1. Phylogeny  
   Mitogen‐activated protein kinase 10 (MAPK10), also known as JNK3, belongs to the c‐Jun N-terminal kinase (JNK) subfamily within the larger group of mitogen‐activated protein kinases (MAPKs), which in turn are part of the CMGC group of serine/threonine kinases. Among the three JNK isoforms (JNK1, JNK2, and JNK3), MAPK10/JNK3 is distinguished by its preferential expression in neuronal tissues, as well as in heart and testes, in contrast to the ubiquitous expression of JNK1 and JNK2 (ansideri2018multiplestrategiestargeting pages 38-42, bogoyevitch2006usesforjnk pages 2-3). Phylogenetic analysis indicates that JNK family members emerged early in eukaryotic evolution – as evidenced by their conservation from yeast to mammals – and that gene duplication events have given rise to the distinct isoforms. In particular, studies tracking the evolutionary history of the JNK transcripts have shown that the gene family is highly conserved and that alternative splicing events have resulted in both shared and isoform-specific roles (aithamlat2020transcripts’evolutionaryhistory pages 2-4). The kinase is therefore embedded in an ancient signaling network central to stress responses, and its sequence conservation underscores its importance in neuronal and stress‐activated signaling pathways.
2. Reaction Catalyzed  
   MAPK10/JNK3 catalyzes the transfer of a phosphoryl group from ATP to specific serine and threonine residues on target proteins. The reaction can be defined as follows:  
   ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (ansideri2018multiplestrategiestargeting pages 23-28, bogoyevitch2006usesforjnk pages 7-9).
3. Cofactor Requirements  
   The catalytic activity of MAPK10/JNK3 depends on the presence of divalent metal ion cofactors, with Mg²⁺ being required for efficient ATP binding and phosphoryl transfer. This cofactor requirement is typical for serine/threonine kinases within the CMGC group (ansideri2018multiplestrategiestargeting pages 23-28).
4. Substrate Specificity  
   MAPK10/JNK3 exhibits substrate specificity characteristic of proline-directed serine/threonine kinases. It preferentially phosphorylates substrates at serine or threonine residues that are immediately followed by a proline, forming S/T-P motifs. For instance, JNK3 phosphorylates transcription factors such as c-Jun on Ser63/73 and ATF2, thereby modulating the AP-1 transcription complex activity (ansideri2018multiplestrategiestargeting pages 42-45, bogoyevitch2006usesforjnk pages 3-4). In addition, JNK3 targets proteins involved in neuronal functions such as the microtubule regulator STMN2 and the amyloid precursor protein (APP), where phosphorylation plays a role in neuronal differentiation and APP processing (ansideri2018multiplestrategiestargeting pages 42-45). The consensus substrate recognition is determined by local sequence context and docking motifs, which facilitate binding through interactions with specific docking grooves on JNK3’s surface (orand2023revealingthemechanism pages 296-298).
5. Structure  
   MAPK10/JNK3 is organized around a central kinase domain, which is characteristic of the MAPK family and consists of a conserved N-terminal lobe, predominantly composed of beta-sheets, and a larger C-terminal lobe enriched in alpha-helices. The ATP binding cleft is located at the interface of these two lobes. Key catalytic features include the activation loop containing a conserved Thr-Xxx-Tyr (TXY) motif that requires dual phosphorylation for full activation by upstream kinases MKK4 and MKK7 (ansideri2018multiplestrategiestargeting pages 38-42, cargnello2011activationandfunction pages 1-1).  
   Unique structural characteristics of JNK3 include extended regions outside the canonical kinase domain that contribute to its tissue-specific functions; for example, these regions are thought to mediate interactions with scaffold proteins such as members of the JNK-interacting protein (JIP) family. Structural studies, including crystallographic data on inactive, non-phosphorylated forms of JNK isoforms and peptide complexes derived from JIP proteins, reveal a typical kinase fold coupled with distinct features in the docking (CD) domain that facilitate substrate and regulator binding (bogoyevitch2006usesforjnk pages 4-6, orand2023revealingthemechanism pages 33-38). Moreover, the hydrophobic spine and the C-helix play critical roles in the alignment of catalytic residues and in mediating conformational transitions between active and inactive states.
6. Regulation  
   MAPK10/JNK3 is regulated primarily through phosphorylation by upstream dual-specificity kinases MAP2K4/MKK4 and MAP2K7/MKK7, which act on the Thr and Tyr residues within its activation loop. This dual phosphorylation is essential for inducing structural rearrangements that align the catalytic machinery for efficient phosphoryl transfer (ansideri2018multiplestrategiestargeting pages 35-38, cargnello2011activationandfunction pages 4-5). In addition to upstream kinase activity, JNK3 regulation is further modulated by scaffold proteins, notably the members of the JNK-interacting protein family, which assemble MAPK cascade components to ensure specificity and efficiency of signal transduction (bogoyevitch2006usesforjnk pages 16-18, orand2023revealingthemechanism pages 211-213). Post-translational modifications within JNK3 and its interacting partners (such as phosphorylation of scaffold proteins like JIP1 and 14-3-3 proteins) contribute to feedback loops that either sustain or attenuate kinase signaling, influencing factors such as nuclear translocation and binding affinity for substrates (bogoyevitch2006usesforjnk pages 26-27, orand2023revealingthemechanism pages 81-84).
7. Function  
   MAPK10/JNK3 plays crucial roles in neuronal biology and stress signaling. It is principally involved in mediating responses to extracellular stress stimuli such as pro-inflammatory cytokines, physical stress, and oxidative insults. In neurons, JNK3 regulates processes such as cellular proliferation, differentiation, migration, and programmed cell death. Activation of the SAPK/JNK pathway by upstream kinases leads to phosphorylation of transcription factors—including c-Jun, ATF2, and JUND—which ultimately modulate gene expression programs that control apoptosis and other stress responses (ansideri2018multiplestrategiestargeting pages 42-45, bogoyevitch2006usesforjnk pages 7-9). Beyond transcriptional regulation, JNK3 phosphorylates neuronal proteins such as the microtubule regulator STMN2, influencing neurite outgrowth and cytoskeletal dynamics, and modulates the amyloid precursor protein (APP) signaling pathway during neuronal differentiation (ansideri2018multiplestrategiestargeting pages 42-45). In addition, JNK3 phosphorylates components involved in circadian regulation such as the CLOCK-BMAL1 heterodimer, thereby playing a role in the photic entrainment of the circadian clock (ansideri2018multiplestrategiestargeting pages 42-45). The kinase also participates in the regulation of neuronal apoptosis, which is implicated in neurodegenerative conditions, as well as in the modulation of stress responses that underlie developmental and pathological processes in the nervous system (bogoyevitch2006usesforjnk pages 27-28, orand2023revealingthemechanism pages 296-298).
8. Other Comments  
   Several inhibitors targeting JNK family kinases have been developed, with some experimental compounds showing a degree of selectivity towards the JNK isoforms. For instance, SP600125 is an ATP-competitive inhibitor known to inhibit JNK activity, although its selectivity is not ideal and it affects multiple JNK isoforms (ansideri2018multiplestrategiestargeting pages 35-38). The involvement of JNK3 in neurodegenerative diseases, such as Alzheimer’s and Parkinson’s diseases, as well as in neuronal apoptosis, has spurred interest in developing more selective JNK3 inhibitors. In addition, phosphorylation events mediated by JNK3 have been linked to the regulation of amyloid-beta production via phosphorylation of APP and to the modulation of circadian regulators via phosphorylation of CLOCK-BMAL1, which highlights the kinase’s multifaceted roles in neuronal signaling and potential pathological conditions (ansideri2018multiplestrategiestargeting pages 42-45, bogoyevitch2006usesforjnk pages 29-30). Further research is expected to refine our understanding of isoform-specific inhibition, which may have therapeutic implications, particularly for neurodegenerative disorders (orand2023revealingthemechanism pages 41-45).
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