**1. Phylogeny:**  
Receptor‐interacting serine/threonine‐protein kinase 1 (RIPK1), encoded by the gene RIPK1 and also known as Cell death protein RIP or Receptor‐interacting protein 1, is a member of the serine/threonine kinase family that falls within the receptor‐interacting protein kinase (RIPK) subfamily. Orthologs of RIPK1 have been identified in a wide range of vertebrate species, indicating a highly conserved role in regulating programmed cell death and inflammatory responses throughout evolution (lv2022comparativeandevolutionary pages 1-3, amin2018regulationofa pages 1-2). Evolutionary analyses based on the protein kinase complement of the human genome have placed RIPK1 among kinases that share a conserved catalytic domain and modular architecture, and these studies have traced its origin back to early metazoans, with subsequent divergence leading to its current specialized role in cell survival and cell death signaling pathways (Manning2002Science, Manning2002Trends). Within the human kinome, phylogenetic studies reveal that RIPK1 is closely related to other members of the RIP kinase family, most notably RIPK3, with which it cooperates during necroptotic signaling, while it is more distantly related to other death domain–containing kinases involved in apoptosis and inflammatory pathways (lv2022comparativeandevolutionary pages 1-3).

**2. Reaction Catalyzed:**  
RIPK1 functions as a serine/threonine kinase and catalyzes the phosphorylation of protein substrates. The chemical reaction it catalyzes can be summarized by the equation:  
ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺.  
This reaction describes the transfer of the gamma-phosphate group from ATP to the hydroxyl group of serine or threonine residues present in its substrate proteins, which is a hallmark of serine/threonine kinase activity (chen2022advancesinripk1 pages 1-2, johnson2023anatlasof pages 1-2).

**3. Cofactor Requirements:**  
The enzymatic activity of RIPK1 is dependent on the presence of divalent metal ions. In particular, Mg²⁺ is required to properly coordinate the binding of ATP within the catalytic site and to facilitate the phosphoryl transfer to the substrate. This requirement is consistent with the general mechanism of action observed for serine/threonine kinases, whereby these metal ions stabilize the negative charges of ATP’s phosphate groups during catalysis (ku2014developmentandapplication pages 1-8).

**4. Substrate Specificity:**  
RIPK1 exhibits substrate specificity in a manner characteristic of serine/threonine kinases. Recent studies have examined the substrate preferences of many kinases, and comprehensive substrate specificity atlases have provided insights into the phosphorylation motifs recognized by RIPK1 (johnson2023anatlasof pages 10-11). For example, RIPK1 engages in reciprocal phosphorylation with RIPK3 during necroptosis, a process wherein both kinases activate one another via mutual phosphorylation events. In addition, RIPK1 phosphorylates DAB2IP at the Ser-728 residue in a tumor necrosis factor-alpha (TNFα)–dependent manner, thereby triggering the downstream activation of the MAP3K5–JNK apoptotic cascade (amin2018regulationofa pages 1-2, chen2022advancesinripk1 pages 1-2). Although a single consensus substrate motif for RIPK1 has not been definitively established, its phosphorylation of target serine and threonine residues generally depends on the local amino acid sequence context, which provides an optimal environment for catalytic recognition and efficient phosphoryl transfer (johnson2023anatlasof pages 10-11, chen2022advancesinripk1 pages 1-2).

**5. Structure:**  
RIPK1 is a multidomain protein whose structure supports its dual functionality as both an active kinase and a scaffolding molecule. The protein is organized into distinct functional regions. At its N-terminus, RIPK1 harbors a serine/threonine kinase domain that is responsible for its catalytic activity. This kinase domain features several conserved elements common to eukaryotic kinases, including an ATP-binding cleft, a conserved activation loop that is critical for its regulatory phosphorylation events, a hydrophobic spine that aligns key catalytic residues, and a regulatory C-helix that contributes to the stabilization of its active conformation (johnson2023anatlasof pages 4-4, ku2014developmentandapplication pages 1-8).

Immediately following the kinase domain, RIPK1 contains an intermediate region that includes the RIP homotypic interaction motif (RHIM). The RHIM is essential for mediating homotypic interactions with other RHIM-containing proteins, most notably RIPK3. This interaction is critical for the formation of necrosomes, which are complexes that drive the necroptotic cell death pathway. Studies based on AlphaFold models and experimental observations indicate that the RHIM facilitates amyloid-like assembly, thereby enabling the propagation of necroptotic signaling (karimbayli2024insightsintothe pages 15-17, karimbayli2024insightsintothe pages 18-19).

At the C-terminal end of the protein, RIPK1 features a death domain (DD). This domain is responsible for mediating protein–protein interactions that are crucial for the recruitment of RIPK1 into receptor complexes such as the TNF receptor signaling complex I (TNF-RSC). The death domain allows RIPK1 to function as a scaffold in assembling multi-protein complexes that help activate the canonical NF-κB pathway, thereby promoting cell survival and the transcription of pro-inflammatory genes (johnson2023anatlasof pages 21-23, martens2020inhibitorstargetingripk1ripk3 pages 4-6). Thus, the overall domain organization of RIPK1—with the N-terminal kinase domain, the intermediary RHIM, and the C-terminal death domain—underpins its bifunctional role in cell signaling.

**6. Regulation:**  
RIPK1 is subject to complex regulation by a variety of post-translational modifications that dictate its activity and its decision to promote cell survival or cell death. Phosphorylation is a central regulatory mechanism for RIPK1. The protein can undergo autophosphorylation as well as phosphorylation by partnering kinases such as IKK1/2, TAK1, MK2, and TBK1. Such phosphorylation events typically occur on key serine/threonine residues and usually exert an inhibitory effect on RIPK1’s kinase activity, thus preventing unwanted activation of downstream cell death pathways (johnson2023anatlasof pages 18-20, liu2021regulatorymechanismsof pages 1-2). For instance, TBK1 and IKKε have been shown to phosphorylate RIPK1 on specific residues, suppressing its kinase activity and thereby mitigating TNF-induced cell death (lafont2018tbk1andikkε pages 15-16).

In addition to phosphorylation, ubiquitination is a critical regulatory modification affecting RIPK1. Within the TNF receptor signaling complex I, RIPK1 is modified by K63-linked as well as linear (M1-linked) ubiquitin chains. These ubiquitin modifications, catalyzed by E3 ubiquitin ligases including cIAP1/2 and the linear ubiquitin chain assembly complex (LUBAC), serve to stabilize RIPK1’s scaffold function, facilitating the recruitment of downstream signaling molecules that activate NF-κB and MAPK pathways (martens2020inhibitorstargetingripk1ripk3 pages 2-4). Conversely, deubiquitinating enzymes such as CYLD and A20 remove these ubiquitin moieties, which shifts RIPK1 from a pro-survival scaffold state toward an active kinase conformation that is able to participate in the assembly of death-inducing complexes (liu2021regulatorymechanismsof pages 2-2, martens2020inhibitorstargetingripk1ripk3 pages 2-4).

Furthermore, proteolytic cleavage by caspase-8 represents an important regulatory circuit. Caspase-8 cleaves RIPK1, thereby limiting its kinase activity and preventing excessive formation of death-inducing complexes that lead to apoptosis or necroptosis. This proteolytic event acts as a negative feedback mechanism that tightly regulates the balance between cell survival and cell death responses (liu2021regulatorymechanismsof pages 2-2, martens2020inhibitorstargetingripk1ripk3 pages 2-4). The interplay among these modifications—phosphorylation, ubiquitination, and caspase-mediated cleavage—determines the functional state of RIPK1 and ultimately influences whether the cell engages in pro-survival or pro-death signaling.

**7. Function:**  
RIPK1 is a pivotal regulator of cell fate downstream of death receptors, notably tumor necrosis factor receptor 1 (TNFR1). In settings where TNF binds to TNFR1, RIPK1 is recruited to the TNF receptor signaling complex I (TNF-RSC), where it performs an essential scaffolding function. Through this function, RIPK1 facilitates the activation of the canonical NF-κB pathway, resulting in the transcription of pro-survival and pro-inflammatory cytokines such as interleukin-6 (IL-6) (johnson2023anatlasof pages 12-18). The scaffold function of RIPK1 ensures cell survival by promoting NF-κB and MAPK signaling cascades.

Under conditions where its kinase activity is activated, RIPK1 plays a central role in the commitment to cell death. When RIPK1’s kinase function is unleashed—often as a consequence of the removal or inhibition of its ubiquitination and inhibitory phosphorylation—it promotes the assembly of two distinct death-inducing complexes. In complex IIa, RIPK1 interacts with FADD and caspase-8 leading to apoptosis through caspase activation. Conversely, in complex IIb (commonly referred to as the necrosome), RIPK1 forms a functional complex with RIPK3 and MLKL that drives necroptosis, a programmed form of necrosis (amin2018regulationofa pages 1-2, martens2020inhibitorstargetingripk1ripk3 pages 1-2). Notably, RIPK1 also restricts RIPK3-dependent necroptosis under normal physiological conditions by recruiting FADD and caspase-8, with caspase-8 cleaving RIPK1 to attenuate the necroptotic signal (liu2021regulatorymechanismsof pages 1-2, li2019humanripk1deficiency pages 1-1).

In addition to its roles in cell death, RIPK1 is crucial for modulating inflammatory responses. Its activity influences the production of pro-inflammatory cytokines and the activation of transcription factors such as NF-κB, thereby linking death receptor signaling to inflammatory gene expression. The reciprocal phosphorylation between RIPK1 and RIPK3 forms a feed-forward loop that amplifies signaling required for both apoptotic and necroptotic cell death pathways, ensuring that the appropriate death modality is executed in response to cellular stresses (chen2022advancesinripk1 pages 22-23, johnson2023anatlasof pages 18-20). RIPK1 is also known to phosphorylate DAB2IP at Ser-728, which subsequently triggers the MAP3K5-JNK apoptotic cascade, thereby establishing a connection between TNF-induced kinase signaling and the activation of stress-responsive apoptotic pathways (amin2018regulationofa pages 1-2, johnson2023anatlasof pages 10-11).

Expression of RIPK1 is relatively widespread, with elevated levels typically found in tissues that are exposed to high levels of inflammatory or stress signals, including various components of the immune system and barrier tissues. During embryonic development, RIPK1 is indispensable; it prevents excessive cell death by inhibiting both caspase-8–mediated apoptosis and RIPK3-mediated necroptosis, a function that is critical for proper tissue morphogenesis and immune regulation (liu2023ripk1inthe pages 2-3, li2019humanripk1deficiency pages 1-1).

**8. Other Comments:**  
Due to its central role in orchestrating cell death and inflammatory responses, RIPK1 has emerged as an attractive therapeutic target, particularly for conditions characterized by aberrant inflammation and tissue degeneration. Several small-molecule inhibitors have been developed that selectively target the kinase activity of RIPK1 without disrupting its essential scaffolding functions that promote cell survival through NF-κB activation. Notable among these are necrostatin-1 (Nec-1) and its improved analogs, as well as compounds such as GSK2982772, which have advanced into clinical trials for inflammatory diseases including rheumatoid arthritis, ulcerative colitis, and psoriasis (martens2020inhibitorstargetingripk1ripk3 pages 6-8, degterev2019targetingripk1for pages 1-2). In addition, comprehensive substrate specificity studies have provided further insights into the enzymology of RIPK1 with respect to its serine/threonine kinase activity, and recent work addressing the intrinsic substrate specificity of kinases—both serine/threonine and tyrosine—has underscored the dual-specificity features that may pertain to related kinases (johnson2023anatlasof pages 1-2, Yaron-Barir2024).

Mutations in RIPK1 that affect either its catalytic function or its ability to properly engage in scaffolding have been linked to severe human disorders. For instance, biallelic loss-of-function mutations in RIPK1 have been associated with combined immunodeficiency and inflammatory bowel diseases, highlighting its critical role in regulating immune responses and maintaining intestinal epithelial homeostasis (li2019humanripk1deficiency pages 1-1). Such disease-associated mutations underline the importance of precisely regulating RIPK1 activity to prevent pathological inflammation and cell death. Ongoing research continues to clarify the broader therapeutic window and the potential risks associated with targeting RIPK1 in various clinical settings (meng2021theregulationof pages 7-7).

Finally, the dual functionality of RIPK1 as both a kinase and a scaffolding protein necessitates a careful balance in drug design; selective inhibition of its kinase activity must be achieved without compromising the cell survival functions mediated by its scaffold properties. This complexity has fostered the development of next-generation inhibitors that aim to achieve this balance, making RIPK1 one of the most intensively studied targets in the field of inflammatory and cell death-related diseases (martens2020inhibitorstargetingripk1ripk3 pages 6-8, degterev2019targetingripk1for pages 1-2).

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