## Phylogeny

Receptor-interacting serine/threonine-protein kinase 4 (RIPK4) belongs to the receptor-interacting protein kinase family (RIPK1-RIPK5) and retains the conserved N-terminal kinase domain that defines the group (Buyse, n.d.; Urwyler-Rösselet et al., 2023). Comparative phylogenetic analyses place RIPK4 (and RIPK5) on a distinct branch characterized by an eleven-ankyrin-repeat C-terminal region that is absent from RIPK1, RIPK2 and RIPK3 (Buyse, n.d.; Lv et al., 2022). Orthologues are present throughout vertebrates, consistent with an evolutionarily conserved role in epithelial and skin biology (Urwyler-Rösselet et al., 2023; Lv et al., 2022).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + H⁺ + protein-O-phospho-Ser/Thr (Huang et al., 2013).

## Cofactor Requirements

Mg²⁺ is required for ATP coordination and catalysis (Cuny & Degterev, 2021).

## Substrate Specificity

RIPK4 phosphorylates serine/threonine residues on several keratinocyte proteins. Documented substrates include interferon regulatory factor 6 (Ser413, Ser424) and plakophilin-1, events that foster epidermal differentiation and cell adhesion (Buyse, n.d.; Kwa et al., 2014). Although a strict consensus motif is not defined, the kinase displays general Ser/Thr selectivity typical of the family (Chirieleison, 2016).

## Structure

The protein is modular: (i) an N-terminal catalytic kinase domain containing canonical catalytic motifs and an activation loop; (ii) a short intermediate segment with putative regulatory sites; and (iii) a C-terminal domain harbouring eleven ankyrin repeats that mediate protein-protein interactions (Chirieleison, 2016; Cuny & Degterev, 2021). Full activation requires kinase-domain dimerisation, as demonstrated by structural and biochemical studies (Chirieleison, 2016). High-confidence AlphaFold models and crystallographic data of the kinase region support this architecture (Chirieleison, 2016).

## Regulation

• Autophosphorylation and dimerisation are essential for maximal catalytic activity (Chirieleison, 2016; Cuny & Degterev, 2021).  
• SCF^β-TrCP-mediated ubiquitination targets phosphorylated serines 379/382/383, controlling protein stability and cortical actin organisation (Tanghe et al., 2018).  
• Caspase-8 cleavage under apoptotic conditions disables NF-κB activation and shifts signalling towards cell death (Torre et al., 2021).

## Function

RIPK4 is a key regulator of keratinocyte differentiation and epidermal homeostasis. As a TP63 transcriptional target, it phosphorylates substrates such as PKP1 and IRF6 to promote cell adhesion and stratification (Buyse, n.d.; Kwa et al., 2014). RIPK4 also activates NF-κB and can modulate Wnt/β-catenin signalling via Dishevelled phosphorylation (Huang et al., 2013). Expression is highest in epithelial tissues, particularly skin; loss in mice causes epidermal defects and perinatal lethality (Urwyler-Rösselet et al., 2023). Tumour-suppressive roles are reported in cutaneous squamous-cell carcinoma, where reduced RIPK4 correlates with tumour aggressiveness (Wolnicka-Głubisz et al., 2021).

## Inhibitors

The BRAF inhibitors vemurafenib and dabrafenib lower RIPK4 protein levels in melanoma cells, indicating an off-target down-regulatory effect (Madej et al., 2023).

## Other Comments

Loss-of-function mutations in RIPK4 cause autosomal-recessive popliteal pterygium syndrome and Bartsocas-Papas syndrome (Kalay et al., 2012). RIPK4 interacts with keratin-14, potentially influencing filament turnover, without affecting heterodimer assembly (Sümer et al., 2019).

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