Phylogeny  
• p38α/MAPK14 is one of four vertebrate p38 stress-activated protein kinase isoforms (α, β, γ, δ).  
• Closely related to the yeast HOG1 kinase and shows ≈50 % sequence identity with ERK2.  
• Forms a distinct branch within the CMGC serine/threonine kinase group; dual-phosphorylation motifs and docking residues are highly conserved.

Reaction Catalyzed  
ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein]

Cofactor Requirements  
Mg²⁺

Substrate Specificity  
• Strong preference for Ser/Thr followed by Pro (S/T-P motif).  
• Docking interactions broaden the spectrum to roughly 200–300 substrates, including ATF1, ATF2, MEF2, Elk-1, TP53, and the kinases MK2, MK3, MNK1, MNK2.

Structure  
• Typical bilobed CMGC kinase core (β-sheet N-lobe, α-helical C-lobe).  
• Activation loop contains a TGY motif; dual phosphorylation triggers the active conformation.  
• Well-defined ATP-binding cleft, hydrophobic spine, and C-helix residues; isoform-specific docking sites distinguish p38α from its paralogs.

Regulation  
• Activated by MKK3/MKK6-mediated phosphorylation of Thr183 and Tyr185 in response to UV, oxidative stress and inflammatory cytokines.  
• Activated kinase shuttles from cytoplasm to nucleus.  
• Dephosphorylated and inactivated by MAPK phosphatases; interaction with casein kinase II modulates autophosphorylation.

Function  
• Key effector in stress and pro-inflammatory signalling.  
• Phosphorylates transcription factors (ATF1/2, MEF2, Elk-1, TP53) to drive immediate-early gene expression and chromatin remodelling.  
• Acts on downstream kinases (MK2/3, MNK1/2) and cytoplasmic proteins such as SIAH2 and ADAM17, influencing inflammation, cell-cycle control, protein degradation and receptor endocytosis.

Inhibitors  
• Widely used ATP-competitive inhibitors include SB203580 and SB202190.

Other Comments  
• Aberrant MAPK14 activity is linked to inflammatory diseases, cancers and developmental anomalies, making it a continuing focus for therapeutic development.

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