Phylogeny  
MAPK4 (also known as ERK4 or PRKM4) is an atypical member of the mitogen-activated protein kinase family. Together with its closest paralogue ERK3, it defines a vertebrate-restricted kinase branch that arose from a gene-duplication event in a chordate ancestor. MAPK4 and ERK3 share ~73 % amino-acid identity within the kinase domain and both lack the canonical Thr–X–Tyr activation-loop motif found in conventional MAPKs. Instead, their activation segment carries a single phospho-acceptor residue in an S-E-G motif, and sub-domain VIII displays an S-P-R sequence in place of the usual A-P-E signature (Al, 2015; Coulombe & Meloche, 2007; Rousseau, 2009).

Reaction Catalyzed  
ATP + [protein]-OH ⇌ ADP + [protein]-O-PO3²⁻ + H⁺ (Al, 2015).

Cofactor Requirements  
Requires divalent Mg²⁺ for catalysis (Al, 2015).

Substrate Specificity  
Substrate range appears narrow. The best-validated target is MAPK-activated protein kinase 5 (MK5/PRAK), whose activation depends on prior phosphorylation of MAPK4 at Ser186 by group I p21-activated kinases (PAK1/2/3). MAPK4 can also phosphorylate microtubule-associated protein 2 (MAP2). No consensus phosphorylation motif beyond these examples has been defined (Al, 2015; Almahi, 2013; Meloche, 2010).

Structure  
The 587-residue (~70 kDa) protein comprises an N-terminal catalytic domain followed by an extended C-terminal tail. Hallmarks of the kinase core are the atypical S-E-G activation-loop and the S-P-R motif in sub-domain VIII. Homology models with ERK3 suggest these deviations influence C-lobe architecture, hydrophobic-spine organization and substrate docking. MAPK4 predominantly localises to the cytoplasm where it forms a stable complex with MK5 (Al, 2015; Coulombe & Meloche, 2007; Barbagallo, 2018).

Regulation  
Catalytic activity is triggered by phosphorylation of Ser186 within the S-E-G motif by PAK1/2/3. Binding to MK5 promotes cytoplasmic retention and can lead to reciprocal phosphorylation of MAPK4 by activated MK5. Additional regulatory inputs (e.g., ubiquitination or further upstream kinases) remain to be clarified (Almahi, 2013; Meloche, 2010; Rousseau, 2009).

Function  
Acts as an atypical signalling kinase whose principal downstream effector is MK5. The MAPK4–MK5 module influences processes such as cell motility, cytoskeletal rearrangement and possibly cell-cycle entry. Knockout studies indicate roles in neuro-behavioural phenotypes, although definitive physiological substrates beyond MK5 have not yet been established. Upstream regulators include group I PAKs; downstream signalling proceeds via MK5-dependent phosphorylation cascades (Al, 2015; Almahi, 2013; Meloche, 2010).

Inhibitors  
No selective MAPK4 inhibitors have been reported (Al, 2015; Rousseau, 2009).

Other Comments  
The atypical activation mechanism and limited substrate list distinguish MAPK4 from classical MAPKs. Its precise contributions to disease, including cancer and neurological disorders, remain unresolved and warrant further investigation (Al, 2015; Barbagallo, 2018).

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