## Phylogeny

• MAP3K19 (YSK4) is positioned in the STE20/SPS1-related branch of the MAP3K tier within the human Ser/Thr kinome (johnson2023anatlasof pages 7-7, osada1997ysk1anovel pages 9-9).  
• The YSK sub-family contains four human paralogues—YSK1, YSK2, YSK3 and YSK4—that form a clade distinct from RAF, MLK and TAK MAP3K sub-families (osada1997ysk1anovel pages 2-4).  
• The MAP3K19 kinase domain shares 60.6 % sequence similarity with the yeast MAPKKKs Ste11, Byr2 and Bck1, indicating evolutionary conservation with classical MAP3K scaffolds (osada1997ysk1anovel pages 6-8).  
• Orthologs outside mammals are not documented in the cited literature (osada1997ysk1anovel pages 1-2).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-Ser/Thr-phosphate (hoang2020theproteinkinase pages 1-2).

## Cofactor Requirements

Cofactor dependence has not been reported in the available biochemical studies (hoang2020theproteinkinase pages 10-11).

## Substrate Specificity

• Confirmed cellular substrates: MEK1/2 (MAP2K1/2) and MKK7 (MAP2K7) (hoang2020theproteinkinase pages 1-2, hoang2020theproteinkinase pages 10-11).  
• MAP3K19 (listed as YSK1/YSK4 in the dataset) is included in the kinome-wide substrate-specificity atlas, but a consensus phosphorylation motif is not provided in the excerpt (johnson2023anatlasof pages 10-11).

## Structure

• Domain organisation: an N-terminal regulatory segment of undefined architecture followed by a C-terminal Ser/Thr kinase domain that contains the conserved VAIK catalytic lysine, HRD catalytic loop and DFG activation-loop motifs typical of MAP3Ks (osada1997ysk1anovel pages 2-4).  
• A stretch enriched in acidic residues immediately precedes the PSTAIR motif, a characteristic feature noted in YSK family members (osada1997ysk1anovel pages 2-4).  
• No crystallographic or cryo-EM structure is available; an AlphaFold model is referenced in the serine/threonine kinome atlas, confirming the canonical bilobal kinase fold (johnson2023anatlasof pages 10-11).

## Regulation

• Catalytic activity is abolished by mutation of the active-site lysine; kinase-dead MAP3K19 fails to phosphorylate MEK, ERK and JNK in cells (hoang2020theproteinkinase pages 10-11).  
• Phosphorylation of downstream MAPKs is reversed by λ-protein phosphatase, demonstrating phosphorylation-dependent signalling (hoang2020theproteinkinase pages 10-11).  
• Autophosphorylation is documented for the paralogous kinase YSK1, indicating a potential self-activation mechanism within the family (osada1997ysk1anovel pages 6-6).  
• No additional post-translational modifications, allosteric regulators or scaffold interactions have been reported in the cited sources (hoang2020theproteinkinase pages 10-11).

## Function

• Signalling: MAP3K19 directly phosphorylates MEK1/2 and MKK7, activating ERK1/2 and JNK pathways; ERK activation persists in the presence of RAF inhibitors, establishing a RAF-independent route to ERK signalling (hoang2020theproteinkinase pages 1-2).  
• Cellular role: Essential for survival and proliferation of KRAS-mutant lung cancer cells; shRNA or inhibitor treatment diminishes ERK/JNK phosphorylation and reduces viability (hoang2020theproteinkinase pages 1-2).  
• Upstream stimuli: Acts as a mediator of cigarette-smoke-induced pulmonary inflammation and is implicated in TGF-β signalling during pulmonary fibrosis (nguyen2022map3kfamilyreview pages 10-12).  
• Expression: Over-expressed in lungs from chronic obstructive pulmonary disease (COPD) patients (hoang2020theproteinkinase pages 1-2).  
• Prognostic associations: High MAP3K19 mRNA correlates with improved survival in bladder, breast, liver and several other carcinomas, but with reduced survival in kidney renal clear cell, kidney renal papillary and lung squamous carcinomas (nguyen2022map3kfamilyreview pages 12-13).

## Inhibitors

• Broad-spectrum kinase inhibitors AT-9283, an NVP compound and multiple GSK series molecules suppress MAP3K19-dependent phosphorylation of MEK/ERK/JNK and decrease viability of KRAS-mutant lung adenocarcinoma cells; direct biochemical potency against purified MAP3K19 was not reported (hoang2020theproteinkinase pages 15-15, hoang2020theproteinkinase pages 15-17).  
• No MAP3K19-selective inhibitor has been described in the cited literature (hoang2020theproteinkinase pages 15-17).

## Other Comments

• Disease associations include COPD, cigarette smoke–induced lung inflammation, idiopathic pulmonary fibrosis and oncogenic signalling in KRAS-mutant lung cancer (hoang2020theproteinkinase pages 1-2, nguyen2022map3kfamilyreview pages 10-12).  
• No disease-linked missense mutations or germline variants have been reported in the referenced studies (hoang2020theproteinkinase pages 1-2).

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