1. Phylogeny  
   MAPK15, also known as ERK7 or ERK8, is classified within the mitogen‐activated protein kinase (MAPK) family as an atypical MAPK that diverges from the canonical ERK1/2 and ERK5 subfamilies based on its unique evolutionary traits and regulatory mechanisms (cargnello2011activationandfunction pages 6-8). MAPK15 orthologs have been identified throughout evolution in diverse eukaryotic organisms including early‐branching unicellular eukaryotes, invertebrates such as Drosophila melanogaster, and across vertebrates, thereby supporting its conservation and placement among the MAPK complement present since before the last eukaryotic common ancestor (huang2024reconstructingthedeep pages 7-10, kalapos2019earlyevolutionof pages 3-5). The evolutionary analyses indicate that MAPK15 belongs to a basal lineage of MAP kinases that retained its ancestral TEY (Thr-Glu-Tyr) phosphorylation motif while other MAPK members, such as ERK3/4, underwent motif changes (li2011evolutionaryhistoryof pages 4-5). Furthermore, phylogenomic reconstructions have consistently placed MAPK15 in a distinct clade that separates it both structurally and functionally from conventional MAPKs, thus underscoring its atypical nature and unique regulation compared to other members of the MAPK family (o’shaughnessy2022notyourmother’s pages 2-5).
2. Reaction Catalyzed  
   MAPK15 catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to a hydroxyl group on serine or threonine residues present in substrate proteins, thereby forming adenosine diphosphate (ADP) and a phosphorylated protein product along with the release of a proton (cargnello2011activationandfunction pages 6-8).
3. Cofactor Requirements  
   The catalytic activity of MAPK15 is dependent on divalent metal ions, with magnesium (Mg²⁺) serving as a critical cofactor that facilitates the binding and proper orientation of ATP in the kinase active site (coulombe2007atypicalmitogenactivatedprotein pages 7-9).
4. Substrate Specificity  
   MAPK15 exhibits substrate specificity that is characteristic of serine/threonine kinases, and in vitro studies have demonstrated its ability to phosphorylate classical MAPK substrates such as myelin basic protein (MBP) and components like FOS, although a definitive consensus substrate motif for MAPK15 has not been firmly established (cargnello2011activationandfunction pages 6-8, li2011evolutionaryhistoryof pages 8-11). In addition, MAPK15 has been implicated in modulating substrates involved in autophagy and ciliary signaling pathways, as it interacts with autophagy regulators such as GABARAP, MAP1LC3B, and GABARAPL1 to facilitate autophagosome formation (cargnello2011activationandfunction pages 6-8). The substrate specificity appears to also encompass interaction with nuclear and cytoplasmic targets, including chromatin and proteins involved in the maintenance of genomic stability, although the precise phosphorylation motifs remain to be fully characterized (cargnello2011activationandfunction pages 8-9, li2011evolutionaryhistoryof pages 12-13).
5. Structure  
   MAPK15 has a kinase domain that is flanked by variable N- and C-terminal regions, with the catalytic core retaining the canonical MAPK fold composed of an N-terminal lobe featuring a predominantly β-sheet structure and a C-terminal lobe dominated by α-helices (coulombe2007atypicalmitogenactivatedprotein pages 7-9). The activation loop in MAPK15 contains the conserved TEY motif, where phosphorylation occurs on the threonine and tyrosine residues, but uniquely for this atypical MAPK, this phosphorylation is predominantly constitutive and occurs via autophosphorylation rather than through upstream MAPK kinases (cargnello2011activationandfunction pages 6-8, dahm2025atypicalmapksin pages 7-8). A notable structural feature of MAPK15 is its extended C-terminal region, which is absent in conventional MAPKs; this C-terminal extension is implicated in directing subcellular localization and modulating autoactivation, and it may contain nuclear localization signals as well as domains involved in protein-protein interactions (dahm2025atypicalmapksin pages 7-8, huang2024reconstructingthedeep pages 16-18). In addition, the kinase domain exhibits a core architecture typical of the CMGC group of protein kinases, including a conserved lysine in the β3 strand for ATP binding, an invariant aspartate in the DFG motif crucial for coordinated magnesium ion binding, and a C-helix that participates in the regulation of catalytic activity through its interaction with the catalytic loop (lindin2014mitogenactivatedproteinkinaseactivated pages 16-22, coulombe2007atypicalmitogenactivatedprotein pages 1-2).
6. Regulation  
   MAPK15 is regulated primarily through autophosphorylation of its activation loop, a process that leads to its constitutive basal phosphorylation state independent of classical upstream MAP2K activity (cargnello2011activationandfunction pages 6-8). In addition to autophosphorylation, the protein levels of MAPK15 are subject to regulation by the ubiquitin–proteasome system; the N-terminal region of the kinase has been implicated in proteasomal degradation, thereby controlling the overall protein turnover and steady-state levels within the cell (dahm2025atypicalmapksin pages 7-8). Post-translational modifications such as phosphorylation have been observed at the TEY motif (specifically Thr175 and Tyr177), and mutation of these residues results in the loss of kinase activity, reinforcing their importance for catalytic function (cargnello2011activationandfunction pages 6-8, coulombe2007atypicalmitogenactivatedprotein pages 7-9). There is also evidence that MAPK15 may be regulated through its interactions with other proteins, such as chromatin components and regulatory factors like ESRRA, where binding can lead to subcellular relocalization and modulation of transcriptional activity (cargnello2011activationandfunction pages 8-9, o’shaughnessy2022notyourmother’s pages 2-5).
7. Function  
   MAPK15 plays multifunctional roles in regulating key cellular processes in a kinase activity–dependent manner. It is known to control both basal and starvation-induced autophagy through direct interactions with members of the ATG8 family (GABARAP, MAP1LC3B, and GABARAPL1) that lead to the formation of autophagosomes, the degradation of SQSTM1, and modulation of inhibitory phosphorylation on MAP1LC3B (cargnello2011activationandfunction pages 6-8). In addition, MAPK15 is involved in the regulation of primary cilium formation by orchestrating the localization of ciliary proteins that are critical for cilium structure, transport, and signaling, thereby playing a role in ciliogenesis (cargnello2011activationandfunction pages 6-8, huang2024reconstructingthedeep pages 14-16). MAPK15 also contributes to the regulation of protein trafficking and secretion; upon amino-acid starvation, it mediates transitional endoplasmic reticulum site disassembly and inhibits secretion by preventing the relocation of glycosylation enzymes from the Golgi to the endoplasmic reticulum (cargnello2011activationandfunction pages 6-8, huang2024reconstructingthedeep pages 16-18). The kinase further functions in the maintenance of genome integrity by binding to chromatin and interacting with proliferating cell nuclear antigen (PCNA), thereby protecting PCNA from degradation mediated by MDM2 (cargnello2011activationandfunction pages 6-8). Moreover, MAPK15 regulates dopaminergic signaling by modulating dopamine transporter (DAT) activity and protein expression via activation of the small GTPase RhoA, and it is involved in post-stress responses by phosphorylating ELAVL1 in response to hydrogen peroxide treatment, which affects the stability of PDCD4 mRNA through microRNA-mediated regulation (cargnello2011activationandfunction pages 6-8, o’shaughnessy2022notyourmother’s pages 15-15). In addition to its kinase-dependent roles, MAPK15 has been reported to exert kinase activity–independent functions as a negative regulator of cellular growth (cargnello2011activationandfunction pages 6-8).
8. Other Comments  
   Currently, there are no specific catalytic inhibitors available for MAPK15/ERK7/ERK8, which limits experimental investigation and therapeutic targeting of this atypical MAPK (cargnello2011activationandfunction pages 6-8, dahm2025atypicalmapksin pages 7-8). Disease associations for MAPK15 remain incomplete; while the kinase is implicated in processes related to autophagy, ciliogenesis, protein trafficking, and genome integrity, detailed in vivo substrate identification and precise links to specific pathological states, such as cancer or neurodegeneration, have not been fully established (cargnello2011activationandfunction pages 6-8, o’shaughnessy2022notyourmother’s pages 2-5). Furthermore, mutation data and structure–function relationships in the context of human diseases are still under investigation. In addition, despite its capacity to phosphorylate substrates like FOS and MBP in vitro, the substrate repertoire in vivo remains poorly characterized, and further research is required to elucidate its complete signaling network (cargnello2011activationandfunction pages 8-9, li2011evolutionaryhistoryof pages 12-13).
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