1. Phylogeny  
   MAPKAPK5, also known as PRAK or p38‐regulated/activated protein kinase (UniProt Q8IW41), is a serine/threonine kinase that is highly conserved among vertebrates. Comparative sequence analyses reveal that its amino acid identity exceeds 87% among species as diverse as mammals, birds, fish, amphibians, and reptiles, with a gene organization that typically comprises 14 exons; such conservation suggests an ancient evolutionary origin within the vertebrate lineage (kostenko2011physiologicalrolesof pages 2-3). Within the kinome, MAPKAPK5 is classified as a member of the MAP kinase-activated protein kinase (MAPKAPK) family and is grouped within the Ca²⁺/calmodulin-dependent protein kinase (CAMK) superfamily, placing it in an evolutionary context alongside other kinases that emerged from gene duplication events in early metazoans (cargnello2011activationandfunction pages 25-26, avruch2007mapkinasepathways pages 3-5). Although it shares considerable sequence homology with related kinases such as MK2 and MK3, MAPKAPK5 is distinct in its mode of activation; while MK2/MK3 are predominantly activated by conventional p38 isoforms, MAPKAPK5 is regulated not only by p38α/β but also by the atypical MAP kinases ERK3 and ERK4, underscoring its placement in a divergent yet conserved branch of MAPKAPK signaling (aberg2006regulationofmapkactivated pages 1-2, avruch2007mapkinasepathways pages 3-5).
2. Reaction Catalyzed  
   MAPKAPK5 catalyzes the phosphorylation reaction that transfers a phosphate group from ATP to a hydroxyl group on L-serine or L-threonine residues within target proteins. The overall chemical reaction can be summarized as follows:  
     ATP + [protein]-(L-serine/L-threonine) → ADP + [protein]-(L-serine/L-threonine)-phosphate + H⁺.  
   This reaction, which is typical of serine/threonine protein kinases, is fundamental for modulating the activity of numerous downstream substrates by altering their conformation, interaction affinities, and subcellular localization (pearson2001mitogenactivatedprotein(map) pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of MAPKAPK5 is dependent on divalent metal ions. In particular, the kinase requires Mg²⁺ as a cofactor to coordinate ATP binding and facilitate the transfer of the phosphate group during the phosphorylation reaction. This requirement is common among serine/threonine kinases and is critical for the proper orientation of ATP within the active site (pearson2001mitogenactivatedprotein(map) pages 1-2).
4. Substrate Specificity  
   MAPKAPK5 exhibits a substrate specificity that is defined by its ability to phosphorylate serine/threonine residues within target proteins that participate in tumor suppression, cell cycle regulation, and stress responses. Its recognized substrates include FOXO3, which upon phosphorylation promotes its nuclear retention and thereby increases the expression of miR-34b and miR-34c; HSP27 (also known as HSPB1), which is involved in cytoskeletal rearrangements; the tumor suppressor p53, phosphorylated at specific residues that contribute to Ras-induced senescence; RHEB, whose phosphorylation by MAPKAPK5 acts as a negative regulatory signal for mTORC1 activity; as well as ERK3 and ERK4, with which MAPKAPK5 forms complexes to mediate atypical MAPK signaling (cargnello2011activationandfunction pages 25-26, kostenko2011physiologicalrolesof pages 11-13, gaestel2016mapkactivatedproteinkinases pages 1-2). Although a precise consensus sequence for its substrates has not been unequivocally defined in the literature provided, the overall recognition appears to be mediated through docking interactions that enable MAPKAPK5 to target serine/threonine residues in proteins carrying appropriate flanking sequences and structural motifs (kostenko2011physiologicalrolesof pages 11-13).
5. Structure  
   The three-dimensional structure of MAPKAPK5 is characterized by a central kinase domain that is highly conserved among members of the MAPKAPK family. This catalytic domain contains the essential motifs for ATP binding and phosphoryl transfer, including an N-terminal lobe harboring a conserved lysine residue required for catalytic activity and a C-terminal lobe that forms the substrate-binding pocket (gaestel2016mapkactivatedproteinkinases pages 1-2, kostenko2011physiologicalrolesof pages 2-3). Unique to MAPKAPK5 is an approximately 100–amino acid C-terminal extension that contains critical regulatory elements such as a nuclear localization signal (NLS) and a nuclear export signal (NES), as well as a docking domain that mediates interactions with upstream MAP kinases including p38, ERK3, and ERK4 (cargnello2011activationandfunction pages 25-26, gaestel2016mapkactivatedproteinkinases pages 4-5). The activation loop, which features threonine 182, is a key phosphorylation site required for the full catalytic activity of the kinase; phosphorylation at this residue induces conformational changes that promote the alignment of catalytic residues and proper substrate orientation (kostenko2011physiologicalrolesof pages 10-11, aberg2006regulationofmapkactivated pages 1-2). Molecular dynamics simulations and comparative structural studies using homology models have further revealed that the overall fold of MAPKAPK5 is consistent with an active kinase conformation, displaying a hydrophobic spine and a well-ordered C-helix that are hallmarks of the kinase active state (lindin2014comparativemoleculardynamics pages 20-22).
6. Regulation  
   The regulation of MAPKAPK5 is complex and is mediated primarily through phosphorylation events and protein–protein interactions. Activation of MAPKAPK5 is predominantly achieved by phosphorylation of its activation loop residue, threonine 182, by upstream kinases such as the p38 MAP kinase isoforms (particularly p38α and p38β) as well as the atypical MAP kinases ERK3 and ERK4; these phosphorylation events are required for full kinase activation (kostenko2011physiologicalrolesof pages 10-11, aberg2006regulationofmapkactivated pages 1-2). In addition to phosphorylation by p38, MAPKAPK5 is subject to regulation by protein kinase A (PKA), which phosphorylates it at serine 115; this modification has been associated with changes in subcellular localization, specifically promoting nuclear export via mechanisms that involve the masking and unmasking of the NLS and NES within the C-terminal extension (kostenko2011physiologicalrolesof pages 9-10, seternes2002bothbindingand pages 1-2). Regulatory binding interactions with proteins such as 14-3-3 also play a role in modulating the stability and localization of MAPKAPK5, ensuring that its kinase activity is appropriately compartmentalized in response to cellular stress conditions (cargnello2011activationandfunction pages 25-26, gaestel2016mapkactivatedproteinkinases pages 5-6). Together, these regulatory events create a dynamic network in which MAPKAPK5 activity and localization are finely tuned by upstream signaling cascades, thereby coordinating its functions in stress response, cell cycle control, and tumor suppression (new2003regulationofprak pages 11-13).
7. Function  
   MAPKAPK5 is a multifunctional serine/threonine kinase that plays critical roles in regulating diverse cellular pathways linked to tumor suppression, stress response, and post‐transcriptional gene regulation. One of its well‐characterized functions is its role in mediating Ras-induced cellular senescence through the phosphorylation of key substrates such as p53, which contributes to the establishment of a growth arrest program (aberg2006regulationofmapkactivated pages 1-2, avruch2007mapkinasepathways pages 3-5). In addition, MAPKAPK5 phosphorylates FOXO3; this modification promotes the nuclear retention of FOXO3, thereby enhancing the expression of microRNAs miR-34b and miR-34c that bind to the 3′ untranslated region (3′UTR) of MYC transcripts, ultimately resulting in repression of MYC translation (information section). Furthermore, MAPKAPK5 negatively regulates mTORC1 signaling through the phosphorylation and inhibition of RHEB, a small GTPase that acts as an essential activator of mTORC1; this regulatory cascade serves to diminish mTORC1 activity under conditions where cell growth and protein synthesis must be curtailed (information section, kostenko2011physiologicalrolesof pages 11-13). MAPKAPK5 also phosphorylates HSP27, a substrate involved in cytoskeletal remodeling, thereby influencing cell motility and potentially modulating metastasis (cargnello2011activationandfunction pages 25-26, avruch2007mapkinasepathways pages 3-5). The formation of complexes with atypical MAP kinases ERK3 and ERK4 further delineates a unique signaling pathway in which MAPKAPK5 participates, although the precise functional implications of these interactions remain to be fully elucidated (aberg2006regulationofmapkactivated pages 1-2, avruch2007mapkinasepathways pages 3-5). Expression studies indicate that MAPKAPK5 is ubiquitously expressed with particularly high levels in heart, skeletal muscle, pancreas, and lung tissues, suggesting that its functions in stress response and cell cycle regulation may be of broad physiological significance (cargnello2011activationandfunction pages 25-26).
8. Other Comments  
   Selective small molecule inhibitors targeting MAPKAPK5 have been reported, and these compounds are being explored for their potential therapeutic benefits in inflammatory conditions and cancer. For example, the diterpenoid alkaloid noroxoaconitine has been identified as an inhibitor of MAPKAPK5, and additional compounds such as GLPG0259 have demonstrated bone-protective as well as anti-inflammatory activities in in vivo rheumatoid arthritis models (moens2013theroleof pages 33-33, kostenko2014phosphorylationofheat pages 1-2). Although the clinical utility of these inhibitors continues to be evaluated, such compounds underscore the therapeutic relevance of MAPKAPK5 given its central roles in tumor suppression and mTORC1 signaling. There is also significant interest in further characterizing the phosphorylation events mediated by MAPKAPK5, as altered activity may be associated with oncogenic transformation and the dysregulation of cell proliferation in various cancer types. No specific disease mutations have been conclusively attributed to MAPKAPK5 at this time, and its role as a tumor suppressor—mediated in part through Ras-induced senescence and the modulation of key effectors such as p53 and FOXO3—has been established primarily through functional studies using genetically modified models (information section, avruch2007mapkinasepathways pages 3-5). Continued investigation into its substrates and regulatory interactions as well as the development of more selective inhibitors will help define its precise contributions to cellular homeostasis and disease pathology.
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