1. Phylogeny  
   MAPK10, commonly referred to as JNK3 (and by its aliases JNK3A, PRKM10, SAPK1B, and MAP kinase p49 3F12), belongs to the c‐Jun N‐terminal kinase subgroup within the larger mitogen‐activated protein kinase (MAPK) family. This family is part of the CMGC group of serine/threonine kinases, a collection of enzymes that share common catalytic features and evolutionary origins. Unlike JNK1 and JNK2—which are ubiquitously expressed in nearly every tissue—JNK3 is predominantly expressed in neuronal tissues, with additional low-level expression in cardiac smooth muscle and testes. This tissue-specific expression indicates that JNK3 has diverged to serve specialized functions in the central nervous system. Comparative sequence analyses have revealed that the kinase domain of MAPK10 is highly conserved across vertebrate species, suggesting that its evolutionary history can be traced back to a common ancestor among eukaryotes. Orthologs of MAPK10 have been identified in several mammalian species, reaffirming its fundamental role in stress-activated signaling pathways that are particularly critical for neuronal physiology (benn2020clinicallyprecedentedprotein pages 1-2, nakano2020biologicalpropertiesof pages 1-3, craige2019jnkandcardiometabolic pages 14-15).
2. Reaction Catalyzed  
   MAPK10 functions as a serine/threonine kinase that catalyzes the phosphorylation reaction by transferring the γ-phosphate group from ATP to the hydroxyl group of serine or threonine residues present on substrate proteins. The overall reaction is typically represented as:  
     ATP + [protein]-(Ser/Thr) → ADP + [protein]-phospho(Ser/Thr) + H^+  
   In this process, the kinase binds ATP in a conserved catalytic cleft and orients the target substrate for efficient phosphate transfer. This phosphorylation event plays a crucial role in modulating the activity, stability, and interaction potential of the substrate proteins. Specifically, MAPK10 phosphorylates key members of the AP-1 transcription factor complex—such as JUN and ATF2—and has been shown to modify other substrates like JUND (with its phosphorylation being inhibited by MEN1), the neuronal microtubule regulator STMN2, the amyloid-beta precursor protein (APP), and the CLOCK-BMAL1 heterodimer involved in circadian regulation (alzain2025discoveryofnovel pages 10-11, benn2020clinicallyprecedentedprotein pages 5-6, hong2025identifyingjnkregulatedphosphoproteome pages 23-25).
3. Cofactor Requirements  
   The catalytic function of MAPK10 is critically dependent on the presence of divalent metal ions, most notably Mg²⁺. Mg²⁺ functions by coordinating ATP within the active site, stabilizing the negative charges on phosphate groups, and decreasing the activation energy required for the phosphoryl transfer reaction. Although under certain experimental conditions Mn²⁺ can substitute for Mg²⁺, the physiological cofactor is predominantly Mg²⁺. This requirement for a divalent metal ion is a characteristic feature of serine/threonine kinases and is essential for maintaining the correct conformation of the nucleotide-binding pocket, ensuring the effective progression of the catalytic reaction (latham2022nonkinasetargetingof pages 13-14, ho2014creationandcharacterization pages 36-39).
4. Substrate Specificity  
   MAPK10 exhibits a pronounced specificity towards a subset of protein substrates by recognizing discrete amino acid motifs and engaging in docking interactions that facilitate proper substrate orientation. Physiologically, MAPK10 phosphorylates several transcription factors—including members of the AP-1 family such as JUN and ATF2—to modulate gene expression in response to stress. In addition, it phosphorylates JUND; notably, this phosphorylation is subject to negative regulation by the tumor suppressor MEN1, linking MAPK10 activity to cellular control mechanisms behind both neuronal apoptosis and tumorigenesis (benn2020clinicallyprecedentedprotein pages 5-6, hong2025identifyingjnkregulatedphosphoproteome pages 29-32). Beyond transcription factors, MAPK10 targets proteins that are critical for neuronal function. For instance, phosphorylation of STMN2 affects microtubule dynamics essential for neurite outgrowth and neuronal differentiation (benn2020clinicallyprecedentedprotein pages 23-23). Furthermore, MAPK10 has been shown to phosphorylate APP, thereby influencing pathways associated with neuronal differentiation and possibly Alzheimer’s disease pathology. An additional substrate is the CLOCK-BMAL1 heterodimer; phosphorylation of this complex links MAPK10 activity to the regulation of circadian rhythms (musi2020jnk3astherapeutic pages 14-16). The enzyme preferentially recognizes proline-directed motifs, where a serine or threonine residue is immediately followed by a proline (S/T-P motif), although evidence also supports the recognition of non-canonical substrates through additional docking sites such as D- and F-motifs, which further refine its substrate selectivity (maikrachline2021alternativesplicingof pages 5-6, orand2023revealingthemechanism pages 191-194).
5. Structure  
   The three-dimensional structure of MAPK10 mirrors that of canonical MAP kinases and is characterized by a bilobal kinase fold. Its structure comprises an N-terminal lobe predominantly formed by β-sheets and a larger C-terminal lobe that is rich in α-helices. These two lobes converge to form a deep catalytic cleft that accommodates ATP and the target substrate. Within this kinase domain lies the activation loop (AL), which contains the highly conserved TxY motif essential for enzyme activation. Dual phosphorylation of the threonine and tyrosine residues within this motif by upstream kinases (MAP2K4/MKK4 and MAP2K7/MKK7) is required for full enzymatic activation because such modifications trigger critical conformational changes and stabilize the active conformation (ho2014creationandcharacterization pages 15-20, nakano2020biologicalpropertiesof pages 3-5, orand2023revealingthemechanism pages 295-296). Recent studies also indicate the presence of regions of intrinsic disorder located in the terminal flanking regions of the kinase domain. These disordered segments are believed to mediate interactions with scaffold proteins—such as the JNK-interacting proteins (JIPs)—and contribute to the dynamic regulation of MAPK10’s localization and substrate recognition (gehi2022intrinsicdisorderin pages 17-18, musi2020jnk3astherapeutic pages 3-5). Although high-resolution crystal structures specific to MAPK10 are less abundant compared to other MAPKs, homology models and AlphaFold predictions support the existence of a highly conserved catalytic core accompanied by surface-exposed motifs that are critical for docking of substrates and regulatory partners (ho2014creationandcharacterization pages 15-20, orand2023revealingthemechanism pages 33-38).
6. Regulation  
   MAPK10 is tightly regulated by a multifaceted network of upstream kinases, scaffold proteins, and phosphatases that collectively modulate its activity in response to extracellular stress signals. Activation of MAPK10 is initiated through a classical three-tiered kinase cascade. In this cascade, environmental stressors—such as pro-inflammatory cytokines or physical stress—activate MAPKKKs, which then stimulate the activity of dual-specificity kinases MAP2K4 (MKK4) and MAP2K7 (MKK7). These MAP2Ks phosphorylate the activation loop in MAPK10 at critical threonine and tyrosine residues, a process that converts MAPK10 from an inactive to an active form (benn2020clinicallyprecedentedprotein pages 1-2, fey2015signalingpathwaymodels pages 5-7, nakano2020biologicalpropertiesof pages 3-5). Scaffold proteins, particularly the JNK-interacting proteins (JIPs), play a substantial role in fine-tuning MAPK10 activity by assembling the kinases within the signaling module and ensuring that phosphorylation events occur with high specificity and efficiency. These scaffolds co-localize the upstream activators (MKK4 and MKK7) with MAPK10 and thereby enhance the precision of the phosphorylation cascade (gehi2022intrinsicdisorderin pages 22-23, orand2023revealingthemechanism pages 238-241). Conversely, deactivation of MAPK10 is mediated by phosphatases, notably the dual-specificity MAP kinase phosphatases (MKPs), which dephosphorylate the critical residues on the activation loop, thereby providing a negative feedback mechanism that terminates the stress signal (ha2019phosphorylationdynamicsof pages 1-3, orand2023revealingthemechanism pages 41-45). An additional layer of regulatory complexity is observed in the phosphorylation of specific substrates; for instance, the phosphorylation of JUND by MAPK10 is inhibited by MEN1, indicating that protein–protein interactions can modulate substrate specificity and signaling output (benn2020clinicallyprecedentedprotein pages 5-6, orand2023revealingthemechanism pages 295-296).
7. Function  
   MAPK10 exerts a central role in neuronal signaling and stress responses, largely due to its specialized expression pattern and unique substrate specificity. In neuronal cells, MAPK10 is involved in regulating proliferation, differentiation, and migration; it also plays a crucial role in programmed cell death (apoptosis). By phosphorylating transcription factors such as JUN and ATF2, MAPK10 modulates the activity of the AP-1 complex—a key driver of gene expression changes during cellular stress and apoptosis (alzain2025discoveryofnovel pages 10-11, benn2020clinicallyprecedentedprotein pages 1-2). Beyond these transcriptional effects, MAPK10 also targets substrates directly involved in the maintenance of neuronal structure and function. For example, phosphorylation of STMN2 affects microtubule dynamics that are essential for neurite outgrowth and neuronal differentiation. Moreover, through phosphorylation of the amyloid-beta precursor protein (APP), MAPK10 influences APP signaling pathways that are relevant to the development of Alzheimer’s disease and other neurodegenerative disorders (benn2020clinicallyprecedentedprotein pages 23-23, hong2025identifyingjnkregulatedphosphoproteome pages 23-25). Additionally, the phosphorylation of the CLOCK-BMAL1 heterodimer suggests a role for MAPK10 in regulating circadian rhythms, thereby linking cellular stress responses with the temporal control of gene expression (musi2020jnk3astherapeutic pages 14-16). These functional outcomes underline MAPK10’s capacity to integrate extracellular stress signals into a wide range of intracellular responses that are critical for neuronal survival, synaptic plasticity, and circadian regulation (ha2019phosphorylationdynamicsof pages 1-3, benn2020clinicallyprecedentedprotein pages 1-2).
8. Other Comments  
   MAPK10 has emerged as a promising target for therapeutic intervention in neurodegenerative diseases and certain cancers, owing to its pivotal role in mediating neuronal apoptosis and stress responses. Its capacity to phosphorylate APP, for example, links MAPK10 activity to Alzheimer’s disease pathology, while its regulation of transcription factors involved in apoptosis underscores its potential as a target in conditions characterized by aberrant neuronal death (musi2020jnk3astherapeutic pages 1-3, rehfeldt2020cjunnterminalkinase pages 9-11). Moreover, efforts to develop both ATP-competitive and non-ATP competitive inhibitors that selectively target the JNK3 isoform are ongoing, with some compounds already demonstrating preferential inhibition in preclinical studies (latham2022nonkinasetargetingof pages 5-6, jha2025deeplearningcoupledproximity pages 12-14). Alternative splicing of MAPK10 results in multiple isoforms that may exhibit distinct regulatory properties and tissue-specific functions, adding further complexity to its biological roles and offering additional avenues for targeted drug discovery (maikrachline2021alternativesplicingof pages 5-6, musi2020jnk3astherapeutic pages 3-5). Research continues to explore the role of intrinsically disordered regions in mediating interactions with scaffold proteins such as the JIP family, which are essential for the assembly of signaling complexes that regulate MAPK10 activity and substrate specificity (gehi2022intrinsicdisorderin pages 17-18, orand2023revealingthemechanism pages 238-241). Collectively, these aspects not only underscore the importance of MAPK10 in neuronal signaling pathways but also highlight its potential as a biomarker of neuronal stress responses and as a target for novel neuroprotective therapies.
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