1. Phylogeny  
   Mitogen‐activated protein kinase 1 (MAPK1), also known as ERK2, belongs to the evolutionarily conserved MAP kinase family, which is a subgroup of the CMGC kinase superfamily that includes CDKs, MAPKs, GSK3, and CLK kinases (cargnello2011activationandfunction pages 2-4). Orthologs of MAPK1/ERK2 have been identified in organisms as diverse as yeast, plants, invertebrates, and vertebrates, indicating that its core signaling role was established before the divergence of major eukaryotic lineages (rousseau2009caractérisationdela pages 29-33). MAPK1/ERK2 is phylogenetically related to ERK1 (MAPK3), which arose from a gene duplication event in bony vertebrates, with ERK2 typically being more evolutionarily conserved and often more abundantly expressed in key tissues such as brain, heart, and skeletal muscle (al2015identificationofnovel pages 13-16, martinvega2023navigatingtheerk12 pages 5-7). Its classification within the human kinome follows the organization provided by seminal studies such as those by Manning et al., situating ERK2 as a member of the conventional MAPKs that are critical for signal transduction in basic cellular processes (baljuls2009differencesandsimilarities pages 162-164).
2. Reaction Catalyzed  
   MAPK1/ERK2 catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to specific serine or threonine residues within substrate proteins, generating adenosine diphosphate (ADP) and a phosphorylated protein, with the concomitant release of a proton (cargnello2011activationandfunction pages 2-4). This phosphorylation reaction is central to signal transduction, where it modulates the activity, localization, or stability of substrates that include transcription factors, kinases, and various regulatory proteins (machne2006modelingofthe pages 9-12). The enzymatic activity is highly specific for serine/threonine residues followed immediately by a proline (S/T-P), a property that is critical for the fidelity of downstream signaling responses (kirsch2021noncanonicalinteractionsof pages 94-97).
3. Cofactor Requirements  
   The catalytic activity of MAPK1/ERK2 requires the presence of divalent cations, with magnesium (Mg²⁺) being the primary cofactor that facilitates ATP binding and proper positioning of phosphate groups during the phosphoryl transfer reaction (cargnello2011activationandfunction pages 2-4, machneUnknownyearmodelingofthe pages 6-9). Mg²⁺ ions are essential for stabilizing the negative charges on the ATP molecule and thereby enhancing kinase activity (rousseau2009caractérisationdela pages 29-33).
4. Substrate Specificity  
   MAPK1/ERK2 exhibits strict substrate specificity characterized by its preference for phosphorylating serine or threonine residues that precede a proline residue in substrate targets, thus recognizing motifs typically denoted as S/T-P (kirsch2021noncanonicalinteractionsof pages 94-97). In addition, substrate binding is facilitated by the presence of docking domains on ERK2 that interact with complementary D-domain or DEF motif sequences present in its substrates, thereby helping to ensure both specificity and efficient phosphorylation (martinvega2023navigatingtheerk12 pages 30-32, martinvega2023navigatingtheerk12 pages 32-33). This proline-directed specificity is a common feature among MAP kinases, which distinguishes them from other serine/threonine kinases (lai2015investigationsofthe pages 1-6).
5. Structure  
   MAPK1/ERK2 possesses a bilobal kinase domain that is typical of eukaryotic protein kinases, with a smaller N-terminal lobe composed mainly of β-strands and a larger C-terminal lobe enriched in α-helices (novak2021impactoferk2 pages 12-18). The active site is located in the cleft between these lobes and contains several highly conserved motifs such as the glycine-rich loop (GxGxxG) that is critical for ATP binding, the catalytic HRD motif essential for phosphoryl transfer, and the DFG motif that coordinates Mg²⁺ ions (rousseau2009caractérisationdela pages 29-33, honzejkova2024structuralstudiesof pages 15-20). A defining structural feature of ERK2 is its activation loop, which includes a conserved TEY motif (threonine-glutamate-tyrosine); dual phosphorylation of the threonine and tyrosine residues within this motif is necessary to trigger a conformational change that leads to full activation of the kinase (lai2016regulatoryrolesof pages 12-14, roux2004erkandp38 pages 3-4). Additionally, ERK2 contains distinct docking sites such as the D-recruitment site (DRS) and the F-recruitment site (FRS), which mediate interactions with substrates and regulatory proteins, thereby ensuring proper substrate alignment and specificity (martinvega2023navigatingtheerk12 pages 33-34, orand2023revealingthemechanism pages 38-41). The overall three-dimensional architecture of ERK2 has been well characterized by X-ray crystallography and high-resolution structural studies, revealing a dynamic enzyme that undergoes significant conformational changes upon activation (novak2021impactoferk2 pages 12-18, kirsch2021noncanonicalinteractionsof pages 4-7).
6. Regulation  
   Activation of MAPK1/ERK2 occurs via dual phosphorylation of the TEY motif within its activation loop, a process performed by the dual-specificity kinases MEK1 and MEK2 following stimulation by upstream effectors such as Ras and Raf (cargnello2011activationandfunction pages 2-4, lai2015investigationsofthe pages 55-60). This phosphorylation induces a conformational change that aligns critical catalytic residues and opens the substrate-binding pocket, thereby increasing the enzymatic activity by up to 1000-fold (rousseau2009caractérisationdela pages 90-94, martinvega2023navigatingtheerk12 pages 66-71). Regulatory mechanisms also include interactions with scaffolding proteins that bring ERK2 into close proximity with its activators and substrates, enhancing both the specificity and efficiency of signal transduction (martinvega2023navigatingtheerk12 pages 13-14, kirsch2021noncanonicalinteractionsof pages 94-97). An additional layer of regulation is provided by dual-specificity phosphatases (DUSPs), such as DUSP1, DUSP4, and DUSP6, which dephosphorylate the activation loop of ERK2, thereby attenuating its activity and contributing to signaling termination (sladecek2016insearchof pages 70-73, sladecek2016insearchof pages 77-81). Furthermore, feedback phosphorylation mechanisms, including ERK2-mediated phosphorylation of its upstream regulators and interacting partners, contribute to dynamic control of the MAPK cascade and fine-tune the cellular response (lai2016regulatoryrolesof pages 12-14, martinvega2023navigatingtheerk12 pages 7-8).
7. Function  
   MAPK1/ERK2 plays an essential role in the MAPK/ERK signaling cascade by mediating diverse cellular responses such as cell growth, adhesion, survival, and differentiation (cargnello2011activationandfunction pages 2-4, martinvega2023navigatingtheerk12 pages 7-8). ERK2 phosphorylates a wide array of substrates, including transcription factors like ELK1, ATF2, FOS, and BCL6; cytoskeletal proteins such as paxillin and MAP2; and regulators of apoptosis, translation, and additional signaling kinases, thereby acting as a central node in the relay of extracellular signals (kirsch2021noncanonicalinteractionsof pages 94-97, rousseau2009caractérisationdela pages 29-33). Owing to its ability to translocate into the nucleus upon activation, ERK2 modulates gene expression programs that control cell cycle progression and differentiation during both development and in the adult organism (martinvega2023navigatingtheerk12 pages 33-34, rousseau2009caractérisationdela pages 78-80). In addition to its well-established role in mitogenic signaling via growth factor receptors such as EGFR and KIT, ERK2 participates in non-canonical signaling pathways that impact endosomal dynamics, Golgi fragmentation during mitosis, and the regulation of spindle assembly checkpoints in dividing cells (cargnello2011activationandfunction pages 2-4, al2015identificationofnovel pages 19-23). Furthermore, by phosphorylating substrates involved in transcription, such as members of the FOS family and other transcription regulators, ERK2 facilitates the rapid modulation of gene expression in response to external stimuli (martinvega2023navigatingtheerk12 pages 32-33, rousseau2009caractérisationdela pages 33-37).
8. Other Comments  
   Among the notable characteristics of MAPK1/ERK2 is its central role as an effector in the Ras-Raf-MEK-ERK signaling axis, which has made it an important target for drug development in oncology and other proliferative disorders (novak2021impactoferk2 pages 50-55, orand2023revealingthemechanism pages 25-29). Several small molecule inhibitors have been developed that target the ATP-binding site or the docking interfaces of ERK2, and these compounds are in various stages of preclinical and clinical development (roux2004erkandp38 pages 5-7, sladecek2016insearchof pages 70-73). Moreover, dysregulation of ERK2 signaling has been implicated in a range of diseases, including various cancers, developmental syndromes, and neurodegenerative disorders, with mutations or altered expression levels contributing to aberrant cell proliferation and survival (novak2021impactoferk2 pages 18-23, rousseau2009caractérisationdela pages 78-80). In addition, ERK2 is known to phosphorylate key regulators in metabolic pathways, such as phosphoglycerate kinase (PGK1) under hypoxic conditions, thereby linking its activity to metabolic reprogramming in cancer cells (cargnello2011activationandfunction pages 2-4). The extensive catalog of approximately 160 substrates for ERK2 further underscores its ability to integrate multiple signaling inputs and coordinate a broad spectrum of cellular processes (kirsch2021noncanonicalinteractionsof pages 94-97). Furthermore, experimental data indicate that additional regulatory mechanisms, including protein–protein interactions with scaffold proteins and modulation by dual specificity phosphatases, are critical for achieving spatio-temporal precision in ERK2 signal transduction (martinvega2023navigatingtheerk12 pages 5-7, orand2023revealingthemechanism pages 33-38). These features not only underscore the biological importance of ERK2 but also highlight its viability as a therapeutic target, particularly in conditions where its regulation is compromised (rousseau2009caractérisationdela pages 90-94, sladecek2016insearchof pages 77-81).
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