## Phylogeny

MAPK6 (ERK3) forms an atypical mitogen-activated protein kinase subfamily that is restricted to vertebrates (Kültz, 1998, pp. 5–9, 13–14). It shares ~73 % amino-acid identity in the kinase domain with ERK4, consistent with a vertebrate-specific gene duplication that generated a distinct ERK3/ERK4 branch within the MAPK family (Coulombe & Meloche, 2007, pp. 2–4). Unlike conventional MAPKs that possess the dual-phosphorylation TXY motif, ERK3 contains a single phosphoacceptor SEG motif, highlighting its evolutionary divergence (Kültz, 1998, pp. 1–2). Large-scale kinome analyses place ERK3 among atypical MAPKs that evolved from an ancestral eukaryotic kinase but subsequently adopted specialized functions (Cargnello & Roux, 2011, p. 1).

## Reaction Catalyzed

ATP + [protein] → ADP + [protein]-phosphorylated + H⁺  
(Coulombe & Meloche, 2007, pp. 1–2)

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Coulombe & Meloche, 2007, pp. 1–2).

## Substrate Specificity

ERK3 shows narrow substrate selectivity relative to classical MAPKs. Verified substrates include microtubule-associated protein 2 (MAP2) and MAPK-activated protein kinase 5 (MK5). Activation involves phosphorylation of ERK3 at Ser189 within the SEG motif and reciprocal phosphorylation of MK5 in its activation loop (Elkhadragy et al., 2024, pp. 2–4; Seternes et al., 2004, pp. 11–12). Consensus recognition sequences remain undefined, but available data indicate preference for Ser/Thr residues in non-canonical contexts (Cargnello & Roux, 2011, pp. 8–9).

## Structure

The 721-residue ERK3 contains:  
• N-terminal kinase domain (≈45–50 % identity to conventional ERKs) harbouring the atypical SEG activation motif (Ser189) (Coulombe & Meloche, 2007, pp. 2–4).  
• Conserved C34 domain adjacent to the kinase domain, shared with ERK4 and implicated in protein–protein interactions (Elkhadragy et al., 2024, pp. 1–2).  
• Extended C-terminal tail enriched in phosphorylation sites that influence activity and turnover (Schumacher et al., 2004, pp. 1–2).  
Key catalytic features include a catalytic loop, hydrophobic regulatory spine, conserved C-helix and an atypical SRP motif replacing the canonical APE in sub-domain VIII (Schröder et al., 2020, pp. 1–3, 10–12). Crystal structures and homology models underpin these observations.

## Regulation

• Activation-loop phosphorylation at Ser189 via autophosphorylation or group I PAKs is essential for kinase activity (Elkhadragy et al., 2024, pp. 15–16).  
• ERK3 forms a complex with MK5; the partners phosphorylate each other, modulating their respective activities (Elkhadragy et al., 2024, pp. 2–4; Seternes et al., 2004, pp. 11–12).  
• Protein stability is controlled by ubiquitin-proteasome–mediated degradation (Schumacher et al., 2004, pp. 1–2; Coulombe & Meloche, 2007, pp. 10–11).  
• Nuclear export signals enable dynamic nucleocytoplasmic shuttling (Schumacher et al., 2004, pp. 1–2).

## Function

ERK3 phosphorylates MAP2 and activates MK5, impacting cytoskeletal organization and cell-cycle entry (Elkhadragy et al., 2024, pp. 2–4). Reciprocal ERK3–MK5 signalling may interface with additional pathways governing cell survival and growth (Schröder et al., 2020, pp. 10–12). Expression is ubiquitous, with higher levels in brain, skeletal muscle and gastrointestinal tract (Coulombe & Meloche, 2007, pp. 1–2). Germ-line deletion studies show non-essential roles under baseline conditions but suggest involvement in differentiation and proliferation processes (Ronkina et al., 2019, pp. 20–23).

## Inhibitors

Structure-guided screens have identified reversible and irreversible small-molecule inhibitors that occupy the ATP-binding site, yet none are clinically validated or ERK3-specific (Schröder et al., 2020, pp. 1–3, 10–12).

## Other Comments

ERK3’s atypical regulatory mechanisms and rapid turnover distinguish it from classical MAPKs, making it an emerging therapeutic target in proliferative disorders and cancer (Elkhadragy et al., 2024, pp. 15–16). Its SEG motif and extended C-terminal tail offer unique opportunities for selective inhibitor design (Schröder et al., 2020, pp. 10–12).

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