1. Phylogeny  
   RIPK2, also known as CARDIAK, RICK, or RIP2, belongs to the receptor‐interacting protein kinase family. Within the human kinome, RIPK2 is classified as one of the five genuine RIP kinases (RIPK1–RIPK5), a grouping that is supported by comparative genomic and phylogenetic analyses. Orthologs of RIPK2 are widely conserved across vertebrate species, and its kinase domain shows strong evolutionary conservation relative to other members of the RIPK family. In phylogenetic trees, RIPK2 clusters with kinases such as RIPK1 and RIPK3, and its evolutionary relationships trace back to early gene duplication events that marked the divergence of vertebrate immune signaling components (lv2022comparativeandevolutionary pages 4-6, urwylerrosselet2023functionsofthe pages 1-3). The conservation of the kinase domain, combined with the presence of a C-terminal CARD domain unique to RIPK2 among the RIP kinases, underscores its evolutionary specialization for mediating innate immune responses through specific protein–protein interactions. This group of kinases is derived from the core set of kinases that emerged in early eukaryotic evolution and have since undergone diversification to take on distinct roles in cell signaling.
2. Reaction Catalyzed  
   RIPK2 catalyzes phosphorylation reactions that involve the transfer of a phosphate group from ATP to the hydroxyl (-OH) group of target amino acid residues. The general chemical reaction can be represented as:  
    ATP + [protein]-(L-serine, L-threonine, or L-tyrosine) → ADP + [protein]-(phosphorylated serine/threonine/tyrosine) + H⁺  
   In the case of RIPK2, the reaction is principally involved in autophosphorylation, wherein the enzyme phosphorylates residues within its own activation loop and other regulatory regions, such as serine 176 and tyrosine 474 among additional sites. This catalytic activity relies on the intrinsic kinase domain of RIPK2 and is central to its function as a signaling mediator in pathways that modulate inflammatory responses (pellegrini2017structuresofthe pages 1-2, zare2022theroleof pages 35-39).
3. Cofactor Requirements  
   The catalytic activity of RIPK2, similar to many protein kinases, depends on the presence of divalent metal ions. Specifically, Mg²⁺ acts as an essential cofactor, coordinating the phosphate groups of ATP within the active site of the kinase domain. This requirement is typical of serine/threonine and tyrosine kinases, where Mg²⁺ stabilizes the negative charges of the phosphate moieties during the phosphoryl transfer reaction (pham2023recentadvancesin pages 1-3, pellegrini2017structuresofthe pages 1-2).
4. Substrate Specificity  
   RIPK2 displays dual-specificity kinase activity; it is capable of phosphorylating serine, threonine, and tyrosine residues. While no definitive consensus substrate motif has been universally ascribed to RIPK2 based solely on published substrate atlases, its autophosphorylation events indicate a substrate specificity that allows modification of multiple residues within its activation loop and possibly on interacting protein substrates. Experimental evidence has identified serine 176 and tyrosine 474 as prominent phospho-acceptor sites, among others, suggesting that the substrate recognition of RIPK2 may be influenced by the surrounding amino acid context in these regions. Overall, RIPK2 appears to preferentially autophosphorylate within its kinase domain activation segment, providing a regulatory mechanism rather than acting on an invariant linear motif found in conventional substrate proteins (topal2021ripk2nodsto pages 6-11, zare2022theroleof pages 35-39).
5. Structure  
   RIPK2 is characterized by a distinct multi-domain architecture that underpins its dual roles as an enzyme and scaffolding protein. The protein comprises an N-terminal kinase domain (approximately residues 1–310) that adopts a typical bilobal structure consisting of an N-lobe and a C-lobe. The kinase domain houses key catalytic features such as the glycine-rich loop, the DFG motif within the activation loop, conserved catalytic residues (including a critical lysine involved in ATP binding and an aspartate crucial for catalysis), and regulatory elements like the hydrophobic spine and the C-helix. High-resolution crystallographic studies and cryo-electron microscopy data have revealed that, upon activation, RIPK2 undergoes conformational rearrangements that align the catalytic motifs optimally for ATP binding and phosphotransfer (pellegrini2017structuresofthe pages 11-13, chirieleison2016syntheticbiologyreveals pages 9-11).

Immediately following the kinase domain is an intermediate, less structurally defined region, whose flexibility may contribute to the dynamic regulation of RIPK2’s catalytic activity and protein–protein interactions. The C-terminal CARD (Caspase Recruitment Domain) is responsible for mediating homotypic CARD–CARD interactions with NOD1 and NOD2 receptors. These interactions are critical for the formation of higher-order signaling platforms, known as RIPK2 filaments or “RIPosomes”, which facilitate downstream signaling events. Structural insights have also uncovered a regulatory hydrophobic pocket within the kinase domain, notably involving residues such as K209 and I212, which is essential for binding to the E3 ubiquitin ligase XIAP. This pocket modulates ubiquitination and, consequently, the signaling competency of RIPK2 (boyle2014insightsintothe pages 5-6, heim2020aregulatoryinterface pages 23-28, lethier2022structuralanalysisshows pages 27-29).

Dimerization of the kinase domain has been observed in both active and inhibitor-bound crystal structures, suggesting that RIPK2 forms symmetrical or asymmetrical dimers that are necessary for autophosphorylation via trans mechanisms. Such dimer formations position the activation loops of the monomers in proximity, thereby facilitating efficient phosphate transfer from ATP to specific residues (pellegrini2017structuresofthe pages 7-9, lv2022comparativeandevolutionary pages 9-10).

1. Regulation  
   RIPK2 is subject to complex regulation involving multiple post-translational modifications, which modulate both its kinase activity and scaffolding functions. Autophosphorylation is a central regulatory event in which RIPK2 phosphorylates key residues within its kinase domain, such as serine 176 and tyrosine 474, leading to conformational changes that promote its active state. In addition to autophosphorylation, RIPK2 is regulated by ubiquitination. Lysine 209, among other lysine residues, is a critical site for Lys-63-linked polyubiquitination, which serves as a docking signal for downstream effectors and facilitates the assembly of signaling complexes. The E3 ubiquitin ligases XIAP, BIRC2, and BIRC3 mediate this ubiquitination, whereas the LUBAC complex adds Met-1-linked polyubiquitin chains that further enhance signal propagation and facilitate NF-κB activation. These modifications are reversible, and deubiquitinases have been implicated in counteracting the ubiquitination events, thereby preventing prolonged or excessive signal activation (hein2019nodsignalingand pages 5-6, heim2020aregulatoryinterface pages 9-12, topal2021ripk2nodsto pages 6-11).

Other regulatory mechanisms include conformational modulation via dimerization and the potential influence of phosphorylation on regions that interact with other regulatory proteins. Although kinase activity per se is not strictly essential for downstream NOD signaling—as underscored by studies where kinase-dead mutants retain scaffolding capabilities—the catalytic activity of RIPK2 contributes to its stability and to the fine-tuning of ubiquitin-dependent signaling events. Thus, the integrated effects of autophosphorylation, ubiquitination, dimerization, and possibly additional regulatory inputs determine the overall signaling output mediated by RIPK2 (boyle2014insightsintothe pages 6-7, shen2025currentadvanceson pages 2-3, zare2022theroleof pages 35-39).

1. Function  
   RIPK2 functions as a key mediator in innate and adaptive immune responses by serving as a critical effector downstream of the intracellular pattern recognition receptors NOD1 and NOD2. Upon detection of bacterial peptidoglycan fragments, NOD1 and NOD2 oligomerize and recruit RIPK2 through homotypic CARD–CARD interactions. This recruitment triggers RIPK2 activation via dimerization and autophosphorylation, which in turn leads to the polyubiquitination of RIPK2 by E3 ligases such as XIAP. The polyubiquitin chains on RIPK2 serve as scaffolds to recruit and activate downstream signaling complexes, culminating in the activation of key transcription factors such as NF-κB and the MAPK pathways. Through these signaling cascades, RIPK2 orchestrates the transcriptional activation of a wide array of pro-inflammatory cytokines, chemokines, and other immune response genes (boyle2014insightsintothe pages 5-6, pham2023recentadvancesin pages 1-3, topal2021ripk2nodsto pages 6-11).

In addition to its role in innate immunity, RIPK2 is involved in adaptive immune modulation. It participates in T-cell receptor signaling, contributing to the phosphorylation of substrates such as BCL10, which is linked to NF-κB activation in adaptive immune cells. Moreover, RIPK2 has been implicated in signaling pathways that regulate cell survival and apoptosis and is thought to contribute to processes such as autophagy through its interactions with diverse regulatory proteins. Despite evidence that the kinase catalytic activity of RIPK2 may be dispensable for certain signaling outputs, the enzyme’s autophosphorylation and ubiquitination events serve as crucial regulators of its activity and cell signaling functions (boyle2014insightsintothe pages 5-6, chirieleison2016syntheticbiologyreveals pages 1-2, zare2022theroleof pages 28-32).

RIPK2 is widely expressed, with significant levels in immune effector cells such as dendritic cells, macrophages, and various epithelial cell types. Its expression and functional activity are particularly important in tissues exposed to microbial pathogens as well as in pathological conditions such as inflammatory bowel disease, certain cancers, and autoimmune disorders. The ability of RIPK2 to integrate signals from NOD receptors to downstream effectors places it at a critical juncture in the control of both inflammatory responses and cellular homeostasis (pham2023recentadvancesin pages 1-3, zare2022theroleofa pages 28-32).

1. Other Comments  
   RIPK2 is the subject of intense pharmacological investigation given its pivotal role in mediating inflammatory signaling cascades. Small-molecule inhibitors targeting the ATP-binding pocket of the kinase domain have been developed, and these compounds typically exert their effects by disrupting the interaction between RIPK2 and its E3 ubiquitin ligase partners, particularly XIAP. Such inhibitors not only block the autophosphorylation activity of RIPK2 but also impair the assembly of downstream ubiquitin-dependent signaling complexes. This therapeutic approach holds promise in treating a range of inflammatory conditions, including inflammatory bowel disease, asthma, and potentially certain cancers where aberrant NOD signaling is implicated (tignoaranjuez2014invivoinhibition pages 12-13, pham2023recentadvancesin pages 4-6).

Additionally, mutations and polymorphisms in components of the NOD-RIPK2-XIAP signaling axis have been linked to various pathological states. For example, genetic alterations in NOD2 are strong risk factors for Crohn’s disease, and deficiencies in XIAP have been associated with very early onset inflammatory bowel disease. Although mutational analyses of RIPK2 itself are less common, the regulatory interplay between its kinase activity, autophosphorylation state, and post-translational modification by ubiquitin underscores its potential as a clinical biomarker and therapeutic target in diseases characterized by dysregulated inflammatory responses (topal2021ripk2nodsto pages 6-11, zare2022theroleof pages 62-65).

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