Phylogeny  
MAPK4 (ERK4) is an atypical MAP kinase belonging to the CMGC group, ERK3/ERK4 sub-family. Clear orthologues exist in vertebrates (Homo sapiens, Mus musculus, Rattus norvegicus, Gallus gallus, Xenopus laevis, Danio rerio), whereas invertebrate and plant genomes lack bona-fide ERK4, indicating a vertebrate-specific duplication that generated ERK3 and ERK4 (Coulombe & Meloche, 2007; Åberg et al., 2006). ERK4 shares 73 % identity within the kinase domain with ERK3 but only ~45 % with classical ERK1/2, underscoring its divergent evolution (Coulombe & Meloche, 2007).

Reaction Catalyzed  
ATP + protein-Ser/Thr ⇌ ADP + protein-O-phospho-Ser/Thr (Kant et al., 2006).

Cofactor Requirements  
Mg²⁺ is required for activity; no alternative divalent cations have been reported (Boudghene-Stambouli et al., 2022).

Substrate Specificity  
Validated substrates are MAPK-activated protein kinase-5 (MK5; Thr182) and microtubule-associated protein-2 (MAP2). Large-scale analysis has not revealed a dedicated ERK4 consensus motif (Åberg et al., 2009; Kant et al., 2006; Coulombe & Meloche, 2007).

Structure  
• N-terminal bilobal kinase domain (residues 1–320).  
• C-terminal extension containing the classical docking (CD) site and FRIEDE motif for MK5 interaction (Åberg et al., 2009).  
• Activation loop carries an atypical S-E-G motif; Ser186 is the sole phospho-acceptor (Perander et al., 2008).  
• Subdomain VIII shows an S-P-R triad replacing the canonical A-P-E, introducing a unique Arg that alters C-lobe electrostatics (Coulombe & Meloche, 2007).  
• Homology models built on ERK3 (PDB 2I6L) retain the VAIK, HRD and DFG catalytic motifs, a correct C-helix, and an intact hydrophobic spine; Ser186 phosphorylation is predicted to stabilise the active conformation (Déléris et al., 2008; Boudghene-Stambouli et al., 2022).  
No experimental ERK4 crystal structure is yet available (Coulombe & Meloche, 2007).

Regulation  
Phosphorylation  
– Group I PAK1-3 kinases phosphorylate Ser186, a prerequisite for catalytic activity and high-affinity MK5 binding (Déléris et al., 2011).  
– MK5 can in turn phosphorylate ERK4, generating a mobility-shifted form; sites are unidentified (Kant et al., 2006).  
– Ser386 is phosphorylated in cells, but its role is unknown (Déléris et al., 2008).

Dephosphorylation  
DUSP2 binds the ERK4 CD/KIM motif and removes the Ser186 phosphate, dampening downstream MK5 activation (Perander et al., 2017).

Protein stability & chaperoning  
ERK4 is an Hsp90 client; Hsp90 inhibition destabilises ERK4 and reduces MK5 phosphorylation (Identification of novel roles…, 2015). Unlike ERK3, ERK4 is intrinsically stable and is not rapidly degraded by the proteasome under basal conditions (Åberg et al., 2006).

Subcellular localisation  
Predominantly cytoplasmic; CRM1-dependent export limits nuclear ERK4, and leptomycin B induces nuclear accumulation (Åberg et al., 2006).

Function  
Expression  
Highest mRNA levels are detected in brain, with substantial expression in colon, eye, heart, kidney, lung, ovary, pancreas, placenta, prostate and skin (Coulombe & Meloche, 2007).

Signalling context  
Upstream: Rac1/Cdc42-activated PAK1-3 phosphorylate and activate ERK4 (Déléris et al., 2011).  
Downstream: Activated ERK4 phosphorylates MK5, enforcing MK5 cytoplasmic localisation and stimulating its activity toward cytoskeletal targets (Åberg et al., 2006). ERK4 also enhances PDK1-AKT/mTOR signalling, promoting oncogenic growth programmes (Boudghene-Stambouli et al., 2022; Han et al., 2023). Cellular roles include promotion of cell-cycle entry and proliferation (Kant et al., 2006).

Inhibitors  
No selective small-molecule or biological inhibitors of ERK4 have been reported (Boudghene-Stambouli et al., 2022).

Other Comments  
Elevated MAPK4 expression sustains androgen-receptor-dependent AKT activation in prostate cancer and confers resistance to PI3K pathway inhibition (Boudghene-Stambouli et al., 2022). MAPK4 knock-down synergises with PARP1 inhibition in triple-negative breast cancer, and cooperative activation of PDK1-AKT by MAPK4 promotes tumour growth and therapy resistance (Boudghene-Stambouli et al., 2022; Han et al., 2023).

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