## Phylogeny

Receptor-interacting protein kinase 1 (RIPK1) is a conserved serine/threonine kinase present in all examined mammals and with orthologues in vertebrates and lower eukaryotes. It clusters with RIPK2, RIPK3 and RIPK4 within the RIP kinase family, reflecting a shared catalytic domain coupled to distinct interaction modules (Dara, 2018; Della Torre et al., 2021; Annibaldi & Meier, 2018).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + O-phospho-L-seryl/threonyl-[protein] + H⁺ (Xie et al., 2013).

## Cofactor Requirements

Mg²⁺ is required for ATP binding and kinase activity (Mifflin et al., 2020).

## Substrate Specificity

Verified substrates include RIPK1 itself (autophosphorylation), RIPK3 during necroptosis, and DAB2IP at Ser-728 in a TNF-α-dependent manner. Overall, RIPK1 phosphorylates serine/threonine residues within proteins that mediate cell-death and inflammatory signalling (Annibaldi & Meier, 2018; Chen et al., 2022; Li & Yuan, 2023).

## Structure

• 671-amino-acid protein composed of:  
– N-terminal kinase domain with catalytic Lys45; adopts an inactive DLG-out conformation when bound by necrostatins (Xie et al., 2013; Chen et al., 2022).  
– Central intermediate domain containing a RIP homotypic interaction motif (RHIM) and a key ubiquitination site, Lys377 (Annibaldi & Meier, 2018; Dara, 2018).  
– C-terminal death domain that interacts with FADD, TRADD and TNFR1 (Dara, 2018; Della Torre et al., 2021).  
This modular organisation supports both catalytic and scaffolding roles (Chen et al., 2022).

## Regulation

• Ubiquitination: cIAP1/2 and LUBAC attach K63-linked or linear (M1) chains, retaining RIPK1 in TNFR1 complex-I; CYLD, A20 and Cezanne remove these chains to enable death-complex formation (Annibaldi & Meier, 2018; Witt & Vucic, 2017; Ju et al., 2022).  
• Phosphorylation: IKK1/2, MK2, TAK1 and TBK1 phosphorylate Ser166, Ser161 and sites near S320/S335 (mouse S321/S336), suppressing kinase activity (Annibaldi & Meier, 2018; Ju et al., 2022).  
• Proteolysis: Caspase-8 cleaves RIPK1 at Asp324, limiting necroptosis (Dara, 2018; Mifflin et al., 2020).  
These modifications create an early TNF-induced cell-death checkpoint (Annibaldi & Meier, 2018).

## Function

As a scaffold, RIPK1 promotes NF-κB activation and expression of anti-apoptotic and inflammatory genes (e.g., cFLIP, Bcl-2, IL-6). Upon de-ubiquitination and kinase activation it forms:  
• Complex-IIa with FADD, caspase-8 and cFLIP to drive apoptosis, or  
• The necrosome/complex-IIb with RIPK3 and MLKL to trigger necroptosis.  
RIPK1 additionally phosphorylates DAB2IP to initiate the MAP3K5–JNK apoptotic cascade. These activities regulate embryogenesis, tissue homeostasis and responses to infection, DNA damage and other stresses (Annibaldi & Meier, 2018; Feoktistova & Leverkus, 2015; Mifflin et al., 2020).

## Inhibitors

Potent small-molecule inhibitors such as Necrostatin-1 and GSK2982772 are in clinical investigation for inflammatory disorders (Annibaldi & Meier, 2018; Martens et al., 2020).

## Other Comments

Dysregulated RIPK1 signalling is implicated in cancer, autoimmune and neurodegenerative diseases, and ischemia-reperfusion injury. The balance between ubiquitination and phosphorylation dictates whether cells undergo NF-κB-mediated survival or apoptosis/necroptosis, making RIPK1 an attractive therapeutic target (Ju et al., 2022; Li & Yuan, 2023).

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