Chapter 8
RIP Kinase-Mediated Programmed Necrosis

Yusuke Murakami, Maki Kayama, Joan W. Miller, and Demetrios Vavvas

Abstract Retinal ganglion cell (RGC) death is the ultimate cause of vision loss in glaucoma. Apoptosis has been thought to be a major form of cell death in various diseases including glaucoma; however, attempts to develop neuroprotective agents that target apoptosis have largely failed. Recent accumulating evidence has shown that non-apoptotic forms of cell death such as necrosis are also regulated by specific molecular machinery, such as those mediated by receptor-interacting protein (RIP) kinases. In this review, we summarize recent advances in our understanding of RIP kinase signaling and its roles in RGC loss. These data suggest that not only apoptosis but also necrosis is involved in RGC death and that combined targeting of these pathways may be an effective strategy for glaucoma.

Keywords Necroptosis • Programmed necrosis • Retinal ganglion cell death • RIP kinase

8.1 Introduction

Glaucoma affects 70 million people worldwide and is characterized by progressive retinal ganglion cell (RGC) death with accompanying optic nerve atrophy [1, 2]. It is often associated with elevated intraocular pressure (IOP) and current

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management aims at lowering IOP. Although IOP-lowering treatments slow the development and progression of glaucoma, approximately 10 % of people who receive proper treatment still experience severe vision loss. Therefore, investigating the mechanisms of RGC death will be important to better understanding of the disease pathophysiology and development of novel therapeutics.

8.2 Two Distinct Forms of Cell Death: Apoptosis and Necrosis

Apoptosis and necrosis are two major forms of cell death defined by morphological appearance [3]. In 1972, Kerr et al. coined the term apoptosis (Greek for "falling off") to describe a specific form of cell death, which shows condensation of the nucleus and cytoplasm, rounding-up of the cell, reduction of cellular volume, and engulfment by resident phagocyte [4]. They suspected apoptosis as a general mechanism of controlled cell deletion, and indeed, accumulating evidence demonstrates that apoptosis is genetically a regulated process of cell death, where the caspase family of cysteine proteases plays a central role for signal transduction and execution [5]. In contrast, necrosis (Greek for "dead") is associated with swelling of the cytoplasm and organelles, a gain in cell volume, plasma membrane rupture, and connections with the extracellular cavity. Although necrosis was traditionally thought to be an uncontrolled process of cell death, it is now known to also have regulated components, such as those mediated by receptor-interacting protein (RIP) kinases [6].

8.3 RIP Kinase-Mediated Programmed Necrosis

RIP kinase-mediated programmed necrosis was discovered from the extensive studies of death receptor-induced cell death. Death ligands such as TNF-α and Fas-L induce apoptosis, but they also cause necrosis in certain types of cells [7]. Intriguingly, Vercammen and colleagues found that, when apoptosis is blocked by caspase inhibitors, cells undergo an alternative necrotic cell death in response to TNF-α or Fas-L [8, 9]. Twelve years later, Holler and colleagues identified that that this death receptor-induced necrosis is mediated by the activation of RIP1 [10]. Furthermore, three independent studies recently showed that interaction between RIP3 and RIP1 is critical for RIP1 kinase activation and subsequent necrosis [11–13]. These advances in our understanding of the molecular basis of necrosis have revealed previously unrecognized roles of necrosis in health and disease.

8.4 RIP Kinase Signaling

Two members of the RIP kinase family proteins, RIP1 and RIP3, are critical mediators of necrosis [6]. RIP1 was originally identified as a protein that interacts with Fas [14]. RIP1 consists of an N-terminal serine/threonine kinase domain, an intermediate domain, a RIP homotypic interaction motif (RHIM), and a C-terminal DD (Fig. 8.1). RIP1 acts as a multifunctional adaptor protein downstream of death receptors and mediates pro-survival NF-κB activation, caspase-dependent apoptosis, and RIP kinase-dependent necrosis [15]. RIP3 was found as a serine/threonine kinase that shares homology with RIP1 but does not possess a DD [16] (Fig. 8.1). RIP3 contains the RHIM domain in its C-terminus and directly binds to and phosphorylates RIP1 [17]. Although the precise biological function of RIP1-RIP3 interaction was unclear for a long period, recent studies have shown that RIP3-dependent phosphorylation of RIP1 kinase in the RIP1-RIP3 complex is critical for the induction of death receptor-induced necrosis [11–13]. This necrosis-inducing protein complex is termed the "necrosome."

8.4.1 RIP1 Polyubiquitination and Pro-survival NF-κB Activation

In response to TNF-α stimulation, RIP1 is recruited to TNFR and forms a membrane-associated complex with TNF receptor-associated death domain (TRADD), TNF receptor-associated factor 2 or 5 (TRAF2/5), and cIAP1/2, the so-called complex I [18]. cIAP1 and cIAP2 are key ubiquitin ligases that induce RIP1 polyubiquitination in the complex [19]. This ubiquitin chain provides an

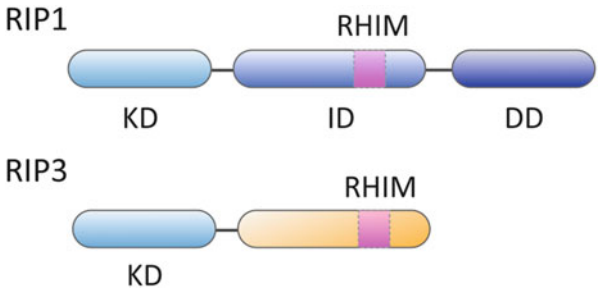

Fig. 8.1 The structure of RIP1 and RIP3. RIP1 consists of an N-terminal serine/threonine kinase domain (KD), an intermediate domain (ID), a RIP homotypic interaction motif (RHIM), and a C-terminal death domain (DD). RIP3 shares homology with RIP1 but does not possess a DD. RIP3 contains the RHIM domain in its C-terminus and directly binds to and phosphorylates RIP1. This phosphorylation in the RIP1-RIP3 complex is critical for the induction of death receptor-induced necrosis. Reproduced with permission from Murakami et al. [40]

assembly site for transforming growth factor-β-activated kinase 1 (TAK1), TAK1-binding protein 2 or 3 (TAB2/3), and inhibitor κB kinase (IKK) complex and mediates NF-κB activation [20]. Activated NF-κB translocates to the nucleus and induces transcription of prosurvival genes such as cIAPs, c-FLIPs, and IL-6 [21]. In addition, it mediates the induction of cylindromatosis (CYLD) or A20, which dephosphorylates RIP1 and acts as a negative feedback loop in NF-κB signaling [22, 23] (Fig. 8.2a).

8.4.2 *RIP1 Deubiquitination and Formation of Cytosolic Pro-death Complex: DISC or Necrosome*

RIP1 switches its function to a regulator of cell death when it is deubiquitinated by CYLD or A20 [24]. Deubiquitination of RIP1 abolishes its ability to activate NF-κB and leads to the formation of cytosolic pro-death complexes, the so-called complex II [18]. These complexes contain TRADD, FADD, RIP1, caspase-8, c-FLIP, and/or RIP3 and mediate either apoptosis or necrosis depending on cellular conditions. Dimerization of caspase-8 in the complex II mediates a conformational change to its active form, thereby inducing apoptosis (Fig. 8.2b). On the other hand, in conditions where caspases are inhibited or cannot be activated efficiently, RIP1 interacts with RIP3 and forms the necrosome (Fig. 8.2c). RIP3-dependent activation of RIP kinase is crucial for necrosis induction in response to TNF-α [11–13]. Other death ligands such as Fas-L are also capable to mediate RIP kinase-dependent necrosis as well as caspase-dependent apoptosis. In contrast to TNF-α, Fas directly recruits RIP1 and FADD to the plasma membrane and forms pro-death complexes with caspase-8 and/or RIP3 [14].

8.4.3 *Regulatory Mechanisms of RIP Kinase Activation*

Because caspase inhibition sensitizes cells to RIP kinase-dependent necrosis, caspases may inhibit RIP kinase activity. Indeed, caspase-8 directly cleaves and inactivates RIP1 and RIP3 [25, 26]. Interestingly, this inactivation does not require proapoptotic caspase-8 activation through its homodimerization, but is mediated by the restricted caspase-8 activity in the heterodimer with c-FLIP, an endogenous inhibitor of caspase-8 [27] (Fig. 8.2). Recent studies have shown that the c-FLIP-caspase-8 heterodimer has a restricted substrate repertoire and mediates pro-survival effect via antagonizing RIP kinase activation [28].

The expression levels of RIP3 are another factor that control RIP kinase activation. Whereas RIP1 is expressed ubiquitously in all cell types, RIP3 expression differs amongst cells and tissue [16]. In addition, the levels of RIP3 correlate with the responsiveness to necrotic cell death induced by TNF-α [12]. The levels of

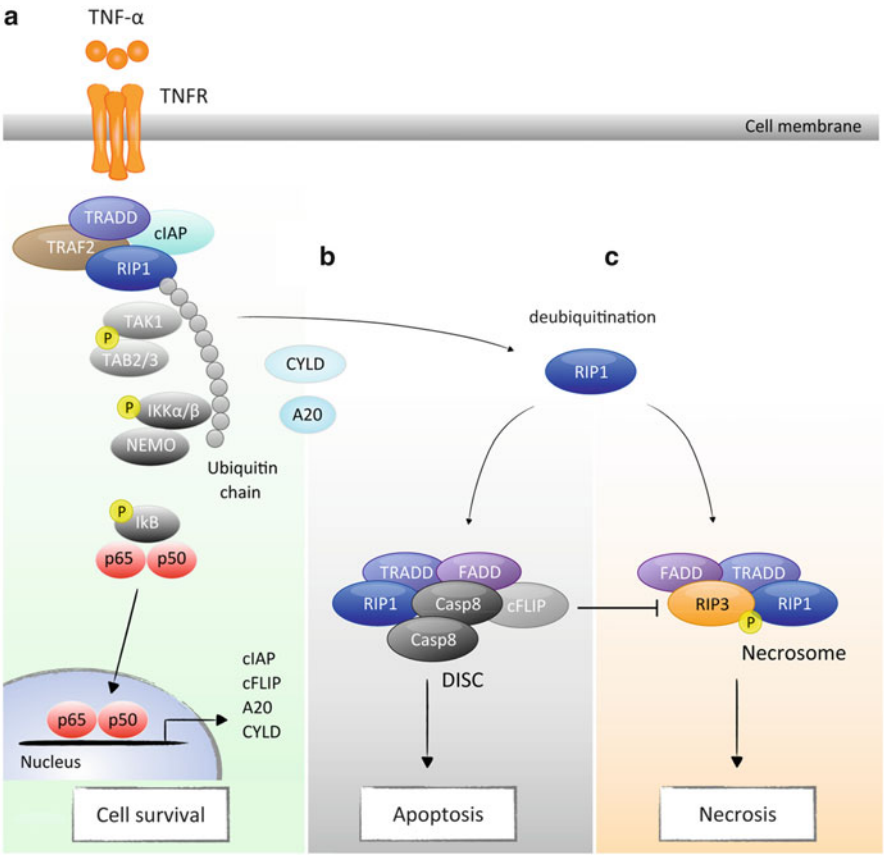

Fig. 8.2 RIP kinase signaling. (**a**) In response to TNF-α stimulation, RIP1 is recruited to TNFR and forms a membrane-associated complex with TRADD, TRAF2 and cIAPs. cIAPs ubiquitinate RIP1, which in turn mediate NF-κB activation. Nuclear translocation of p65/p50 subunits promotes the production of pro-survival genes such as cIAPs and c-FLIPs as well as deubiquitinating enzymes such as CYLD and A20, which act as a negative feedback loop in NF-κB signaling. (**b**) and (**c**). RIP1 switches its function to a regulator of cell death when it is deubiquitinated by CYLD or A20. Deubiquitination of RIP1 abolishes its ability to activate NF-κB and leads to the formation of cytosolic pro-death complexes. These complexes contain TRADD, FADD, RIP1, caspase-8, c-FLIP, and/or RIP3 and mediate either apoptosis or necrosis depending on cellular conditions. Multimerization of caspase-8 in the DISC mediates a conformational change to its active form, thereby inducing apoptosis (**b**). The catalytic activity of caspase-8-c-FLIP heterodimer complex cleaves and inactivates RIP1 and RIP3. In conditions where caspases/c-FLIPs are inhibited or cannot be activated efficiently, RIP1 forms the necrosome with RIP3, thereby promoting necrosis (**c**). Reproduced with permission from Murakami et al. [40]

caspases also change depending on cellular types and conditions. Caspase-dependent apoptosis is downregulated in the mature neurons because of reduced caspase-3 expression after development [29]. Caspase-8 expression is substantially lower in RPE cells compared with other ocular epithelial cells or tumor cells, which

may protect the RPE from apoptosis [30]. Therefore, it is likely that the balance between caspases and RIP3 may be important to decide the cell fate (i.e., apoptosis or necrosis) in response to death receptor stimulation or other signals.

8.5 RIP Kinase Inhibitors

Degterev and colleagues identified small compounds named necrostatin that specifically inhibit death receptor-mediated necrosis in a cell-based screening of ~15,000 chemical compounds [31]. Necrostatin-1 (Nec-1) has been shown to strongly inhibit RIP1 kinase phosphorylation, and structure-activity relationship analysis demonstrated that Nec-1 binds to the adaptive pocket on RIP1 and stabilizes the inactive conformation of RIP1 kinase [32]. Importantly, other two necrostatins, which have different structures than Nec-1, also inhibit RIP1 kinase phosphorylation, suggesting that necrostatins target RIP1 kinase.

However, there are some reports raising concerns about the specificity of necrostatins. For instance, it was shown that Nec-1 partially affects the PAK1 and PKAcα activity on a panel screening of 98 human kinases [33]. More recently, Takahashi and colleagues demonstrated critical issues on the specificity and activity of Nec-1. They report that Nec-1 is identical to methyl-thiohydantoin-tryptophan (MTH-Trp), an inhibitor of indoleamine 2,3-dioxygenase (IDO) [34]. IDO is the rate-limiting enzyme in tryptophan catabolism and modulates immune tolerance. Hence, interpretation of the results obtained by using Nec-1 requires consideration of its nonspecific effect, and additional experiments using RIP3-deficient mice or RNAi knockdown of RIP kinase will help the precise understanding of the role of RIP kinase in diseases.

8.6 Knockout Animals for RIP Kinases

RIP1 is a multifunctional protein that is critical for both cell survival and death, and *Rip1*$^{-/-}$ mice exhibit postnatal lethality with reduced NF-κB activation and extensive cell death in lymphoid and adipose tissues [35]. In contrast, *Rip3*$^{-/-}$ mice are viable and do not show gross abnormality in any of the major organs including the retina [36]. Although *Rip3*$^{-/-}$ mice are indistinguishable from WT mice in physiological conditions, recent studies have revealed that they display marked reduction in death receptor-induced necrosis [12, 11]. Hence, *Rip3*$^{-/-}$ mice have been used as an instrument of investigating death receptor-induced necrosis in physiological and pathological conditions. Using *Rip3*$^{-/-}$ mice, we have investigated the role of RIP kinase in photoreceptor cell death in retinal degenerative diseases such as retinal detachment, retinitis pigmentosa, and age-related macular degeneration [37–40].

8.7 The Role of RIP Kinase in RGC Death

In experimental models of glaucoma, dying RGCs show not only apoptotic but also necrotic features [41]. However, most of studies investigating the mechanisms of RGC death have mainly focused on apoptosis, because of the general concept that necrosis is an uncontrolled process of cell death. Unfortunately, despite more than a decade of work on apoptosis, attempts to prevent or delay RGC degeneration in glaucoma have been unsuccessful, and it would be important to investigate the role of other mechanisms of cell death in glaucoma.

Accumulating evidence indicates that TNF-α is a critical mediator of RGC death in glaucoma [42]. TNF-α is elevated in the aqueous humor of glaucoma patients [43]. Moreover, neutralization of TNF-α prevents RGC death in several models of experimental glaucoma [44, 45]. However, the mechanism by which TNF-α mediates RGC death remains unclear. RIP1 is a key adaptor protein activated downstream of TNF-α [6]. Given the emerging role of RIP kinase in necrosis induction, it can be hypothesized that RIP kinase may be involved in RGC in glaucoma. Rosenbaum and colleagues addressed this question by testing Nec-1 in the retinal ischemia-reperfusion injury model. They showed that intravitreal injection of Nec-1 protects RGC loss and provides functional improvement [46], suggesting the involvement of programmed necrosis in RGC death. We also evaluated the role of RIP kinase-dependent necrosis in other models of RGC death and found that not only caspase pathway but also RIP kinase pathway is important for RGC death (MK, DGV et al. unpublished data). Consistent with these in vivo findings, Lee and colleagues demonstrated that RIP3 mediates rat RGC death through phosphorylation of Daxx after oxygen glucose deprivation in vitro [47]. Taken together, these findings suggest RIP kinase-dependent necrosis as a novel mechanism of RGC death and as a therapeutic target.

8.8 Conclusion

Although apoptosis has been thought to be a major form of cell death in retinal and neurodegenerative diseases, recent studies have shown that non-apoptotic forms of cell death are also important. RIP kinase is a crucial regulator of programmed necrosis and contributes to neuronal cell death in various conditions, including RGC death. Further studies investigating the role of RIP kinase-dependent necrosis in glaucoma will be important for better understanding of the mechanisms of RGC death and development of novel therapeutics to prevent or delay RGC loss.

Competing Interests Statement The Massachusetts Eye and Ear Infirmary has filed patents on the subject of neuroprotection in retinal degenerations. YM, MK, JWM, and DGV are named inventors.

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