1. Phylogeny  
   RIPK1 (Receptor-interacting serine/threonine-protein kinase 1) is a widely conserved serine/threonine kinase that belongs to the RIP kinase family, a subgroup within the broader kinome of serine/threonine kinases. Within this family, RIPK1 is distinguished by its modular architecture consisting of an N-terminal kinase domain, an intermediate domain containing a conserved RIP homotypic interaction motif (RHIM), and a C-terminal death domain. These domains enable it to interact with other RIP kinases, most notably RIPK3, to orchestrate programmed cell death processes such as necroptosis. Evolutionary studies indicate that RIPK1 and RIPK3 share a common ancestry with other death domain–containing kinases and have been conserved throughout mammalian evolution, with orthologs identified in mouse, human, and likely other vertebrates, ensuring similar functions in inflammatory and cell death signalling across species (OpenTargets Search: -RIPK1, quarni2016vdrripk1interactionand pages 15-20). Moreover, phylogenetic analyses based on substrate motif selectivity have clustered RIPK1 within the RIPK/WNK subgroup of serine/threonine kinases, emphasizing its evolutionary relationships with kinases that share both catalytic and regulatory features (johnson2023anatlasof pages 4-5).
2. Reaction Catalyzed  
   As a protein kinase, RIPK1 catalyzes the transfer of a phosphate group from ATP to the hydroxyl group of serine or threonine residues on specific substrate proteins. The canonical reaction is:  
     ATP + [protein] (serine/threonine residue) → ADP + [protein]-phospho-(serine/threonine) + H⁺.  
   This catalytic activity facilitates both autophosphorylation and trans-phosphorylation events. Notably, RIPK1 engages in reciprocal phosphorylation with RIPK3 in the necroptotic signaling cascade, although the full spectrum of its direct substrates remains incompletely delineated. One well-characterized substrate is DAB2IP, phosphorylated at Ser-728 in a TNF-α–dependent manner, thereby triggering downstream signalling cascades such as activation of MAP3K5-JNK (Protein Function information, meng2021theregulationof pages 13-15). In addition to phosphorylating other proteins, RIPK1’s autophosphorylation (including critical sites such as S161 and S166) plays a pivotal role in regulating its kinase activity and subsequent signal propagation in cell death pathways (meng2021theregulationof pages 8-9).
3. Cofactor Requirements  
   The kinase activity of RIPK1, like that of many serine/threonine kinases, is dependent on divalent metal ions, with magnesium (Mg²⁺) being the most common cofactor required to coordinate ATP binding and facilitate phosphoryl transfer. Although explicit experimental data on metal ion dependency is not extensively detailed in the current excerpts, it is standard for kinases of this class to utilize Mg²⁺, and no additional non‐metal cofactors have been highlighted for RIPK1 (OpenTargets Search: -RIPK1, mitroshina2023necroptosisincns pages 10-11).
4. Substrate Specificity  
   RIPK1 exhibits substrate specificity that is characterized by its ability to phosphorylate itself (autophosphorylation) and select downstream target proteins implicated in cell death and inflammatory responses. Its physiological substrates include RIPK3, with which it forms a reciprocal phosphorylation relationship essential for necroptosis, and DAB2IP, where phosphorylation at Ser-728 triggers the activation of the MAP3K5–JNK apoptotic cascade (Protein Function information, meng2021theregulationof pages 13-15). Although specific consensus phosphorylation motifs for RIPK1 have not been definitively established in the provided literature, the fact that it phosphorylates serine/threonine residues suggests that it recognizes structural features common to its substrates. The atlas of substrate specificities for human serine/threonine kinases (johnson2023anatlasof pages 4-5) implies that RIPK1, as a member of this kinase family, might share preferences that could be revealed by motif analysis in large-scale phosphoproteomic studies. However, compared to classical substrate motifs found in other kinases, RIPK1’s substrate recognition appears to be closely linked to its recruitment into multiprotein complexes (e.g., the necrosome) and to its autophosphorylation status (meng2021theregulationof pages 8-9).
5. Structure  
   RIPK1 is architecturally organized into three main domains that contribute to its dual roles as both a catalytic enzyme and a scaffold protein.  
   • The N-terminal kinase domain (approximately the first 300 amino acids) harbors the ATP-binding pocket and contains critical autophosphorylation sites (e.g., S161, S166) that are vital for its catalytic activity. This domain is responsible for executing the phosphorylation reaction and regulating subsequent cell death signals (quarni2016vdrripk1interactionand pages 20-25, zhou2024ripk3signalingand pages 1-2).  
   • The intermediate domain, approximately 300 amino acids long, includes the conserved RHIM motif that enables homotypic interactions with RIPK3. This interaction is essential for the formation of the necrosome, a key complex in necroptotic cell death (quarni2016vdrripk1interactionand pages 15-20, meng2021theregulationof pages 3-4).  
   • The C-terminal death domain mediates interactions with other proteins involved in death receptor signalling, such as FADD and TRADD, thereby facilitating the assembly of signaling complexes (TNF-RSC/complex I) that determine cell survival versus death outcomes (quarni2016vdrripk1interactionand pages 29-33, meng2021theregulationof pages 4-5).  
   Recent structural studies, including comparisons of the murine RIPK1 modeled via Robetta with the human kinase domain structure (PDB ID 7FD0), have validated the conservation of the kinase domain structure and highlighted key catalytic residues within the ATP binding pocket, although detailed atomic-level descriptions of all domains are still evolving (malireddi2023wholegenomecrisprscreen pages 16-16).
6. Regulation  
   RIPK1 is subject to complex multilayered regulation through an array of post-translational modifications (PTMs) that modulate its catalytic activity, interaction capabilities, and overall function in cell death and inflammatory signalling pathways.  
   • Phosphorylation: RIPK1 is phosphorylated at multiple serine residues including S6, S14/15, S25, S89, S161, and S166 within the kinase domain and additional sites in the intermediate region (S321, among others). While autophosphorylation (notably at S161 and S166) is a hallmark of its activation, phosphorylation by external kinases such as IKK1/2, TAK1, MK2, and ULK1 exerts inhibitory effects that prevent excessive activation of cell death pathways like necroptosis (meng2021theregulationof pages 7-7, meng2021theregulationof pages 8-9, quarni2016vdrripk1interactionand pages 20-25).  
   • Ubiquitination: The addition of ubiquitin chains, particularly K63-linked and M1-linked chains, on residues such as K376 (or equivalent K377 in human RIPK1) plays a crucial role in scaffolding functions by retaining RIPK1 within the TNF receptor–associated complex (complex I) to promote NF-κB activation and cell survival. Conversely, K48-linked ubiquitination by enzymes like CHIP targets RIPK1 for proteasomal degradation, thereby modulating its levels and activity (meng2021theregulationof pages 9-11, quarni2016vdrripk1interactionand pages 29-33).  
   • Proteolytic Cleavage: Caspase-8–mediated cleavage of RIPK1 acts as a negative regulator by truncating RIPK1 and inhibiting its ability to drive necroptosis (Protein Function information, meng2021theregulationof pages 4-5).  
   • Allosteric Modulation: Binding of small molecule inhibitors like Necrostatin-1 (Nec-1) changes the conformational dynamics of RIPK1, leading to inhibition of its kinase activity and subsequent prevention of necroptosis, illustrating a form of allosteric regulation (mitroshina2023necroptosisincns pages 10-11, oh2024spatiotemporalcontrolof pages 16-17).  
   Together, these PTMs create a regulatory network that fine-tunes RIPK1’s function, balancing its kinase-dependent activities (e.g., initiation of necroptosis) against its scaffold role in promoting NF-κB–mediated cell survival (meng2021theregulationof pages 7-8, quarni2016vdrripk1interactionand pages 20-25).
7. Function  
   RIPK1 plays a central role in modulating cell fate decisions in response to extracellular signals, particularly those initiated by tumor necrosis factor (TNF). Its functions can be broadly categorized into two interrelated aspects:  
   • Kinase-Dependent Functions: The catalytic activity of RIPK1 is critical for the induction of programmed cell death. Upon TNF receptor activation, when apoptotic signalling is compromised (for example, by caspase-8 inhibition), activated RIPK1 promotes the assembly of a death-inducing complex (complex IIb) with RIPK3 and MLKL, ultimately triggering necroptosis. Similarly, its kinase activity contributes to the formation of complex IIa (comprising RIPK1, FADD, and caspase-8) to drive apoptosis under certain conditions. These kinase-dependent processes ensure that cells can be eliminated in a controlled manner, which is particularly important during immune responses and tissue homeostasis (Protein Function information, meng2021theregulationof pages 1-2, mitroshina2023necroptosisincns pages 10-11).  
   • Scaffold Functions: Independent of its kinase activity, RIPK1 acts as a scaffold protein when recruited to the TNF receptor 1 signaling complex (complex I). In this context, it facilitates the activation of the NF-κB pathway, promoting the transcription of pro-survival and pro-inflammatory genes such as interleukin-6 (IL6). This activity is crucial not only for cell survival but also for mounting effective inflammatory responses (Protein Function information, meng2021theregulationof pages 4-5, OpenTargets Search: -RIPK1).  
   In development, RIPK1 is essential for preventing aberrant activation of caspase-8–dependent apoptosis, thus ensuring normal embryogenesis by limiting interactions that would otherwise lead to excessive cell death (Protein Function information, quarni2016vdrripk1interactionand pages 29-33).  
   Furthermore, by phosphorylating substrates like DAB2IP, RIPK1 can also activate apoptotic cascades such as the MAP3K5-JNK pathway, linking it to additional layers of cell fate regulation (Protein Function information, meng2021theregulationof pages 13-13).  
   Collectively, RIPK1 integrates signals from death receptors and innate immune pathways, dictating whether a cell undergoes apoptosis, necroptosis, or survives via NF-κB–mediated transcriptional programs (OpenTargets Search: -RIPK1, zhou2024ripk3signalingand pages 1-2).
8. Other Comments  
   RIPK1 is emerging as both a promising drug target and a biomarker for several diseases. Genetic studies and pathway analyses have strongly linked RIPK1 with inborn errors of immunity, neurodegenerative diseases, severe acute respiratory syndrome, autoinflammatory syndromes, and immunodeficiency disorders (OpenTargets Search: -RIPK1). The development of small molecule inhibitors, such as Necrostatin-1 and other clinical candidates like DNL788, underscores the therapeutic potential of targeting RIPK1 kinase activity to modulate necroptosis and inflammatory responses (mitroshina2023necroptosisincns pages 11-12, oh2024spatiotemporalcontrolof pages 16-17). Moreover, because of its dual role in regulating apoptosis and necroptosis and acting as a scaffold for NF-κB activation, dysregulation of RIPK1 can have profound implications in cancer, autoimmune disorders, and inflammatory diseases. Recent research continues to focus on mapping the complete repertoire of RIPK1’s post-translational modifications and uncovering how these modifications coordinate with cellular signaling networks (meng2021theregulationof pages 7-8, quarni2016vdrripk1interactionand pages 25-29). Notable mutations affecting key phosphorylation and ubiquitination sites have not been detailed in the available excerpts; however, the emphasis on these modification sites suggests that even subtle alterations could critically impact RIPK1 activity. Exploration of the interplay between RIPK1 and its interacting partners, such as RIPK3, FADD, and TRADD, remains an active area of investigation with potential for yielding novel therapeutic insights (quarni2016vdrripk1interactionand pages 96-99, OpenTargets Search: -RIPK1).
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