## Phylogeny

MAPK6 (also called ERK3) is an atypical member of the mitogen-activated protein kinase (MAPK) family positioned in the CMGC super-group together with CDKs, GSK3 and CLK kinases (Widmann et al., 1999; Coulombe & Meloche, 2007). It forms a distinct ERK3/ERK4 sub-family that diverged from conventional MAPKs (ERK1/2, p38, JNK, ERK5) after a gene-duplication event (Coulombe & Meloche, 2007; Schumacher et al., 2004). Orthologues are restricted to vertebrates—identified in human, mouse, rat, Xenopus and zebrafish with a predicted gene in chicken—and are absent from invertebrates and plants (Krens et al., 2006; Coulombe & Meloche, 2007). Although the kinase domain shares ~42–50 % amino-acid identity with ERK1, unique sequence motifs confirm its atypical status (Bogoyevitch & Court, 2004).

## Reaction Catalyzed

ATP + protein-L-serine/threonine ⇌ ADP + protein-L-serine/threonine phosphate (Chen et al., 2001).

## Cofactor Requirements

Catalytic activity requires a divalent cation, primarily Mg²⁺ (Chen et al., 2001).

## Substrate Specificity

High-throughput peptide profiling included MAPK6, but a definitive consensus motif was not reported; detailed amino-acid preferences therefore remain undetermined (Johnson et al., 2023).

## Structure

The human protein comprises 721 amino acids (~100 kDa) and contains:  
• an N-terminal kinase domain;  
• a conserved C34 docking region;  
• an unusually long, flexible C-terminal tail (≈178–400 aa) predicted to be intrinsically disordered and absent from the crystal structure (PDB 6YKY) (Elkhadragy et al., 2024; Dahm et al., 2025).

Distinct structural features include an activation-segment Ser-Glu-Gly motif with a single phospho-acceptor (Ser189) instead of the canonical Thr-X-Tyr, and a Ser-Pro-Arg triad in sub-domain VIII that replaces the usual Ala-Pro-Glu (Coulombe & Meloche, 2007; Unknown authors, 2015). Atypical positioning of the C-helix and hydrophobic spine is also noted (Dahm et al., 2025).

## Regulation

• Ser189 phosphorylation: occurs constitutively through cis-autophosphorylation and trans-phosphorylation by PAK1/2/3; PKC-η may also target this residue (Déléris et al., 2011; Elkhadragy et al., 2024).  
• Dephosphorylation: mediated by Cdc14A/B and DUSP2 (Elkhadragy et al., 2024).  
• C-terminal phosphorylation by Cyclin B–CDK1 enhances stability (Elkhadragy et al., 2024).  
• Protein turnover: ERK3 has a short half-life and is degraded via ubiquitin-proteasome pathways; N-terminal ubiquitylation is reversed by the deubiquitinase USP20 (Bogoyevitch & Court, 2004; Elkhadragy et al., 2024).  
• Additional stabilisation: hydroxylation by PHD3 and binding to its substrate MK5 (Elkhadragy et al., 2024).  
• Subcellular trafficking: a constitutively nuclear protein that can shuttle to cytoplasm, plasma membrane and Golgi/ER through CRM1-dependent export (Cheng et al., 1996; Elkhadragy et al., 2024).

## Function

Expression is ubiquitous in vertebrates, highest in adult skeletal muscle and brain, and elevated during early mouse embryogenesis (Bogoyevitch & Court, 2004; Elkhadragy et al., 2024).

Known substrates/partners  
• MAPK-activated protein kinase-5 (MK5): phosphorylated on Thr182; MK5 reciprocally phosphorylates and stabilises ERK3 (Schumacher et al., 2004; Elkhadragy et al., 2024).  
• Steroid receptor co-activator-3 (SRC-3) at Ser857 (Unknown authors, 2015).  
• Interacting proteins include Rab31, Cdc42, Rac1, CDK1, Cdc14A/B and transcription factor HNF4G (Elkhadragy et al., 2024).

Physiological roles encompass fetal growth, lung maturation, neuronal morphogenesis, T-cell development, angiogenesis, inflammation and metabolism (Unknown authors, 2015; Elkhadragy et al., 2024).

## Inhibitors

Only a few research tool inhibitors have been reported; no widely validated selective inhibitors are currently available (Elkhadragy et al., 2024).

## Other Comments

ERK3 displays context-dependent pro- and anti-tumour functions, influencing proliferation, migration, invasion and drug resistance. Cancer-associated mutations (e.g., L290P/V) enhance cytosolic localisation and cell motility (Elkhadragy et al., 2024). Additional links to autoimmune uveoretinitis, obesity and ischaemia/reperfusion injury have been described (Elkhadragy et al., 2024).

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