1. Phylogeny  
   MAPK1, commonly designated as ERK2, is a member of the conventional mitogen‐activated protein kinase (MAPK) family within the CMGC group. Orthologs of ERK2 are found across eukaryotic species and its evolutionary conservation is evident among metazoans, fungi, and plants. In vertebrates, ERK2 and its close isoform ERK1 (MAPK3) emerged from an ancestral gene duplication event and are ubiquitously expressed, although ERK2 is often essential for normal development, with knockout studies underscoring its nonredundant roles in embryogenesis and cell survival (cargnello2011activationandfunction pages 2-4, kultz1998phylogeneticandfunctional pages 1-2, busca2016erk1anderk2 pages 1-2).
2. Reaction Catalyzed  
   ERK2 catalyzes the transfer of a phosphate group from ATP to specific serine or threonine residues on substrate proteins. This reaction is represented as:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This phosphorylation event modulates protein function by altering conformation or interaction properties without direct interpretation of downstream effects (cargnello2011activationandfunction pages 2-4).
3. Cofactor Requirements  
   The kinase activity of ERK2 requires divalent metal ion cofactors, with Mg²⁺ serving as the preferred ion to coordinate the phosphates of ATP and facilitate phosphoryl transfer (kultz1998phylogeneticandfunctional pages 2-3).
4. Substrate Specificity  
   ERK2 is classified as a proline‐directed serine/threonine kinase. It exhibits a substrate specificity characterized by the recognition of phosphorylatable serine/threonine residues that are immediately followed by a proline, forming a consensus motif of [S/T]–P. In addition, substrate binding and specificity are refined by docking interactions involving distinct docking motifs such as the D-domain and the DEF domain present in many of its substrates; these motifs interact with complementary docking grooves on ERK2 thereby ensuring efficient catalysis and substrate selection (cargnello2011activationandfunction pages 2-4, roux2004erkandp38 pages 1-1, martinvega2023navigatingtheerk12 pages 32-33).
5. Structure  
   ERK2 features a bilobed kinase domain that is typical of protein kinases. The N-terminal lobe is predominantly composed of β-strands and contains the glycine-rich loop critical for ATP binding, while the larger C-terminal lobe is mainly α-helical and houses the catalytic loop. Central to its structure is the activation loop, which contains a highly conserved TEY (threonine–glutamate–tyrosine) motif; dual phosphorylation at the threonine and tyrosine residues within this loop is required for full catalytic activation. In addition, ERK2’s structure includes a conserved C-terminal common docking (CD) domain that is essential for binding substrates, upstream activators, and phosphatases. These structural elements—including the hydrophobic spine and correctly positioned C-helix—are pivotal for stabilizing the active conformation of the kinase and for facilitating efficient phosphoryl transfer reactions (kultz1998phylogeneticandfunctional pages 15-17, meister2013mitogenactivatedprotein(map) pages 1-4, martinvega2023navigatingtheerk12 pages 33-34).
6. Regulation  
   ERK2 is regulated via multiple mechanisms. The primary mode of activation is through dual phosphorylation of the TEY motif located in the activation loop by MAP kinase kinases (MEK1 and MEK2). This phosphorylation event induces conformational rearrangements that realign catalytic residues and open the substrate binding cleft. In addition to activation, ERK2 is subject to deactivation by dual specificity phosphatases (MKPs) such as DUSP6, which dephosphorylate both the threonine and tyrosine residues, thereby attenuating its activity. Furthermore, regulatory proteins and scaffolds contribute to the spatial and temporal control of ERK2 signaling. For example, interactions with scaffold proteins help sequester ERK2 in specific subcellular compartments and modulate its access to both substrates and upstream kinases, while feedback phosphorylation events on upstream components also contribute to tightly regulated signal output (cargnello2011activationandfunction pages 2-4, busca2016erk1anderk2 pages 19-19, theodosiou2002mapkinasephosphatases pages 8-9).
7. Function  
   ERK2 is a central component of the MAPK/ERK signaling cascade and plays a vital role in transmitting extracellular signals to intracellular targets. It is ubiquitously expressed and phosphorylates a broad spectrum of substrates, including transcription factors (such as ATF2, ELK1, FOS), cytoskeletal proteins, regulators of apoptosis, and components involved in translation control. Through these phosphorylations, ERK2 influences diverse biological processes including cell growth, adhesion, survival, and differentiation. ERK2 is also implicated in the regulation of cell cycle progression during meiosis and mitosis, and it contributes to postmitotic functions by modulating protein interactions and gene expression in differentiated cells. Furthermore, its involvement in signaling pathways initiated by activated receptor tyrosine kinases such as KIT underscores its pivotal role in both development and maintenance of normal cellular functions (cargnello2011activationandfunction pages 2-4, dickinson2006diversephysiologicalfunctions pages 1-3, martinvega2023navigatingtheerk12 pages 7-8).
8. Other Comments  
   Several pharmacological inhibitors targeting the MAPK/ERK pathway have been developed owing to the central role of ERK2 in oncogenic processes. Inhibitors that act on upstream activators (e.g., MEK inhibitors such as PD184352 and PD0325901) indirectly affect ERK2 activation, while there is ongoing research into direct ERK2 inhibitors. Dysregulation of ERK2, including aberrant phosphorylation and altered substrate interactions, is associated with various cancers and developmental disorders. Mutations or altered regulation of upstream pathway components such as Ras or Raf can lead to constitutive activation of ERK2, contributing to uncontrolled cell proliferation and tumorigenesis. Additionally, specific docking domain mutations that affect substrate or regulatory protein binding may also contribute to disease. The broad substrate repertoire of ERK2, which includes over 160 identified substrates, highlights both its complexity and its potential as a therapeutic target when its regulation is compromised (roux2004erkandp38 pages 1-2, busca2016erk1anderk2 pages 22-22).
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