Sangdun Choi
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RCAN1

► RCAN

RCAN2

► RCAN

RCAN3

► RCAN

RCCP2

► Hepatocyte Growth Factor Receptor

RCN-1

► Regulator of Calcineurin 1 (RCAN1)

RCN-1, RCN1, Rcn1p

► RCAN

Receptor (Calcitonin) Activity Modifying Protein

► Ramp

Receptor Activity-Modifying Protein

► Ramp

Receptor Interacting Protein 140

► Nuclear Receptor-Interacting Protein 1 (NRIP1)

Receptor Related to FPR (RFP)

► FPR2/ALX

Receptor Tyrosine-Protein Kinase ErbB-1

► Epidermal Growth Factor Receptor

Receptor-Interacting Protein 1 (RIP1)

► Receptor-Interacting Protein Kinase

Receptor-Interacting Protein 140

► Nuclear Receptor-Interacting Protein 1 (NRIP1)

Receptor-Interacting Protein 2 (RIP2)

► Receptor-Interacting Protein Kinase

Receptor-Interacting Protein Kinase

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Synonyms

Ankyrin repeat domain-containing protein 3; CARD-containing IL-1 β ICE-kinase RIP-like-interacting CLARP kinase; CARD-containing interleukin-1 β-converting enzyme-associated kinase; Cell death protein RIP; Dardarin; Dual serine/threonine and tyrosine protein kinase (DSTY kinase): Dusty protein kinase; KIAA1790; PARK8; PKC-δ-interacting protein kinase; Receptor-interacting protein 1 (RIP1); Receptor-interacting protein 2 (RIP2); RIP-homologous kinase; RIPK6; RIPK7; Serine/threonine-protein kinase; Sugen kinase 496 (SgK496); Tyrosine-protein kinase

Historical Background

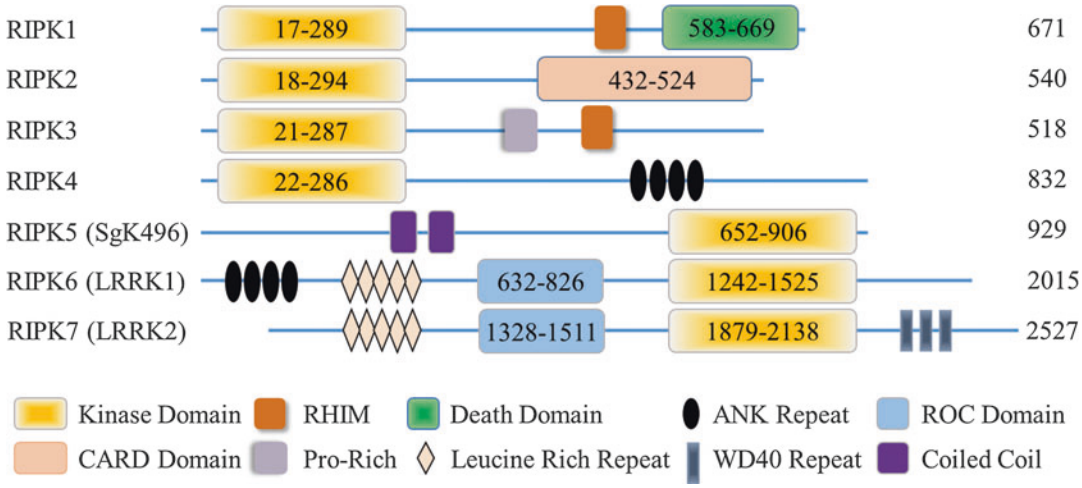
Receptor-interacting protein kinases (RIPKs) fall under the category of serine/threonine protein kinases that not only share architectural organization but also have functional similarities. The significant and shared physiological functions of these kinases include cell death regulation, inflammation, and cell differentiation. These kinases are closely similar to interleukin-(IL)-1 receptor-associated kinases (IRAKs), which are integral mediators of signaling pathways of Toll-like receptors (TLRs), pointing their overlapping roles with TLR signaling (Zhang et al. 2010). The first member of this family was identified through analysis of protein-protein interactions in 1995 and was named RIPK1 (Stanger et al. 1995). This study has been conducted to isolate a protein shared between FAS and tumor necrosis factor (TNF) receptor pathways. Since then, based on structural and functional similarities, seven RIPK members have been reported and are named RIPK1 through RIPK7. A variety of signaling stimuli can activate these kinases through different receptors such as TNFR, IL1R, and TLRs; however, most of these signaling pathways show overlapping responses, for example, nuclear factor κB (NF-κB) and/or activated protein 1 (AP-1) activation, in addition to the ensuing cell death (Declercq et al. 2009; Zhang et al. 2010). Here, we present a brief overview of the current knowledge about these RIPKs and the status of their involvement in shaping a cellular response when various ligands bind to their cognate receptors.

Receptor-Interacting Protein Kinase 1

RIPK1 is the first enzyme of this family and was identified in 1995 in a study on protein-protein-interactions in yeast to elucidate novel binding partners of Fas (CD95), with which RIPK1 interacts via its C-terminal death domain (Stanger et al. 1995). Besides, RIPK1 has a conserved kinase domain at its N terminus – the characteristic of this family – and a disordered intermediate domain (Fig. 1).

RIPK1 establishes contact with several other proteins, prominently those with death domains, for instance, tumor necrosis factor receptor 1 (TNFR1), TNF-related apoptosis-inducing ligand receptors 1 and 2, TNFR-related apoptosis-mediating proteins, Fas-associated death domain (FADD), TNFR-associated death domain (TRADD), RIP-associated ICH-1/CED-3-homologous protein with a death domain, Toll/IL-1 receptor domain-containing adaptor inducing interferon-β (TRIF), TNF receptor-associated factor 1 (TRAF1), TRAF2, TRAF3, and A20 (Fig. 2) (Hsu et al. 1996a; Varfolomeev et al. 1996; Wertz et al. 2004). Furthermore, RIPK1 can interact with other proteins through its intermediate domain, and these partners include RIP3, focal adhesion kinase, mitogen-activated protein/extracellular signal-regulated kinase kinase 1 (MEKK1), and MEKK3. The vast interactome of RIPK1 signifies the vital role of this protein in cell physiology (Zhang et al. 2010).

The essential role of RIPK1 in cell development could not be discerned owing to premature embryonic death in cases when caspase 8, FADD, or FLICE-like inhibitory protein ($FLIP_L$; a



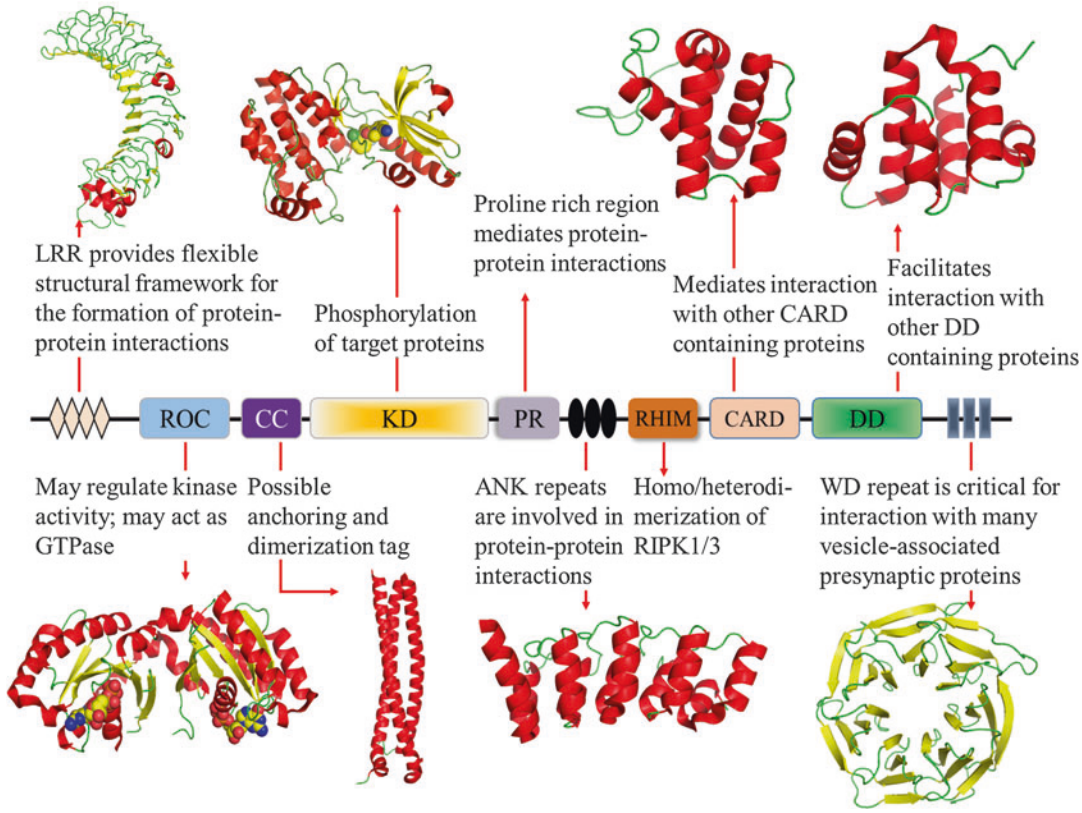
Receptor-Interacting Protein Kinase, Fig. 1 The structural organization of receptor-interacting protein kinases (RIPKs). The RIPK family includes seven members, with a conserved kinase domain in all members. The domain organization with the length of prominent domains, the approximate position of each domain, and the total protein lengths are presented. The legend is also provided below regarding the domain types

caspase 8 (FLICE)-like regulatory molecule) were ablated, resulting in embryonic death and inability to vascularize the yolk sac (Kelliher et al. 1998). It had been thought that these proteins are involved in cellular pathways such as the cell cycle, NF-κB activation, cell adhesion and migration, and suppression of inflammation, which are essential for development. Nonetheless, the reevaluation of functions of these proteins via a knockout of two or more molecules may predispose the animal to various clinical conditions that point to the vital roles of these proteins (Kelliher et al. 1998). For instance, caspase 8 and RIPK3 deficiency in mice do not cause premature death, and animals develop normally. Similarly, ablation of FADD, $FLIP_L$, and RIPK1 causes the embryonic death, highlighting the important roles of these molecules (Hsu et al. 1996b).

The expression pattern of RIPK1 is constitutive in various tissues, but inducible expression is observed during TNF-α treatment or T-cell activation. RIPK1-deficient cells in culture show high sensitivity to TNF-α, whereas the importance of RIPK1 for T-cell survival is evident in the profound apoptosis in lymphoid tissues when RIPK1 is knocked out (Kelliher et al. 1998).

In the cellular signaling network, RIPK1 represents a bifurcating node that equally influences two contrasting arms, cell survival and cell death. The deletion of RIPK1 irreversibly culminates in cell death, in contrast to its kinase-inactivated mutants that develop normally (Wang et al. 1998; Micheau and Tschopp 2003). RIPK1 can perpetuate vastly different signals such as those from TNF family cytokines, TLR3/4 ligands, sensors of viral infections, and interferons, while these signals can be translated either into the activation of MAP kinases and NF-κB or cell death (either apoptosis or necrosis) (Moriwaki et al. 2015).

In TNF-α signaling, the binding mode and kinase activity of RIPK1 determine the potential outcome (Fig. 3). In the first complex (termed complex I), TNF-R1, TRADD, RIPK1, TRAF2, and cIAP1 (cellular inhibitor of apoptosis 1) aggregate and thereby spontaneously activate NF-κB, which in turn induces the expression of numerous antiapoptotic proteins, including TRAF1 and 2, cIAP1 and 2, and notably cellular FADD-like IL-1β-converting enzyme inhibitory protein: a potent inhibitor of death receptor-induced apoptosis (Micheau and Tschopp 2003). In addition, TRAF2 and RIPK1 also mediate the activation of MAPKs such as c-Jun N-terminal kinase (JNK), p38, and extracellular regulated kinase (ERK). The ERK activation requires intact kinase activity of RIPK1, which is dispensable for

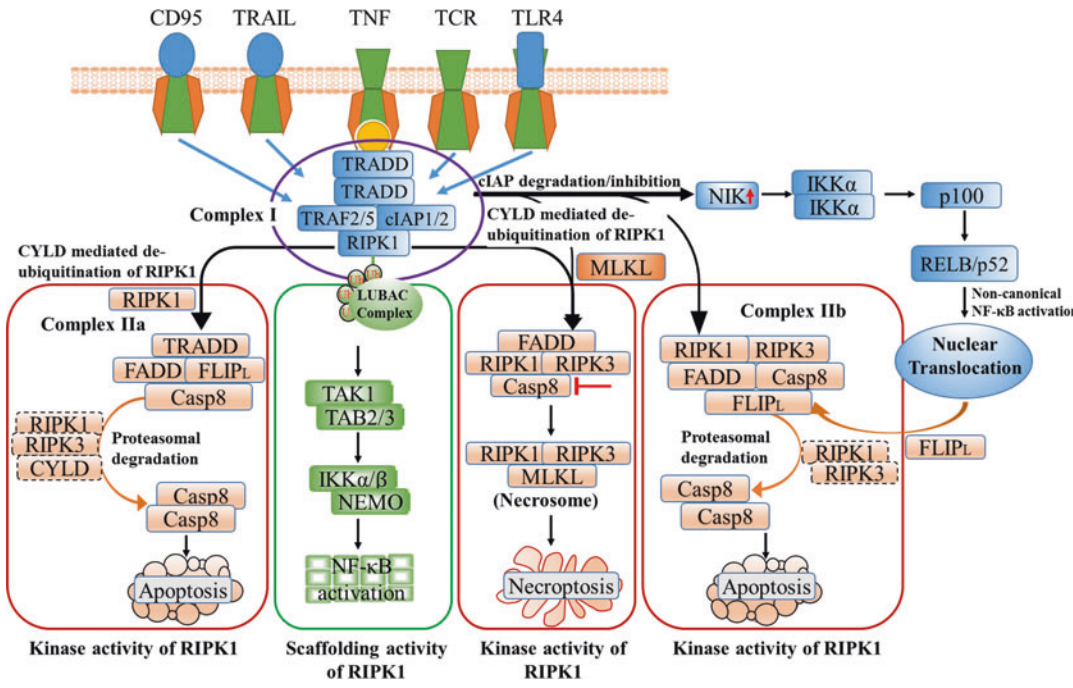


Receptor-Interacting Protein Kinase, Fig. 2 An overview of the structure and function of domains and motifs. Each member possesses different domains and motifs for its proper functioning along with a kinase domain. The possible location of each domain or motif in various members, its structure (or the representative structure in a family member), and the possible function attributed to this structural entity are shown. The Protein Data Bank (PDB) identifiers of various structures are as follows: LRR (2ID5), ROC (2ZEJ), CC (2HMG), KD (4ITJ), ANK repeats (3V2O), CARD (2N7Z), DD (2OF5), and WD (2CE9). Abbreviations. *LRR* leucine-rich repeats, *ROC* Ras of complex proteins, *CC* coiled coil, *KD* kinase domain, *PR* proline-rich, *RHIM* RIP-homotypic interaction motif, *CARD* caspase activation and recruitment domain, *DD* death domain

activation of p38, JNK, and NF-κB signaling (Lee et al. 2004).

In complex II, proteins TRADD, RIPK1, FADD, procaspase 8, and caspase 10 accumulate and form a larger complex that activates the principal initiator of caspase-dependent apoptosis, caspase 8. The switch from complex I to complex II occurs only when NF-κB cannot induce ample antiapoptotic proteins, and this happens due to poor binding of RIPK1, inhibition of various proteins, cell type-specific effects, or an insufficient posttranslational level of RIPK1 (Hsu et al. 1996b). Moreover, caspase 8 inhibition may divert the pathway into yet another route termed *necroptosis:* programmed necrosis. Furthermore, RIPK1 activity can be modulated by RIPK3, which, in TNF-α signaling, forms a heterodimer with RIPK1 through its RHIM motifs and phosphorylates RIPK1, thus causing necrosis.

RIPK1 can be either phosphorylated or ubiquitylated, and the type and intensity of the modification determine its prosurvival or death-related activities. During signaling initiation, RIPK1 is autophosphorylated and ubiquitinated, and the latter change occurs at both sites, i.e., K48 and K63 of ubiquitin. The K63-linked polyubiquitination of RIPK1 mediated by cIAP1 and cIAP2 initiates TNF-induced activation of NF-κB and MAPKs, which promotes expression of prosurvival proteins (Lawrence and Chow 2005;



Receptor-Interacting Protein Kinase, Fig. 3 The role of RIPK1 and RIPK3 in cell survival and cell death. Stimulated TNFR1 recruits TRADD, which facilitates the recruitment of RIPK1, cIAP1 and 2, and TRAF2 or 5. cIAPs then ubiquitinates RIPK1, which thus acts as a scaffold for TAB/TAK and IKK complexes. This assembly activates NF-κB, which is enhanced by the recruitment of LUBAC, which also interacts with ubiquitinated IRAK1. Activation of NF-κB is the prosurvival arm of this complex pathway. When CYLD deubiquitinates RIPK1 thus destabilizing the complex, RIPK1 dissociates from this complex and starts interacting with TRADD, FADD, caspase 8, and $FLIP_L$ (complex IIa). $FLIP_L$ and caspase 8 form a heterodimer that degrades RIPK1, RIPK3, and CYLD to prevent necroptosis. This complex IIa allows for homodimerization of caspase 8, which ultimately results in apoptosis. RIPK1 and RIPK3 can form a heterodimer through the RHIM motif (when caspase 8 is inhibited) and give rise to necrosomes. In this complex, RIPK1 and RIPK3 facilitate auto- and cross-phosphorylation, and later recruitment and phosphorylation of MLKL initiate necroptosis. Several other events can also participate in necroptosis such as ROS production, JNK activation, and translocation of the necrosome to the mitochondrial membrane. In another scenario, the inhibition of cIAPs hinders ubiquitination of IRAK1, thus upregulating NIK and the noncanonical activation of NF-κB. Moreover, in the absence of cIAPs, complex IIb forms (known as the ripoptosome) that consists of RIPK1, RIPK3, FADD, and $FLIP_L$. In this case, RIPK1 and -3 are inactivated by the caspase 8–$FLIP_L$ dimer, which releases caspase 8 homodimer that culminates in apoptosis. However, in case of caspase 8 inhibition, necroptosis is induced. The arrows (↑) and blunted lines (⊤) indicate upregulation and inhibition of the indicated molecules, respectively. The molecules with a dashed line are subject to proteasomal degradation. Abbreviations. *Casp* caspase, *CD* cluster of differentiation, *CIAP* cellular inhibitor of apoptosis protein, *CYLD* cylindromatosis, *FADD* Fas-associated death domain, *$FLIP_L$* FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein (large subunit), *IKK* inhibitor of κB kinase, *LUBAC* linear ubiquitin chain assembly complex, *MLKL* mixed lineage kinase domain-like, *NEMO* NF-κB essential modulator, *NF-κB* nuclear factor κB, *NIK* NF-κB-inducing kinase, *P100* protein 100 kD, *RELB* Rel B family member, *RHIM* RIP-homotypic interaction motif, *RIPK* receptor-interacting protein kinase, *TAB* TAK-binding protein, *TAK* transforming growth factor β-activated kinase 1, *TCR* T-cell receptor, *TNF* tumor necrosis factor, *TRADD* TNF receptor-associated death domain, *TRAF* TNF receptor-associated factor, *TRAIL* TNF-related apoptosis-inducing ligand, *TLR* Toll-like receptor

Wilson et al. 2009). This K63-linked RIPK1 ubiquitination, however, is removed by deubiquitinases, A20, and cylindromatosis. A20 is recruited to the TNF-R1 complex, then hydrolyzes the K63-linked ubiquitin molecules from RIPK1, and promotes ubiquitination of RIPK1 via the K48 linkage, which promotes RIPK1 degradation through the canonical 26S proteasome complex, resulting in termination of NF-κB signaling and potentiation of cell death.

Receptor-Interacting Protein Kinase 2

First identified as a novel RIPK-like enzyme that can execute NF-κB activation and apoptosis via three independent groups, RIPK2 is also known as caspase activation and recruitment domain (CARD)-containing IL-1β-converting enzyme-associated kinase due to the presence of the CARD domain or RIP-like-interacting caspase-like apoptosis-regulatory protein kinase domain (Fig. 1) (Inohara et al. 1998; McCarthy et al. 1998). RIPK2 shares similarities with RIPK1 in that its kinase domain is dispensable for NF-κB activation, and it can interact with TRAFs (TRAF1, −2, −5, −6), cIAP1, and cellular FLIP (cFLIP); and overexpression of RIPK2 can also activate two MAPKs: ERK2 and JNK (Chin et al. 2002). Nevertheless, kinase activity of RIPK2 is required for ERK2 activation as opposed to JNK activation and may activate p38 under certain conditions. Moreover, cytokine production is attenuated during signaling via IL-1 and IL-18 and TLRs, and a dramatic reduction in proliferation is observed during T-cell receptor (TCR) signaling in RIPK2$^{-/-}$ cells (Kobayashi et al. 2002).

RIPK2 is also involved in transmission of a signal from nucleotide-binding oligomerization domain-containing protein 1 (NOD1) and NOD2, which sense the presence of pathogens. RIPK2 interacts with these receptors via CARD-CARD interaction and triggers NF-κB activation and regulates the innate immune response (Nembrini et al. 2009). RIP2's kinase activity is important for protein stability and thus plays a crucial role in the preservation of NOD1- and NOD2-mediated innate immune responses. A knockdown of RIPK2 may downregulate vital proteins involved in epithelial-to-mesenchymal transition, and its polymorphism may be involved in systemic lupus erythematosus (Li et al. 2012; Wu et al. 2012).

X-linked inhibitor of apoptosis protein (XIAP) was shown to interact with RIPK2 through its BIR2 domain and participates in NOD1 and NOD2 signaling, and its deficiency reduces NF-κB activation, pointing to XIAP's involvement in innate immune regulation. TRIP6 (a LIM-domain containing protein) can also functionally associate with RIPK2 and facilitate NF-κB activation in IL-2, TNF, TLR2, and NOD1 pathways (Krieg et al. 2009a). MAPK (MEK4) may also interact with RIPK2 and makes it unavailable for NOD2 signaling, thereby weakening the NF-κB response. Ubiquitination is also important for RIPK2 regulation because ITCH, an E3 ubiquitin ligase, ubiquitinates RIPK2 at K-63 and inhibits the NOD2-induced NF-κB activation. Nonetheless, ITCH E3 ligase activity is responsible for optimal NOD2-induced JNK and p38 activation; this observation is suggestive of an important role in inflammatory signaling (Tao et al. 2009). Apart from these, RIPK2 interacts with caspase 1 through CARD to induce IL-1β maturation as well as Fas-mediated apoptosis by promoting caspase 8 activity.

Furthermore, evidence exists that the RIPK2 protein level is inducible by certain stimuli. For instance, in response to proinflammatory cytokines TNF-α, IL-1β, and interferon γ, the increase in RIPK2 transcription and translation can be detected in endothelial cells (Yin et al. 2010).

Recently, a splice variant of RIPK2 was reported and named RIPK2b, which encodes a truncated kinase domain at the N terminus, while being devoid of the intermediate domain and CARD (Krieg et al. 2009b). This reduced variant cannot trigger NF-κB and MAPK activation, IL-1β secretion, and caspase 8-mediated apoptosis.

Receptor-Interacting Protein Kinase 3

The third member of this family is RIPK3, which contains an N-terminal kinase domain, an RHIM motif, and a unique C-terminal disordered region lacking any well-defined secondary structure. RIPK3 overexpression can activate NF-κB or induce apoptosis depending the cell type, but RIPK3 also interacts with (and phosphorylates) RIPK1, which halts NF-κB activation in the TNF pathway, thus playing a controversial role. On the other hand, RIP3-deficient mice do not show any changes in NF-κB activation induced by TNF-α (Pazdernik et al. 1999).

TNF-α-induced apoptosis has been observed in many cells, and this process can be inhibited

by a caspase inhibitor, benzyloxycarbonyl-Val-AlaAsp(OMe)-fluoromethylketone (zVAD), but in this scenario, TNF-α can still trigger necrosis in some cell lines, and the latter process requires intact kinase activity of RIPK3. This observation has been corroborated by a microarray analysis of the NIH-3T3 cell line, which undergoes apoptosis and necrosis during TNF-α treatment via RIPK1 and RIPK3 expression, respectively (Newton et al. 2004). Apoptosis can be blocked by the inhibitor zVAD, whereas necrosis is unaffected by this treatment. Downregulation of RIPK3 by means of a short hairpin RNA (shRNA) in the presence of zVAD can inhibit necrosis. Further studies confirmed that the presence of the RHIM motif and an intact kinase domain are necessary to drive necrosis (Fig. 3).

RIPK3 is necessary for caspase-independent necrosis as elucidated by genome-wide RNA interference (RNAi) screening of the TNF-α signaling pathway (along with Smac mimetics and zVAD). In this signaling pathway, RIPK3 phosphorylates RIPK1 and mixed lineage kinase-like (MLKL) protein, which promotes formation of the necrosis-specific complex: complex II (necrosome). MLKL later forms an oligomeric structure that travels to the cell membrane and initiates necroptosis (Fig. 3) (Rodriguez et al. 2016).

Reactive oxygen species (ROS) originating in mitochondria determine the initiation of necrosis in a caspase-independent pathway, and this phenomenon has also been observed in N cells, L929 fibroblasts, and other macrophages under the influence of death-inducing stimuli (Zhang et al. 2010). Other than that, RIPK3 can form complexes with many other enzymes such as glycogen phosphorylase (PYGL) in the liver, glutamate dehydrogenase 1 (GLUD1), and glutamate ammonia ligase (GLUL). These enzymes perform a critical function in glucose and amino acid metabolism and in the regulation of energy status.

Receptor-Interacting Protein Kinase 4

RIPK4 was identified in a yeast two-hybrid screen as an interacting partner of protein kinase C (PKC). In mice, the same protein interacts with PKC-β. Further studies based on structural homology and kinase domain characterization revealed its homology with RIP family members, which prompted its reclassification as RIPK4 (Chen et al. 2001). RIPK4 contains a kinase domain at the N terminus, whereas at its C terminus, RIPK4 has ANK repeats linked with an intermediate region (Holland et al. 2002; Meylan et al. 2002).

NF-κB and JNK can be activated during RIPK4 overexpression, and the former process requires IKK-α and IKK-β but not NF-κB essential modulator. The kinase activity of RIPK4 is necessary to activate NF-κB during treatment with phorbol ester and Ca^{2+}-ionophore; however, this activity is dispensable for TNF-α, IL-1β, and NOD1 signaling. A functional link has been suggested between RIPK4 and PKC, because dominant negative-RIPK4-mediated NF-κB inhibition is reversed by coexpression of PKC-β. Bcl-10 and Bimp1, which are mediators of PKC-β signaling, cannot hinder RIPK4-induced NF-κB activation (Muto et al. 2002). RIPK4 has interactions with TRAF family members (TRAF1, −3, or −6), and dominant negative forms of these TRAFs block NF-κB activation (Meylan et al. 2002). Moreover, RIPK4 may be involved in the regulation of Wnt signaling, where it phosphorylates so-called disheveled proteins (Huang et al. 2013).

RIPK4 prosurvival activity can be terminated by cleavage at Asp340 and Asp378 of the intermediate domain by caspases, which in turn enhance apoptosis (Meylan et al. 2002). RIPK4 may have a function in MAPK signaling, because MEKK2 and MEKK3 phosphorylate RIPK4. Inactivation of RIPK4 may reduce the number of peripheral B cells, hamper keratinocytic differentiation, and result in a loss of the cornified layer. Mice lacking RIPK4 are perinatally lethal and have shorter hind limbs and tails as compared to their wild-type counterparts; these phenomena are indicative of abnormal morphogenesis. Finally, the phenotypes of RIPK4-deficient mice are similar to those of mice lacking IKK-α; this observation is suggestive of a common role played by these kinases in epidermal development and homeostasis.

Receptor-Interacting Protein Kinase 5

Sugen kinase 496 (Sgk496) contains a conserved kinase domain similar to that in other family members, though this kinase domain is in the C-terminal region, and two coiled-coil regions are at the N terminus. As the salient feature of this family, RIPK5 overexpression triggers apoptotic cell death (Zha et al. 2004). Moreover, DNA fragmentation has been observed in cells overexpressing RIPK5, and this effect could be halted when the caspase inhibitor crmA is used. Nonetheless, crmA does not affect the RIPK5-induced apoptotic morphological features; this observation points to the dual role of RIPK5 as a caspase-dependent and caspase-independent cell death inducer. Genome-wide studies have established a link of this kinase with congenital urinary tract or kidney aberrations associated with fibroblast growth factor signaling and the platelet count and volume, respectively (Sanna-Cherchi et al. 2013; Shameer et al. 2014). Further studies are needed to delineate its biological functions in detail.

Receptor-Interacting Protein Kinases 6 and 7

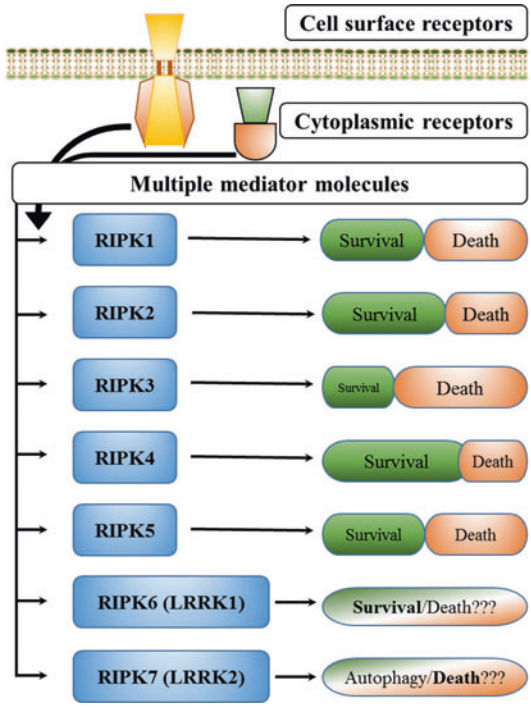
RIPKs 6 and 7 contain leucine-rich repeats in their N-terminal region, and based on these repeats, they are also known as leucine-rich repeat kinases (LRRKs) 1 and 2. Nevertheless, their kinase domains are similar to those of the RIPK family, and for this reason, they have often been classified as RIPK6 and RIPK7. The domain organization of these kinases is unique in the sense that they possess Ros of complex proteins/C terminus of Roc domains (ROC); RIPK6 contains ankyrin repeats, and RIPK7 has WD40 motifs (Fig. 1).

These kinases resemble each other more than other family members in domain organization, hence their similar biological functions (Fig. 2). This observation has been reinforced by studies showing that they play a role in Parkinson's disease (Paisan-Ruiz et al. 2004; Greggio et al. 2007).

The rare variant of RIPK6 has been weakly implicated in Parkinson's disease in a genome-wide association study (Schulte et al. 2014). Furthermore, this family member participates in epidermal growth factor receptor (EGFR) endosomal trafficking during EGFR signaling (Ishikawa et al. 2012). In case of RIPK7, various studies have established a link between RIPK7 mutation and Parkinson's disease, and this relation does not correlate with various populations (Greggio et al. 2007; Haugarvoll et al. 2007). These mutations are distributed throughout RIPK7, and this situation severely compromises the kinase and other domain activities of the protein. Two mutations, G2019S and R1441C/G, are particularly well studied. The former enhances the kinase activity, while the latter impairs the GTPase activity along with disruption of the kinase activity. Moreover, it has been established that all three domains of RIPK7 – the kinase domain, GTPase domain, and WD40 domain – are associated with neurotoxicity (Anand and Braithwaite 2009). Although many research efforts have been made in this regard, further studies are needed to clarify RIPK7's role in Parkinson's disease.

Summary

Since the discovery of RIPKs and their vital role in cell death, many research groups around the world have focused on these proteins and tried to understand the biological functions of various members of this family. These kinases take part in many signaling pathways that greatly influence the inflammatory response, cell survival, and cell death (Fig. 4). The principal shared function of RIPK family members is modulation of the NF-κB pathway and cell death program. Despite the homology in structural features, different RIPK family members participate in diverse biological processes because of their specific domains. RIPK1 is the most intensively studied RIP kinase and is widely known to perform a decisive function in death receptor-initiated intracellular signaling. The biological function of RIPK2 in immune responses and the key role of RIPK3 in necrosis were also discovered during past years. The information regarding the biological role of RIPK6 and RIPK7 is still limited, but their participation in the development of Parkinson's disease has been



Receptor-Interacting Protein Kinase, Fig. 4 An overview of functions of receptor-interacting protein kinases in the cell. RIPKs are crucial for cell survival and cell death pathways. The relative role of each member of this family in cell survival and death is indicated by the box length (*green*/*orange*) and boldface or normal fonts (likely or less likely role in the indicated phenomena, respectively). The roles of RIPK6 and RIPK7 are not well established in either pathway and need further studies. Nonetheless, RIPK6 and RIPK7 are thought to be related to cell survival and cell death (particularly neuronal cell death), respectively

demonstrated. Although the studies on other RIPK family members are currently scarce, it is expected that their functional importance will be revealed in the coming years. Current knowledge about RIPKs suggests that they may serve as therapeutic targets in diseases related to inflammation, ischemia, and neurodegeneration.

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