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RIPK1 Mediated Regulation Of ZBP1 Activation: An Emerging Mechanism In Cell Death, Inflammation And Development

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Abstract

Regulated cell death and inflammation are critical in orchestrating cellular homeostasis, development and host defense responses. The RIP-homotypic interaction motif (RHIM) containing proteins, RIPK1, RIPK3, TRIF and ZBP1, play an important role in triggering cell death and inflammation via assembling signaling complexes. RIPK1 and ZBP1 independently promote RIPK3-MLKL mediated inflammatory cell death called necroptosis. The RIPK1-RIPK3 signaling axis is well described in the death-receptor, TLR and other innate immune receptor signaling pathways for triggering necroptosis and in embryonic development. ZBP1 is a Z-nucleic acid sensor that promotes virus induced RIPK3 activation and necroptosis. This review focuses on recent findings that led to the identification of RIPK1 function in counteracting ZBP1 activation in physiological conditions and its importance in defining new intracellular mechanisms of cell death and inflammation.

Keywords: Necroptosis; RIPK1; RIPK3; ZBP1; MLKL; Inflammation; Cell death; Z-RNA

Introduction

Regulation of cellular homeostasis is essential for tissue maintenance, organismal development and for resisting stress responses [1-3]. Disruption of cellular homeostasis triggers molecularly regulated cell death programs for eliminating damaged or unfit cells [4,5]. This regulated cell death is also activated in response to microbial infections to promote host defense *via* controlling microbial replication and initiation of protective inflammatory responses [6-8]. Deregulation in cell survival signaling and cellular homeostasis triggers cell death during development which lead to embryonic or perinatal lethality in mice [1,2,9]. Understanding the mechanisms regulating this cell death during physiological conditions is critical to define cellular signaling programs controlling proper development of an organism and immune system.

Receptor-interacting serine/threonine protein (RIP) kinase 1 (RIPK1), RIPK3, Toll/IL-1 receptor domain containing adapter protein-inducing IFN-β (TRIF) and Z-DNA binding protein (ZBP1) are inflammation and cell death signaling proteins that consists of a RIP-homotypic interaction motif (RHIM) [2,10-12]. The RHIM domain facilitates protein-protein interactions among RHIM proteins which is critical to assemble signaling complexes triggering cell death and inflammation [1-3,9]. The RHIM-mediated formation of the RIPK1 and RIPK3 complex is a widely studied signaling complex in response to the activation of death receptor, toll-like receptor (TLR) and many other innate immune receptors signaling pathways [1,2,9,13-15]. The RHIM-mediated protein interactions license the activation of the specific cell death and pro-inflammatory responses to drive cell fate decision in physiological conditions and microbial infections. In physiological conditions, RIPK1 and apoptosis inducing caspase-8 (CASP8) play a critical role in restricting activation of the RIPK3 [1,9]. Inhibition of the CASP8 promotes the RHIM mediated interaction of RIPK1 and RIPK3 which in turn promotes RIPK3 oligomerization and phosphorylation [13-16]. This results in the activation of mixed lineage kinase domain-like pseudokinase (MLKL) followed by its membrane translocation for inducing an inflammatory cell death called necroptosis [2,17-20]. RIPK1 deficiency induces embryonic lethality in mice which is mediated by CASP8 induced apoptosis and RIPK3-MLKL mediated necroptosis [21-23]. Thus, the association of the RIPK1 and RIPK3 is crucial determinant of the cell fate decisions which impacts cellular homeostasis and organismal development by controlling necroptosis. ZBP1 (also known as DAI or DLM-1) is a Z-nucleic acid sensor with RHIM domains which mediates RIPK3-MLKL dependent necroptosis during viral infections [6,11,24,25]. RIPK1 and ZBP1 are the upstream activators of RIPK3-MLKL dependent necroptosis [26,27]. Although the role of RIPK1 in cellular homeostasis regulation is well studied, the precise regulation of the ZBP1 in cell fate decisions is still an active field of research. The recent identification of the interplay of RIPK1 and ZBP1 in cell death, inflammation and development brought new directions to understand key physiological functions regulated by them. This review summarizes recent studies that unraveled RIPK1's role in controlling ZBP1 mediated cell death, inflammation and perinatal lethality.

RIPK1-A Key Signaling Kinase Regulating Cell Death, Inflammation And Perinatal Lethality

RIPK1 is a protein kinase that regulates cell survival, death and inflammation to orchestrate host defense responses and organismal homeostasis [2,3,28]. RIPK1 functions are described mainly in the form of its kinase activity and kinase-independent scaffolding function. RIPK1 kinase activity is essential for regulating death receptor induced cell death, including CASP8 mediated apoptosis and RIPK3 regulated necroptosis [1,2,9]. RIPK1 also regulates RIPK3 independent autoinflammation *via* release of IL-1 cytokines [29,30]. Recent studies

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find that this kinase activity of RIPK1 regulates NLRP3 inflammasome inducing pyroptosis, an inflammatory cell death, and release of signal peptide lacking pro-inflammatory cytokines IL-1β and IL-18 [31-33]. The RIPK1 also facilitates CASP8 mediated activation of membrane pore forming Gasdermin D (GSDMD) and pyroptosis [31,32,34,35]. In addition to its protein kinase domain, RIPK1 consists of a death domain (DD) at its C-terminus and a RHIM in its intermediate domain. These DD and RHIMs of the RIPK1 promote homotypic interactions with other cell death proteins to assemble into various signaling complexes with distinct functional properties [2,3,9]. These homeostatic functions regulated by RIPK1 are essential for proper development of the immune system during development [3,21,23]. Loss of RIPK1 expression promotes perinatal lethality in mice because of the excessive cell death [21-23]. These $Ripk1^{-/-}$ mice are viable only when CASP8 and RIPK3 or Fas-associated death domain (FADD) and RIPK3 are genetically deleted. Thus, RIPK1 is a central cellular homeostasis regulator which controls aberrant activation of the CASP8 mediated apoptosis and the RIPK3 driven necroptosis. In addition, conditional loss of RIPK1 in the intestine activates apoptosis and premature death in mice [36,37]. However, the loss of RIPK1 in epidermis induces skin inflammation and this depends on predominantly RIPK3 mediated necroptosis [36,38]. The specific cell death signaling pathways controlled by RIPK1 may be tissue specific while its function in regulating epithelial cell homeostasis and death is conserved.

ZBP1-A Z-Nucleic Acid Sensor In Necroptosis And Perinatal Lethality

ZBP1 consists of N-terminal Zα domains which preferentially bind to nucleic acids in Z-conformation [26,39]. In addition, the ZBP1 consists of tandem RHIM domains and interacts with RIPK3 *via* RHIM mediated association and triggers necroptosis [10,11]. Both DNA and RNA viruses trigger RIPK3-MLKL mediated necroptosis as a host defense response to restriction viral infections [6,24,40]. Studies on cell death induced by murine cytomegalovirus (MCMV) infection establish the critical role of ZBP1 in activating RIPK3 mediated necroptosis [24,25]. Further studies established the role of ZBP1 in sensing influenza A virus (IAV) infection and activating RIPK3-CASP8 signaling axis which triggers apoptosis, necroptosis and NLRP3 inflammasome and pyroptosis [41,42]. In case of IAV infection, ZBP1 activation is demonstrated to trigger PANoptosis (pyroptosis, apoptosis, necroptosis) *via* assembling a signaling complex called PANoptosome [43-47]. Type I IFNs are essential for the expression of the ZBP1 in response to IAV infection and to promote ZBP1 mediated cell death [41,48]. Several studies proposed that the sensing of viral RNAs in Z-RNA conformation is critical for ZBP1 activation during viral infections [41,42,48-52]. A recent study demonstrate the formation of viral Z-RNAs in the nucleus during IAV infection and its association with ZBP1, providing a direct evidence of Z-RNA sensing by the ZBP1 [53]. In addition, the specific deletion of the Zα2 domain of the ZBP1, which contain Z-RNA binding residues, is shown to be sufficient to inhibit ZBP1 induced cell death and inflammation during IAV infection [42,52]. This ZBP1-RIPK3 mediated necroptosis is critical for promoting antiviral host defense *in vivo* [54,55]. The ZBP1 also promote antiviral responses in response to West Nile virus (WNV) and ZIKA virus (ZIKV) infections, however, *via* cell death independent mechanisms [56,57].

Functional Association of RIPK1 And ZBP1-A New Regulatory Mechanism in Physiology

Even though complete loss of the RIPK1 expression ($Ripk1^{-/-}$) triggers perinatal lethality during development, RIPK1-kinase inactive mutant mice are viable and show normal development [58,59]. This suggests a critical role of kinase independent scaffolding function of the RIPK1 in regulating aberrant cell death during development preferably by controlling CASP8 and RIPK3-MLKL signaling pathways [1,2,5,9]. The seminal observations by Lin et al., and Newton et al., identify that mutating the RHIM of RIPK1 (mice are named $Ripk1^{RHIM/RHIM}$, $Ripk1^{mRHIM/mRHIM}$ or $Ripk1^{mR/mR}$) leads to perinatal lethality and epidermal hyperplasia in mice unlike the RIPK1-kinase mutant mice [38,60]. Mutating the RIPK1-RHIM lead to the autophosphorylation of RIPK3 and triggers MLKL mediated necroptosis and genetic deletion of RIPK3 or MLKL in $Ripk1^{mRHIM/mRHIM}$ mice restore viability of these mice [38,60]. These findings establish a definitive role for the RIPK1-RHIM in controlling RIPK3-MLKL mediated necroptosis in mice development. Importantly, the activation of the ZBP1 is critical for engaging RIPK3-MLKL signaling in $Ripk1^{mRHIM/mRHIM}$ mice suggesting the role of RIPK1 in controlling spontaneous activation of the ZBP1 *in vivo* [38,60]. Epidermis specific deletion of the RIPK1 ($Ripk1^{E\text{-}KO}$) or mutating its RHIM drives keratinocyte necroptosis and skin inflammation [36,38]. This necroptosis driven skin inflammation also depends on the ZBP1 mediated activation of the RIPK3-MLKL cell death signaling [38]. Moreover, mutating RHIM or catalytically inactive form of RIPK3 rescue perinatal lethality in $Ripk1^{mRHIM/mRHIM}$ mice [60]. Thus, the activation of ZBP1 also plays a role in development by controlling RIPK3-MLKL mediated necroptosis and this pathways is restricted by the RIPK1 [38,60]. Type I interferon (IFN) signaling upregulates ZBP1 expression and increased levels of IFNs appear in the absence of RIPK1 or loss of RIPK1-RHIM [38,60]. Loss of IFN signaling components or ZBP1 increases viability of the mice lacking RIPK1 suggesting additional *in vivo* regulatory mechanisms of the ZBP1 *via* IFNs [61]. These studies delineate the important regulation of RIPK1, ZBP1 and RIPK3 *via* RHIM mediated interactions and established a new role for RIPK1 in controlling spontaneous activation of the ZBP1 (Figure 1).

A Critical Role Of Z-Nucleic Acid Binding Zα Domains Of The ZBP1 In Perinatal Lethality

The recent studies on understanding the role of ZBP1 demonstrate that the sensing of viral RNAs is essential for the activation of the ZBP1 and RIPK3-MLKL mediated necroptosis [26]. How ZBP1 is activated in sterile conditions during development that promotes necroptosis and perinatal lethality? Several new studies unravel the importance of Zα domains, which bind to Z-RNAs, in activating RIPK3-MLKL mediated necroptosis during development, skin and colon inflammation [52,62-64]. Either mutating critical Z-nucleic acid binding residues or deletion of the Zα domains abolish perinatal lethality in $Ripk1^{mRHIM/mRHIM}$ mice and skin inflammation in $Ripk1^{E\text{-}KO}$ mice [52,62,63]. Importantly, the sensing of Z-nucleic acids by Zα domains also mediate colitis in mice lacking CASP8 and FADD in the intestine [63]. Thus, Z-nucleic acid sensing by Zα domains of the ZBP1 is a key activating mechanism to license activation of the RIPK3-MLKL necroptosis and inflammation in physiological conditions (Figure 1).

The ZBP1 consists of two Zα domains (Zα1 and Zα2) at its N-terminus followed by tandem RHIM sequences. Interestingly, disruption of the Zα2 domain of the ZBP1 is sufficient to block RIPK3-MLKL mediated necroptosis and rescue perinatal lethality of the $Ripk1^{mRHIM/mRHIM}$ mice [52,63]. Mutating the first RHIM sequence of the ZBP1 is sufficient to rescue mice from perinatal lethality and skin inflammation [63]. Mutating Z-nucleic acid binding residues in Zα domains do not seem to affect ZBP1 interaction with RIPK3 in overexpression systems [62]. Thus, the activation of ZBP1, in the absence of RIPK1 or when RIPK1-RHIM mutated, appeared to be a two-step process. The loss of RIPK1 homeostatic function leads to Z-nucleic acid sensing by Zα domains

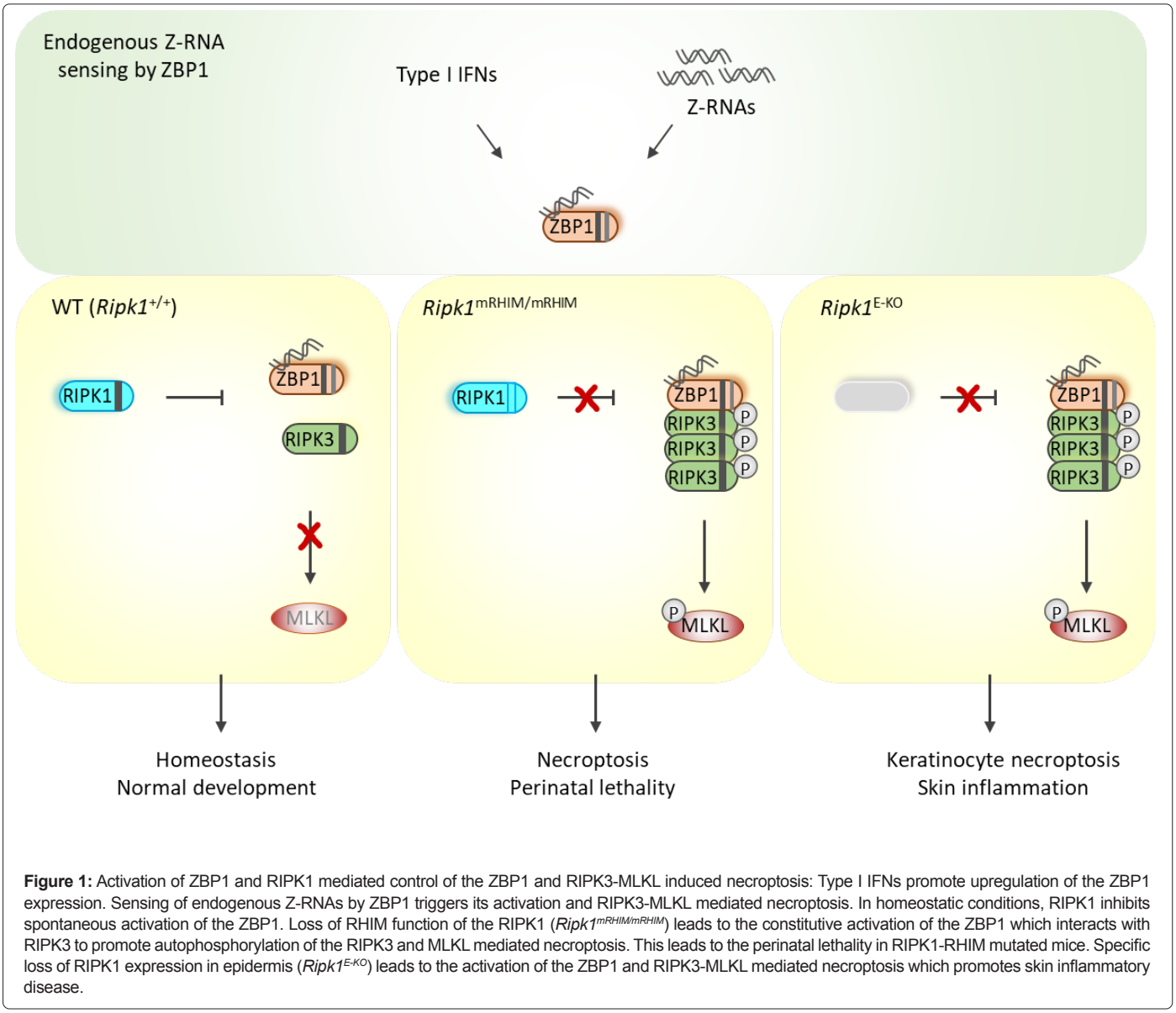

Figure 1: Activation of ZBP1 and RIPK1 mediated control of the ZBP1 and RIPK3-MLKL induced necroptosis: Type I IFNs promote upregulation of the ZBP1 expression. Sensing of endogenous Z-RNAs by ZBP1 triggers its activation and RIPK3-MLKL mediated necroptosis. In homeostatic conditions, RIPK1 inhibits spontaneous activation of the ZBP1. Loss of RHIM function of the RIPK1 (*Ripk1*$^{mRHIM/mRHIM}$) leads to the constitutive activation of the ZBP1 which interacts with RIPK3 to promote autophosphorylation of the RIPK3 and MLKL mediated necroptosis. This leads to the perinatal lethality in RIPK1-RHIM mutated mice. Specific loss of RIPK1 expression in epidermis (*Ripk1*$^{E-KO}$) leads to the activation of the ZBP1 and RIPK3-MLKL mediated necroptosis which promotes skin inflammatory disease.

that triggers ZBP1 activation and this in turn facilitates the activation of ZBP1-RIPK3-MLKL signaling induced necroptosis (Figure 1).

The RIPK1 Mediated Regulation of the ZBP1 Activation

RIPK1, RIPK3 and ZBP1 can interact *via* RHIM-driven homotypic interactions in endogenous and overexpression systems [10,11]. However, recent Ripk1$^{mRHIM/mRHIM}$ mice studies find that the RIPK1 does not directly interact with the ZBP1 which exclude the idea of the ZBP1 sequestration by RIPK1 to inhibit necroptosis [38,60]. How RIPK1-RHIM restricts the formation of the ZBP1-RIPK3 complex without physically interacting with ZBP1? The accessibility of the RHIM domain of the ZBP1 is critical for its association with the RIPK3. Due to the lack of structural information, it is unclear whether the RHIM domain of the ZBP1 is surface accessible before its activation. The critical requirement of Z-nucleic acid sensing for promoting ZBP1 activation suggests a possible inactive conformation of the ZBP1 at homeostasis in which the RHIM domain is buried to remain inaccessible for RIPK3 interaction [26]. Upon activation by Z-nucleic acids, ZBP1 may attain an active conformation where the RHIM domain is readily accessible for associating with the RIPK3. In contrast to the direct sequestration of the ZBP1, it is possible that RIPK1-RHIM suppresses the association of ZBP1 and RIPK3 either *via* the ripoptosome complex (RIPK1-FADD-CASP8), which promotes CASP8 mediate proteolysis of RIPK3, or by the putative protein complex that is modulated by the ripoptosome [63]. Type I IFN signaling promotes upregulation of the ZBP1 during viral infections [26]. Similarly, increase in type I IFN signaling precedes activation of the ZBP1 in the absence of RIPK1 function [38,60,62,63]. This suggests an intricate connection of RIPK1 function with type I IFNs and regulation of ZBP1 activation. In addition, it appears that the association of the ZBP1-RIPK3 complex is more favorable than RIPK1-ZBP1 interaction and it remains to be investigated how RIPK1 succeeds in disrupting the ZBP1 from interacting with RIPK3 in endogenous settings.

Z-RNA Sensing and Activation of the ZBP1 And Necroptosis

Identifying the critical role of the Zα domains in physiological functions supports the idea that ZBP1 sensing of endogenous Z-RNAs triggers its activation. In vitro studies indicate that the ZBP1 binds to endogenous RNA [50]. A recent study demonstrates that the ZBP1 binds to endogenous RNAs *via* Zα domains [63]. Enrichment of endogenous retroviral elements (ERVs) is associated with activation of the ZBP1 [63,64]. This suggests a viral mimicry of double stranded RNAs derived from ERVs that represent potential Z-RNA forming nucleic acids. Another recent study showed that the genome instability in intestinal stem cells triggers ZBP1 mediated necroptosis and gut inflammation [64]. Decreased levels of a histone-lysine N-methyltransferase, SETDB1, are associated with the risk of inflammatory bowel disease. SETDB1 participates in genome stability and its loss is associated with the expression ERV elements which are otherwise suppressed in homeostatic conditions [64]. These ERVs mimic viral infections which promotes ZBP1 mediated necroptosis and loss of intestinal epithelial barrier function and cause bowel inflammation [64]. Furthermore, a new study demonstrates that the IAV infection generates nuclear Z-RNAs which promote ZBP1 activation and RIPK3-MLKL mediated necroptosis [53]. This study provides a direct association of Z-RNAs in ZBP1 activation further establishing the role of Z-RNAs in cellular functions. These recent seminal studies establish biochemical and genetic evidences for the sensing of endogenous and viral Z-RNAs by ZBP1 to regulate cell biological functions.

Conclusion

Mechanisms regulating cell survival, necroptosis and inflammation have drawn much attention because of their importance in inflammatory diseases and microbial infections. Specific c ontribution o f R IPK1, RIPK3 and ZBP1 which regulate activation of the necroptosis provide opportunities for therapeutic targeting in chronic inflammatory diseases. In addition, the recent identification of the RIPK1 mediated regulation of ZBP1 activation describe new fundamental mechanisms of necroptosis regulation and highlights the significance of the Z-RNA sensing in development and disease. Several questions remain to be studied in future studies: Why did the ZBP1 evolve to sense the loss of the RIPK1 function? Why do host cellular systems evolved to sense Z-RNA species? Does the expression of ERVs/Z-RNAs define a perturbation in cellular homeostasis in general? The n ew fi ndings of ne croptosis ac tivation and the intricate association of RIPK1 and ZBP1 functions unraveled the complex regulation of cellular functions which may facilitate the exploration of these pathways for targeting inflammatory diseases.

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