1. Phylogeny  
   MAPK6, also known as ERK3, is classified as an atypical mitogen‐activated protein kinase that belongs to a distinct subfamily of MAP kinases found exclusively in vertebrates (kultz1998phylogeneticandfunctional pages 5-9). It shares approximately 73% amino acid identity in its kinase domain with its closest relative, ERK4, indicating a common ancestry through a gene duplication event that gave rise to a separate subgroup within the MAPK family (coulombe2007atypicalmitogenactivatedprotein pages 2-4). Evolutionary analyses place ERK3 alongside other MAPKs in which the canonical dual‐phosphorylation motif (TXY) is absent, instead possessing a single phosphoacceptor motif (SEG) that distinguishes its regulatory mechanism from conventional MAPKs (kultz1998phylogeneticandfunctional pages 1-2). Its restricted orthology, with no counterparts reported in invertebrates or plants, underscores its vertebrate-specific role in cellular signaling (kultz1998phylogeneticandfunctional pages 13-14). The phylogenetic context is further supported by large-scale studies of the human kinome that outline its evolution from a common ancestral kinase present in early eukaryotes, with subsequent divergence to perform specialized functions distinct from those of classical ERKs (cargnello2011activationandfunction pages 1-1).
2. Reaction Catalyzed  
   MAPK6/ERK3 catalyzes the transfer of a phosphate group from ATP to substrate proteins containing serine/threonine residues. The chemical reaction can be represented as: ATP + [protein] → ADP + [protein]-phosphorylated + H⁺ (template). This phosphorylation reaction is typical of serine/threonine kinases and forms the basis for its role in modulating downstream signaling events (coulombe2007atypicalmitogenactivatedprotein pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of MAPK6/ERK3 depends on the presence of divalent cations, with magnesium (Mg²⁺) being a required cofactor for its kinase activity (template). This requirement facilitates the binding of ATP and proper positioning within the active site during the phosphorylation reaction (coulombe2007atypicalmitogenactivatedprotein pages 1-2).
4. Substrate Specificity  
   MAPK6/ERK3 displays a narrow substrate specificity relative to classical MAPKs. It has been shown to phosphorylate microtubule-associated protein 2 (MAP2) and the MAP kinase-activated protein kinase 5 (MK5), with the latter interaction involving a complex set of reciprocal phosphorylation events (Information section). The kinase activity of ERK3 involves phosphorylation at serine 189 within its atypical SEG activation motif and the subsequent activation of MK5 through phosphorylation at its activation loop residue, a process that is further coupled with a feedback loop wherein MK5 phosphorylates ERK3 (elkhadragy2024roleofthe pages 2-4). Although detailed consensus substrate motifs have not been comprehensively defined in the literature, the available data indicate that ERK3 preferentially targets substrates requiring phosphorylation on serine/threonine residues within non-canonical sequence contexts (cargnello2011activationandfunction pages 8-9).
5. Structure  
   MAPK6/ERK3 is a 721-amino acid protein featuring a distinct domain organization. The N-terminal region incorporates a kinase domain that shows roughly 45–50% sequence homology with conventional ERKs, yet it is distinguished by the presence of a single phosphoacceptor serine within the SEG activation motif instead of the typical TXY motif found in classical MAPKs (coulombe2007atypicalmitogenactivatedprotein pages 2-4). Adjacent to this kinase domain is a conserved C34 domain which is shared with ERK4, suggesting a role in mediating protein–protein interactions and possibly influencing subcellular localization (elkhadragy2024roleofthe pages 1-2). The C-terminal region is unusually long compared to classical MAPKs and is enriched in multiple phosphorylation sites that contribute to the regulation of its catalytic activity and turnover (schumacher2004scaffoldingbyerk3 pages 1-2). Structural studies based on crystallography and homology models, as reported for related atypical MAPKs, have identified key catalytic features such as the catalytic loop, the activation segment containing the SEG motif (with Ser189 being crucial), the hydrophobic regulatory spine, and a conserved C-helix (schroder2020crystalstructureand pages 1-3). In addition, the presence of an atypical SRP (serine–arginine–proline) motif in lieu of the canonical APE motif in subdomain VIII further contributes to its unique structural and functional properties (coulombe2007atypicalmitogenactivatedprotein pages 2-4). These unique structural features underscore the divergence of ERK3 from conventional MAPKs and provide the structural basis for its atypical regulation and substrate interactions (schroder2020crystalstructureand pages 10-12).
6. Regulation  
   The regulation of MAPK6/ERK3 occurs primarily through non-canonical mechanisms that involve both phosphorylation and protein turnover. A critical regulatory event is the phosphorylation of the activation loop at serine 189, which can occur via autophosphorylation or through the action of group I p21-activated kinases (PAKs) (elkhadragy2024roleofthe pages 15-16). This phosphorylation event is essential for the subsequent formation of a signaling complex with MAPKAPK5 (MK5), whereby ERK3 and MK5 undergo reciprocal phosphorylation events that modulate their respective activities (elkhadragy2024roleofthe pages 2-4, seternes2004activationofmk5prak pages 11-12). In addition to phosphorylation, ERK3 regulation is also achieved at the level of protein stability using ubiquitin-proteasome pathways, although detailed ubiquitination mechanisms are more extensively described in other atypical MAPKs (schumacher2004scaffoldingbyerk3 pages 1-2, coulombe2007atypicalmitogenactivatedprotein pages 10-11). Nuclear export signals (NES) within its structure contribute to its dynamic nucleocytoplasmic shuttling and thereby influence its access to substrates (schumacher2004scaffoldingbyerk3 pages 1-2). These regulatory mechanisms ensure that the kinase activity of ERK3 is tightly moderated, allowing precise control over the phosphorylation events that influence various downstream signaling pathways (elkhadragy2024roleofthe pages 15-16).
7. Function  
   MAPK6/ERK3 is implicated in phosphorylating key substrates that are involved in diverse cellular processes. Notably, ERK3 phosphorylates microtubule-associated protein 2 (MAP2) and plays an integral role in the activation of MAPKAPK5 (MK5) through a signaling module that involves reciprocal phosphorylation events (Information section, elkhadragy2024roleofthe pages 2-4). The formation of a complex with MK5, where ERK3 is phosphorylated at Ser189 and subsequently facilitates MK5 activation, constitutes an essential component of its function (seternes2004activationofmk5prak pages 11-12). This module has been associated with the promotion of cell cycle entry, although the precise mechanistic details remain to be fully elucidated (Information section). Expression studies indicate that ERK3 is ubiquitously expressed in several tissues, with relatively higher levels observed in brain, skeletal muscle, and the gastrointestinal tract (coulombe2007atypicalmitogenactivatedprotein pages 1-2). Furthermore, the kinase is implicated in modulating cellular processes such as cytoskeletal organization and potentially transcription regulation through its substrates and interacting partners, thereby playing roles in cellular differentiation and proliferation (ronkina2019germlinedeletion pages 20-23). The reciprocal activation between ERK3 and MK5 might also interface with other signaling pathways that govern cell survival and growth (elkhadragy2024roleofthe pages 2-4, schroder2020crystalstructureand pages 10-12).
8. Other Comments  
   Preliminary studies using structural analyses and inhibitor screening have identified several compounds with reversible and irreversible inhibitory effects on ERK3, although no inhibitor has yet been exclusively validated for clinical use (schroder2020crystalstructureand pages 10-12). Additionally, the atypical regulatory mechanisms, such as the utilization of non-canonical phosphorylation events and fast turnover via the ubiquitin-proteasome system, distinguish ERK3 from classical MAPKs and make it an emerging therapeutic target in the context of aberrant cell cycle progression and cancer biology (elkhadragy2024roleofthe pages 15-16). Although the direct causal associations with specific disease states are still under investigation, the reported role of ERK3 in forming a signaling complex with MK5 and its potential influence on cell cycle entry may have implications in tumorigenesis and proliferative disorders (ronkina2019germlinedeletion pages 20-23). Recent crystallographic efforts have provided insight into its ATP-binding site and active conformation, thereby laying the groundwork for future rational drug design aimed at selectively targeting this atypical MAPK (schroder2020crystalstructureand pages 1-3).
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