1. Phylogeny  
   RIPK1 is a member of the receptor‐interacting protein (RIP) kinase family, a subgroup of serine/threonine protein kinases that are evolutionarily conserved among metazoans. Orthologs of RIPK1 can be identified in all vertebrate species, and more broadly in eukaryotes, indicating that the kinase emerged early in evolution along with the other members of the TNF receptor-associated kinases. RIPK1 is closely related to other members of the RIP kinase family (e.g., RIPK2 and RIPK3) that share structural features such as the kinase domain and interaction motifs, although the family has diversified evolutionarily to adopt distinct functional roles such as mediating necroptosis versus NF-κB activation (engin2021proteinkinasemediateddecision pages 15-17, bailey2016necroptosisanovel pages 33-36).
2. Reaction Catalyzed  
   RIPK1 catalyzes the transfer of a phosphate group from ATP to a serine or threonine residue on its substrate protein. The overall chemical reaction can be represented as:  
   ATP + [substrate protein]-(L-serine or L-threonine) → ADP + [substrate protein]-(L-serine/threonine)-phosphate + H⁺ (johnson2023anatlasof pages 1-2).
3. Cofactor Requirements  
   The kinase activity of RIPK1, as is typical for serine-threonine kinases, requires Mg²⁺ as a critical cofactor. Mg²⁺ ions stabilize the negative charges on ATP, facilitating proper binding and catalysis at the active site of RIPK1 (kugler2024impactofprotein pages 27-28).
4. Substrate Specificity  
   Global profiling of human serine/threonine kinases has revealed that RIPK1 falls within a specific substrate motif group. Although the precise consensus substrate motif for RIPK1 is not explicitly detailed in every report, large-scale peptide library screens indicate that RIP kinases, including RIPK1, are grouped with kinases showing motifs characterized by basic residues flanking the phospho-acceptor site on both the N-terminal and the C-terminal sides, with a dominant preference for an aromatic residue at the +3 position relative to the phosphorylated serine or threonine (johnson2023anatlasof pages 2-3). These findings are derived from position-specific scoring matrix (PSSM) analyses that cluster kinases with shared motif preferences, thus suggesting that RIPK1’s substrate specificity is defined by a unique pattern of positively charged and aromatic residues in the vicinity of the phosphorylation site (johnson2023anatlasof pages 9-10).
5. Structure  
   RIPK1 is a ~74 kDa protein that exhibits a modular structural organization comprised of three distinct domains. The N-terminal region contains the kinase domain that is responsible for its serine/threonine phosphorylation activity; this domain displays typical kinase features such as the conserved ATP-binding cleft, an activation loop (T-loop), a hydrophobic spine, and a C-helix critical for positioning catalytic residues. Following the kinase domain, RIPK1 possesses an intermediate domain that harbors a RIP homotypic interaction motif (RHIM), which is essential for mediating homotypic interactions with other RHIM-containing proteins such as RIPK3 and ZBP1. The C-terminal region of RIPK1 contains a death domain (DD) that facilitates interactions with death receptors and adaptor proteins (e.g., TRADD, FADD) during the assembly of TNF receptor-signaling complexes (yeo2018regulationofnuclearfactor pages 35-39, engin2021proteinkinasemediateddecision pages 9-12). In several structural studies and crystallographic data (for example, the published structure in PDB: 6HHO referenced in related discussions), the kinase domain of RIPK1 demonstrates the canonical bilobal architecture common to protein kinases, with a smaller N-lobe usually made up of β-sheets and a larger C-lobe dominated by α-helices. Unique structural features of RIPK1 include the presence of regulatory phosphorylation sites within the activation loop and conformational changes upon binding to inhibitors that have been characterized using protein–small molecule interaction studies (kugler2024impactofprotein pages 9-11, yeo2018regulationofnuclearfactor pages 39-43).
6. Regulation  
   RIPK1 is subject to multifaceted regulatory mechanisms that modulate its function in cell death and inflammatory signaling pathways. Post-translational modifications are a hallmark of RIPK1 regulation. Phosphorylation events, such as autophosphorylation and phosphorylation by other kinases (notably by MK2 within the TNF receptor 1 complex), play central roles; for example, phosphorylation at serine 166 is frequently used as a readout of RIPK1 catalytic activation (bailey2016necroptosisanovel pages 113-116, engin2021proteinkinasemediateddecision pages 30-31). Conversely, phosphorylation at other sites modulates its kinase-dependent pro-death activity. Ubiquitination is another key layer of regulation. Upon engagement of TNF receptors, RIPK1 is recruited to the TNFR1 signaling complex (complex I) where it is polyubiquitinated with K63- and M1-linked ubiquitin chains by enzymes including the E3 ubiquitin ligases cIAP1/2 and the linear ubiquitin chain assembly complex (LUBAC). Ubiquitination serves to scaffold the recruitment of downstream kinases such as TAK1 and the IKK complex that drive NF-κB activation, thereby promoting cell survival (dostert2019thetnffamily pages 5-6, engin2021proteinkinasemediateddecision pages 34-35). When deubiquitinated by enzymes like CYLD, RIPK1 is released from the membrane complex and can participate in the formation of cytosolic death-inducing complexes. Additionally, RIPK1 is proteolytically cleaved by caspase-8 in certain contexts, which limits its ability to propagate necroptotic signaling and thereby acts as a regulatory checkpoint for apoptosis versus necroptosis (samir2020thepanoptosomea pages 3-4, engin2021proteinkinasemediateddecision pages 24-26).
7. Function  
   RIPK1 plays a dual role depending on its mode of activity. As a serine/threonine kinase, its enzyme activity is essential for orchestrating programmed cell death modalities, specifically apoptosis and necroptosis. Upon activation by stimuli such as TNF-α, RIPK1 becomes part of the TNF receptor 1 signaling complex where its kinase activity facilitates the assembly of distinct death-inducing complexes. In complex IIa, RIPK1 engages FADD and caspase-8 to drive Caspase-8-mediated apoptosis. Alternatively, under circumstances where caspase-8 activity is impaired, RIPK1 partners with RIPK3 and MLKL to form the necrosome (complex IIb), thereby promoting necroptosis—a form of regulated necrosis (bailey2016necroptosisanovel pages 33-36, engin2021proteinkinasemediateddecision pages 26-28). Independently of its kinase activity, RIPK1 can function as a scaffold that facilitates the recruitment of downstream signaling molecules such as TRAF2 and adaptor proteins, leading to the activation of the canonical NF-κB pathway and transcriptional production of pro-inflammatory cytokines including interleukin-6 (IL-6) (bailey2016necroptosisanovel pages 113-116, engin2021proteinkinasemediateddecision pages 30-31). This scaffold function is particularly important during TNF receptor-mediated cell survival signaling, as it inhibits aberrant caspase-8 activation and preserves cell viability during embryonic development (engin2021proteinkinasemediateddecision pages 15-17, yeo2018regulationofnuclearfactor pages 35-39). Furthermore, RIPK1 is implicated in additional signaling pathways, for example promoting ZBP1-induced NF-κB activation in response to DNA damage, and phosphorylating downstream proteins such as RIPK3 and DAB2IP, thereby linking inflammatory and apoptotic cascades (Information section, PubMed:15310755; engin2021proteinkinasemediateddecision pages 28-30).
8. Other Comments  
   Pharmacological inhibition of RIPK1 kinase activity has been explored for therapeutic intervention in various pathological conditions including inflammatory diseases, ischemia-reperfusion injury, and certain cancers. Inhibitors such as Necrostatin-1 (Nec-1) and its derivatives (e.g., Nec-1s, GSK547) have been employed experimentally to block RIPK1-dependent necroptosis and attenuate inflammation (kugler2024impactofprotein pages 11-12, mifflin2020receptorinteractingproteinkinase pages 2-3). Additionally, mutations that affect RIPK1 cleavage by caspase-8 have been associated with dominant autoinflammatory phenotypes, underscoring the clinical relevance of maintaining balanced RIPK1 activity. Aberrant RIPK1 function, whether due to dysregulation of its kinase activity or disruptions in its scaffold function, has been implicated in diseases characterized by excessive cell death or chronic inflammation, including immune disorders and neurodegenerative conditions (samir2020thepanoptosomea pages 11-12, zare2022theroleof pages 62-65). The dual nature of RIPK1’s functions—kinase-dependent promotion of apoptosis and necroptosis versus kinase-independent support of NF-κB signaling—makes it a unique and critical regulatory node in cell fate decisions (Information section; engin2021proteinkinasemediateddecision pages 31-33).
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