore prevent the irreversible loss of visual function. The involvement of the intrinsic, extrinsic and caspase-independent pathways has helped to identify potential therapeutic tar-

gets. These include Bax [89], Fas receptor/ligand [20, 21, 90] and AIF [22, 54]. A summary of the potential therapeutic agents tested is provided in table 1.

Conclusion

Understanding the pathogenesis of RD is of great clinical significance. Manipulation of photoreceptor apoptosis provides a logical strategy for protecting photoreceptors. Administration of a drug that can prevent pho-

toreceptor death and loss between onset of RD and reattachment surgery would be highly desirable. Tremendous efforts have been undertaken to identify potential therapeutic targets for the prevention of visual loss in various retinal disorders associated with RD.

Disclosure Statement

The authors report no proprietary or commercial interest in any concept discussed in this article.

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