1. Phylogeny  
   MAP2K7 (also known as MKK7, JNKK2, MEK7, PRKMK7, or SKK4) is a member of the mitogen‐activated protein kinase kinase (MAP2K) sub‐family within the larger STE (Sterile 20) group of protein kinases, and it is evolutionarily conserved across eukaryotes, with orthologs identified in organisms ranging from yeast (e.g., the Schizosaccharomyces pombe MAP2K homolog Wis1) to mammals (kim2014aprotoberberinederivative pages 7-8). This kinase is situated phylogenetically alongside its close homolog MAP2K4 (MKK4), with which it shares approximately 49–50% sequence identity; both kinases contribute to the activation of the stress‐activated protein kinases (SAPKs) in the c‐Jun N‐terminal kinase (JNK) pathway, although they differ in their phosphorylation site preferences (tournier2001mkk7isan pages 1-2, keshet2010themapkinase pages 5-7). According to large‐scale analyses of the human kinome, including the seminal works by Manning and colleagues, MAP2K7 belongs to a conserved evolutionary core found in all eukaryotes, and its presence in higher organisms reflects its critical function in stress response and developmental pathways (avruch2007mapkinasepathways pages 5-6, cargnello2011activationandfunction pages 1-1). As an ortholog found in mammals, MAP2K7 is part of a regulatory network that has emerged early in evolution through the expansion and diversification of kinase families from a common ancestor (keshet2010themapkinase pages 9-11, park2019mkk7theessential pages 1-2).
2. Reaction Catalyzed  
   MAP2K7 catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to its protein substrates, primarily the JNK family of mitogen‐activated protein kinases, via dual phosphorylation mechanisms. In this reaction, ATP and the appropriate hydroxyl group of the substrate (specifically the threonine residue in the Thr-Pro-Tyr motif of JNKs) yield adenosine diphosphate (ADP) and the phosphorylated substrate along with a proton, which is the canonical reaction catalyzed by protein kinases (pearson2001mitogenactivatedprotein(map) pages 24-24, tournier2001mkk7isan pages 6-7). Notably, MAP2K7 exhibits a kinetic preference for phosphorylating the threonine residue within the TPY activation motif of JNK isoforms, a modification that is sufficient for triggering JNK activity, while full activation of JNK may require additional phosphorylation of the tyrosine residue by MAP2K4 (kim2014aprotoberberinederivative pages 7-8, tournier2001mkk7isan pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of MAP2K7 is dependent on the presence of ATP as a phosphate donor, and like most protein kinases, its enzymatic function requires divalent metal ions, primarily Mg²⁺, which coordinate with ATP to facilitate efficient phosphoryl transfer (roskoski2012erk12mapkinases pages 2-4, pearson2001mitogenactivatedprotein(map) pages 1-2).
4. Substrate Specificity  
   MAP2K7 is highly specific for its downstream substrates, the JNK protein kinases (MAPK8/JNK1, MAPK9/JNK2, and MAPK10/JNK3), recognizing them primarily through the phosphorylation of the threonine residue within the Thr-Pro-Tyr motif located in the activation loop. The substrate specificity of MAP2K7 is determined by a precise arrangement of amino acid residues in its activation loop, such as Arg283, Lys288, Thr291, and Arg292, which establish critical molecular contacts with the substrate and contribute to selective binding; these residues also play an important role in defining the binding pocket for substrate and inhibitor interactions (kim2014aprotoberberinederivative pages 8-9, tournier2001mkk7isan pages 5-6). This enzymatic precision ensures that monophosphorylation on the threonine position is sufficient to trigger moderate JNK activity, while phosphorylation of the tyrosine residue by MAP2K4 further enhances the activation state (park2019mkk7theessential pages 2-4, cargnello2011activationandfunction pages 5-6).
5. Structure  
   MAP2K7 possesses a canonical protein kinase domain composed of a smaller N-terminal lobe primarily made up of β-sheets and a larger C-terminal lobe predominantly consisting of α-helices, with the ATP binding pocket located in the cleft between these lobes (schroder2020catalyticdomainplasticity pages 1-4). Within this structure, several key regulatory elements are evident: the activation loop (also known as the T-loop), which must undergo phosphorylation for full catalytic activity; the conserved DFG (Asp-Phe-Gly) motif, which adopts different conformations (DFG-in for the active state and DFG-out for the inactive state) that underlie the dynamic catalytic domain plasticity; and the helical C-helix, which is repositioned upon activation to form critical salt bridges that support substrate binding and catalysis (schroder2020catalyticdomainplasticity pages 11-14, schroder2020catalyticdomainplasticity pages 16-18). An additional structural feature is an N-terminal regulatory helix that plays an essential role in relieving auto-inhibition and inducing the active conformation of MAP2K7; this regulatory element is similar to that found in related MAP2Ks such as MEK1/2 (schroder2020catalyticdomainplasticity pages 18-20, park2019mkk7theessential pages 1-2). Moreover, MAP2K7 contains one or more docking sites or D domains within its sequence that facilitate selective interactions with its downstream substrates (JNK isoforms) and scaffold proteins, thereby ensuring signaling fidelity (kragelj2015structureanddynamics pages 1-1, keshet2010themapkinase pages 9-11). Unique to MAP2K7 is also the presence of a reactive cysteine residue (commonly identified as Cys218 in structural studies) that has been exploited in the design of covalent inhibitors, providing a strategy for selective targeting of this kinase (schroder2020catalyticdomainplasticity pages 9-11, katzengruber2023mkk4inhibitors—recentdevelopment pages 2-4).
6. Regulation  
   MAP2K7 is regulated by multiple mechanisms that ensure precise control of its catalytic activity. Its activation requires dual phosphorylation of specific serine/threonine residues within the activation loop by upstream MAP kinase kinase kinases (MAP3Ks) such as ASK1, MLK3, and TAK1, which are themselves activated in response to cellular stress and pro-inflammatory cytokines (tournier2001mkk7isan pages 1-2, park2019mkk7theessential pages 2-4). Post-translational modifications, particularly phosphorylation at key sites, result in conformational changes that transition the kinase from an autoinhibited state—characterized by a distorted P-loop and DFG-out conformation—to an active state that is competent for substrate phosphorylation (schroder2020catalyticdomainplasticity pages 4-6, monter2019mkk7theessential pages 5-7). In addition, regulatory interactions with scaffold proteins such as JNK-interacting proteins (JIP1, JIP2, JIP3) and POSH help localize MAP2K7 within multiprotein signaling complexes, thereby enhancing its ability to specifically phosphorylate JNK isoforms (pearson2001mitogenactivatedprotein(map) pages 12-12, park2019mkk7theessential pages 1-2). Allosteric regulation is also evident from studies showing that certain small-molecule inhibitors bind to previously unrecognized pockets located in the N-terminal lobe of MAP2K7, thereby modulating its activity by inducing alternative conformations (schroder2020catalyticdomainplasticity pages 9-11). The conformational plasticity of MAP2K7, as revealed by crystallographic and NMR studies, provides evidence that both auto-inhibition and activation of the kinase involve multiple dynamic rearrangements, including changes in the positioning of the activation loop, the C-helix, and the DFG motif (schroder2020catalyticdomainplasticity pages 14-16, tournier2001mkk7isan pages 6-7).
7. Function  
   MAP2K7 is an essential dual-specificity protein kinase that functions predominantly within the stress-activated protein kinase/c-Jun N-terminal kinase (SAP/JNK) signaling cascade. Its primary role is to phosphorylate and thereby activate JNK isoforms (MAPK8/JNK1, MAPK9/JNK2, and MAPK10/JNK3), and it does so preferentially by targeting the threonine residue in the highly conserved TPY activation motif of these kinases (kim2014aprotoberberinederivative pages 7-8, tournier2001mkk7isan pages 1-2). The activation of JNK by MAP2K7 is pivotal for regulating cellular responses to various stress signals, including those emanating from pro-inflammatory cytokines such as tumor necrosis factor (TNFα) and interleukin-1 (IL-1), as well as from environmental stressors like UV irradiation and oxidative stress (park2019mkk7theessential pages 1-2, tournier2001mkk7isan pages 6-7). In addition to its role in the immediate stress response, MAP2K7 has been implicated in controlling programmed cell death (apoptosis), cell proliferation, and differentiation, thereby influencing processes such as development, immune responses, and tumorigenesis (park2019mkk7theessential pages 7-9, cargnello2011activationandfunction pages 5-6). The enzyme’s unique substrate specificity and selective activation of JNK isoforms underscore its function as a key modulator within a larger network of kinases that integrate extracellular signals and orchestrate complex transcriptional programs (zhang2007regulatorymechanismsof pages 1-3, keshet2010themapkinase pages 7-9).
8. Other Comments  
   Several inhibitors have been developed to target MAP2K7, reflecting its therapeutic potential in diseases characterized by dysregulated JNK signaling. One noteworthy example is the protoberberine derivative HWY336, which selectively inhibits both MAP2K7 and its close homolog MAP2K4 by binding non-competitively at the activation loop region, thus preventing substrate access without competing with ATP binding (kim2014aprotoberberinederivative pages 8-9). In addition, covalent inhibitors such as ibrutinib have been shown to bind to the reactive cysteine residue (Cys218) within the ATP-binding pocket of MAP2K7, and other type-I and type-II inhibitors have been identified through structure-based drug design approaches that exploit the kinase’s conformational plasticity (schroder2020catalyticdomainplasticity pages 9-11, park2019mkk7theessential pages 9-10). Dysregulation of MAP2K7 activity has been linked to pathological conditions including various cancers (such as T-cell acute lymphoblastic leukemia and colon cancer metastasis), inflammatory disorders, and possibly neurodegenerative diseases, making it an attractive target for drug development (park2019mkk7theessential pages 4-5, park2019mkk7theessential pages 12-13). Ongoing research continues to refine inhibitor specificity and potency, with comparative studies exploring the selectivity profiles of compounds against both MAP2K7 and related MAP2Ks, thereby enhancing the prospects for clinical translation (katzengruber2023mkk4inhibitors—recentdevelopment pages 16-18, liu2016aconservedmotif pages 10-10).
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