## Phylogeny

MAPK1 (ERK2) is a conventional mitogen-activated protein kinase within the CMGC group. Orthologs occur throughout eukaryotes—including metazoans, fungi and plants—highlighting deep evolutionary conservation (Kültz, 1998; Ligterink & Hirt, 2001). In vertebrates, ERK2 and its paralog ERK1 (MAPK3) arose from an ancestral duplication; knockout studies show that ERK2 is frequently essential for embryogenesis and cell viability, indicating non-redundant functions (Cargnello & Roux, 2011; Buscà et al., 2016).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Cargnello & Roux, 2011)

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Kültz, 1998).

## Substrate Specificity

ERK2 is a proline-directed Ser/Thr kinase that prefers motifs in which the phosphorylated Ser/Thr is immediately followed by Pro ([S/T]-P). High-affinity recognition is further refined through docking interactions between substrate D-domains or DEF motifs and complementary grooves on the kinase (Cargnello & Roux, 2011; Roux & Blenis, 2004; Martin-Vega & Cobb, 2023).

## Structure

The protein adopts the canonical bilobed kinase fold: a β-strand-rich N-lobe containing the glycine-rich loop and an α-helical C-lobe bearing the catalytic loop. The activation segment harbours the conserved TEY motif whose dual phosphorylation is obligatory for full activation. A C-terminal common docking (CD) domain mediates binding to substrates, activators and phosphatases. Additional structural elements, including the hydrophobic spine and properly positioned C-helix, stabilise the active state (Kültz, 1998; Meister et al., 2013; Martin-Vega & Cobb, 2023).

## Regulation

Activation is achieved by MEK1/2-mediated dual phosphorylation of the TEY motif, which induces conformational changes that align catalytic residues. Activity is attenuated by dual-specificity phosphatases (e.g., DUSP6) that remove both phosphates. Scaffold proteins govern spatial and temporal signalling by localising ERK2 with upstream kinases or substrates, while feedback phosphorylation of pathway components fine-tunes signal strength (Cargnello & Roux, 2011; Buscà et al., 2016; Theodosiou & Ashworth, 2002).

## Function

ERK2 is a central node of the MAPK/ERK cascade and is ubiquitously expressed. It phosphorylates numerous targets, including transcription factors (ATF2, ELK1, FOS), cytoskeletal proteins, regulators of apoptosis and translational machinery, thereby influencing cell growth, adhesion, survival and differentiation. ERK2 also controls cell-cycle progression during meiosis and mitosis and modulates post-mitotic functions in differentiated cells. Signalling initiated by receptor tyrosine kinases such as KIT prominently engages ERK2 (Cargnello & Roux, 2011; Dickinson & Keyse, 2006; Martin-Vega & Cobb, 2023).

## Inhibitors

Clinical MEK inhibitors (e.g., PD184352, PD0325901) indirectly suppress ERK2 activity, and efforts to develop direct ERK2 inhibitors are ongoing (Roux & Blenis, 2004; Buscà et al., 2016).

## Other Comments

Constitutive ERK2 activation—often due to mutations in upstream Ras or Raf—or mutations in docking interfaces is linked to diverse cancers and developmental disorders. More than 160 substrates have been catalogued, underscoring both the breadth of ERK2 signalling and its potential as a therapeutic target (Roux & Blenis, 2004; Buscà et al., 2016).

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