## Phylogeny

Mitogen-activated protein kinase 3 (MAPK3; ERK1) is a member of the CMGC group of serine/threonine protein kinases and, within it, the conventional MAPK ERK subfamily (Manning et al., 2002; Coulombe & Meloche, 2007; Cargnello & Roux, 2011; Lavoie et al., 2020). Orthologues are present throughout eukaryotes, including in Drosophila and zebrafish (Cargnello & Roux, 2011; Martín-Vega & Cobb, 2023). In bony vertebrates, MAPK3/ERK1 and MAPK1/ERK2 arose from a gene-duplication event and now share ~84 % sequence identity and considerable functional redundancy (Pan et al., 2022; Martín-Vega & Cobb, 2023).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Roskoski, 2012; Cargnello & Roux, 2011).

## Cofactor Requirements

Requires Mg²⁺ coordinated by the conserved DFG motif in the kinase domain (Cargnello & Roux, 2011; Roskoski, 2012; Barbosa et al., 2021).

## Substrate Specificity

MAPK3 is a proline-directed kinase that preferentially phosphorylates Ser/Thr followed by Pro (consensus PX(S/T)P). Peptide-library profiling reveals additional preferences for basic residues (Arg/Lys) at –2 and –3 positions and strong exclusion of certain charged residues at other sites (Johnson et al., 2023). Docking interactions via the D- and F-recruitment sites on the kinase further increase specificity toward substrates bearing complementary docking motifs (Cargnello & Roux, 2011; Barbosa et al., 2021).

## Structure

The enzyme adopts the conserved bilobal protein-kinase fold: an N-terminal β-sheet/αC-helix lobe containing the glycine-rich P-loop and a predominantly α-helical C-lobe. The activation loop extends from the DFG to the APE motif and includes the regulatory T-E-Y sequence that must be dually phosphorylated for activity (Pan et al., 2022). Additional structural features include a MAPK insert and docking grooves for substrates/regulators (Lavoie et al., 2020; Martín-Vega & Cobb, 2023). High-resolution structures of the closely related ERK2 (e.g., PDB 2ERK) serve as templates for ERK1 (Martín-Vega & Cobb, 2023).

## Regulation

• Activation: Dual phosphorylation of Thr202 and Tyr204 in the T-E-Y motif by MEK1/2 increases catalytic activity up to 50 000-fold (Barbosa et al., 2021; Pan et al., 2022).  
• Deactivation: Dual-specificity phosphatases (e.g., DUSP5, DUSP6) remove the activating phosphates (Cargnello & Roux, 2011; Martín-Vega & Cobb, 2023).  
• Feedback: ERK1 can phosphorylate and inhibit MEK1, creating negative feedback (Martín-Vega & Cobb, 2023).  
• Localization: Nuclear–cytoplasmic shuttling is controlled by interactions with PEA-15, importin-7, and nucleoporins (Pan et al., 2022; Martín-Vega & Cobb, 2023).

## Function

MAPK3 operates in the RAS–RAF–MEK–ERK cascade, a master regulator of cell proliferation, differentiation, survival, metabolism, adhesion, and migration (Roskoski, 2012; Lavoie et al., 2020). It is widely expressed across tissues. Upon activation, ERK1 translocates to multiple subcellular compartments. In the nucleus it phosphorylates transcription factors such as Elk1, c-Fos, Myc and Ets to drive immediate-early gene expression; in the cytoplasm it targets kinases RSK/MSK and the focal-adhesion protein paxillin (Barbosa et al., 2021). Scaffold proteins KSR1/2 and IQGAP1 help organize pathway components (Roskoski, 2012).

## Inhibitors

Small-molecule ERK1/2 inhibitors include ATP-competitive, covalent, irreversible, and allosteric agents (Pan et al., 2022; Roskoski, 2012). Non-ATP-competitive compounds that block the common docking/ED cleft disrupt substrate binding; “compound 22” binds this site on ERK2 with Kd ≈ 5 µM and selectively blocks substrate phosphorylation (Unknown Authors, 2011; Pan et al., 2022).

## Other Comments

Hyperactivation of the MAPK/ERK pathway—most often due to oncogenic RAS or BRAF mutations rather than mutations in MAPK3 itself—is implicated in roughly one-third of human cancers and promotes tumour growth, invasion, angiogenesis and metastasis (Roskoski, 2012; Cargnello & Roux, 2011; Barbosa et al., 2021). Dysregulation is also linked to diabetes, cardiac hypertrophy, inflammatory disorders and brain injury (Roskoski, 2012). Constitutively active ERK variants possess oncogenic potential (Martín-Vega & Cobb, 2023).

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