## Phylogeny

Orthologous kinases are present from yeast to mammals, e.g. S. cerevisiae Fus3 and Slt2/Mpk1, D. melanogaster rolled, C. elegans mpk-1, X. laevis Erk2 and M. musculus Mapk1, indicating deep evolutionary conservation of the ERK branch (Goshen-Lago et al., 2016; Kushnir et al., 2020; Yashar et al., 1993). Within the kinome, ERK2 belongs to the CMGC group → MAP kinase family → ERK sub-family (Roskoski, 2012; Coulombe & Meloche, 2007). ERK2 shares ~84 % sequence identity with its paralogue ERK1, and the two form a clade distinct from p38, JNK and ERK5 families (Roskoski, 2012).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-Ser/Thr-phosphate (Roskoski, 2012).

## Cofactor Requirements

Catalysis requires divalent cations, preferably Mg²⁺; Mn²⁺ can substitute (Roskoski, 2012).

## Substrate Specificity

• Minimal consensus: Pro-X-Ser/Thr-Pro with an obligatory +1 Pro; Pro at –2 and Lys/Arg at –3 enhance efficiency (Roskoski, 2012).  
• Kinome-wide peptide profiling confirms enrichment for +1 Pro and –3 Lys/Arg in ERK2 substrates (Johnson et al., 2023).  
• High-affinity recognition is strengthened by substrate D-sites ((R/K)₂₋₃-X₂₋₆-Φ-X-Φ) and F-sites (Φ-X-Φ-P) that dock to ERK2 D- and F-recruitment surfaces (Roskoski, 2012).  
• Proximity-induced catalysis via distal docking domains has been demonstrated with ETS-family substrates (Rainey et al., 2005).

## Structure

ERK2 displays the canonical bilobal protein-kinase fold: a five-stranded β-sheet and αC-helix form the N-lobe, while an α-helical C-lobe houses the activation segment and substrate interface (Roskoski, 2012). Key motifs include VAIK (Lys54–Glu71 ion pair), HRD, and DFG, the latter coordinating Mg²⁺/ATP (Roskoski, 2012). Dual phosphorylation of Thr183 and Tyr185 in the activation loop aligns the hydrophobic spine and closes the catalytic cleft (Roskoski, 2012).

Additional features:  
• Common docking (CD) domain centred on Asp318/Asp321 for partner binding; charge-reversal mutations impair stability and catalysis (Novak et al., 2023).  
• 31-residue C-terminal extension (helices 1L14/2L14) modulates conformational transitions (Roskoski, 2012).  
• Hinge-region dynamics underpin allostery; mutations here alter global motions (Taylor et al., 2019).  
• Representative coordinates: inactive 2OJG, active 2ERK, MEK-bound 6OPL, and AlphaFold AF-P28482-F1 (Goshen-Lago et al., 2016; Impact of ERK2 missense variants, 2021).  
• Compared with p38 MAPK, ERK2 exhibits a wider inter-lobe angle and distinct activation-loop topology (Wang et al., 1997).

## Regulation

• Activation by MEK1/2-mediated dual phosphorylation of the TEY motif increases catalytic efficiency ~5 × 10⁴-fold (Roskoski, 2012; Novak et al., 2023).  
• Termination by dual-specificity phosphatases (DUSPs) (Roskoski, 2012).  
• Acetylation of Lys72 (and Lys48, Lys203, Lys344) by CBP/p300 reduces activity; HDAC6-mediated deacetylation restores it (Regulation of ERK by HDAC6, 2017; Wu et al., 2018).  
• Ubiquitination has been reported but sites and E3 ligases are unassigned (Regulation of ERK by HDAC6, 2017).  
• Allosteric modulation: CD-site (e.g., D321N, E322K) or hinge mutations perturb inter-lobe coupling and substrate turnover (Novak et al., 2023; Taylor et al., 2019).

## Function

ERK2 is ubiquitously expressed, with highest levels in placenta, heart and brain (Aouadi et al., 2006; Muslin, 2008). Genetic ablation in mice causes embryonic lethality due to placental and mesodermal defects (Aouadi et al., 2006).

Signalling context: Ras-GTP → RAF → MEK1/2 → ERK2, assembled by scaffolds KSR1/2 and MP1 (Coulombe & Meloche, 2007; Roskoski, 2012). Phosphorylated ERK2 targets nuclear factors (e.g., c-Fos, Elk-1) and cytoplasmic effectors (RSK1/2, cytoskeletal regulators) to control proliferation, differentiation, adhesion and survival (Roskoski, 2012; Impact of ERK2 missense variants, 2021). ERK2 also participates in KIT/KITLG and other RTK pathways (Roskoski, 2012).

## Inhibitors

Ulixertinib (BVD-523) is a reversible ATP-competitive inhibitor (K\_i ≈ 0.04 nM) effective in BRAF- or MEK-inhibitor-resistant cancer models (Germann et al., 2017). SCH772984 is a mixed type I/II inhibitor that occupies the ATP site and an adjacent allosteric pocket (Germann et al., 2017). Additional ATP-competitive compounds include FR180204, AZD0364 and KO-947 (Roskoski, 2012; Germann et al., 2017).

## Other Comments

Persistent ERK activation driven by oncogenic RAS or BRAF occurs in ~30 % of human cancers, making ERK2 a validated drug target (Germann et al., 2017; Roskoski, 2012). Gain-of-function ERK2 mutations in the CD domain or hinge region enhance signalling and can confer drug resistance (Novak et al., 2023; Taylor et al., 2019). Hyperactivation of the pathway also underlies developmental disorders collectively termed RASopathies (Roskoski, 2012).

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