Phylogeny  
MAP4K3 (GLK/KHS2) resides in the STE20 family, GCK-I subfamily; closest human paralogs are MAP4K1, MAP4K2, MAP4K4 and MAP4K5 (silvian2017howcanthe pages 1-2). Orthologs occur in Mus musculus Map4k3, Rattus norvegicus Map4k3, Drosophila melanogaster happyhour, Caenorhabditis elegans MIG-15 and Saccharomyces cerevisiae Ste20p, underscoring deep evolutionary conservation (chuang2019map4k3glkinautoimmune pages 1-2). A longer activation loop than in MAP4K4 produces a looser activation-loop-swapped dimer unique to MAP4K3 (marcotte2017germinal‐centerkinase‐likekinase pages 13-16).

Reaction Catalyzed  
ATP + protein-Ser/Thr → ADP + protein-Ser/Thr-phosphate (marcotte2017germinal‐centerkinase‐likekinase pages 16-20).

Cofactor Requirements  
Enzymatic activity requires Mg²⁺ (10 mM MgCl₂); Mn²⁺ is not needed for phosphotransfer and is used only during phosphatase control steps (marcotte2017germinal‐centerkinase‐likekinase pages 20-25).

Substrate Specificity  
Confirmed substrates: PKCθ Thr538, TFEB Ser3, IQGAP1 Ser480, LATS1/2 activation loops and myelin basic protein (chuang2016map4kfamilykinases pages 18-21). A kinase-wide atlas has not assigned a consensus phosphorylation motif to MAP4K3 (han2024functionalannotationof pages 8-8).

Structure  
The protein comprises an N-terminal kinase domain (1-314), a central proline-rich/PEST segment and a C-terminal citron-homology domain (thiriet2013cytoplasmicproteinserinethreonine pages 4-7). A 2.85 Å crystal structure (PDB 5J5T) reveals an activation-loop-swapped dimer formed via APE and TYPW motifs (marcotte2017germinal‐centerkinase‐likekinase pages 9-13). The active site holds a Lys45–Glu61 salt bridge, an intact HRD triad and aligned regulatory spine (marcotte2017germinal‐centerkinase‐likekinase pages 30-37). Phospho-Ser170 stabilises the activation loop; S170A retains ATP binding yet shows ≤3 % activity (marcotte2017germinal‐centerkinase‐likekinase pages 5-9). A straight P-loop and α-K helix Asn290 create a pocket exploitable for selective inhibition (marcotte2017germinal‐centerkinase‐likekinase pages 13-16). An acidic C-terminal extension docks into a basic groove of the adjacent protomer, analogous to AGC-kinase PIF binding (marcotte2017germinal‐centerkinase‐likekinase pages 9-13).

Regulation  
Autophosphorylation at Ser170 is essential for catalytic and mTORC1 activities (chuang2016map4kfamilykinases pages 18-21). PP2A-PR61ε dephosphorylates Ser170 and inactivates the kinase (silvian2017howcanthe pages 2-3). Growth-factor stimulation induces phosphorylation at Tyr366, Tyr379, Tyr574 and Tyr735 (chuang2019map4k3glkinautoimmune pages 1-2). TRAF2-dependent K63 ubiquitination augments kinase activation and JNK output (chuang2016map4kfamilykinases pages 25-29). The STRN4-containing STRIPAK complex binds and suppresses MAP4K3, limiting Hippo pathway signalling (seo2020map4kinteractomereveals pages 1-4). Active dimerisation collapses upon Ser170 dephosphorylation (marcotte2017germinal‐centerkinase‐likekinase pages 30-37).

Function  
MAP4K3 is ubiquitously expressed and up-regulated in T and B cells after TCR, TNF-α or Wnt3a stimulation (diener1997activationofthe pages 2-4). In T cells, GLK binds SLP-76 and phosphorylates PKCθ Thr538, activating IKK/NF-κB and promoting Th1/Th2/Th17 cytokine production (chuang2016map4kfamilykinases pages 18-21). Over-expression stimulates the MEKK1→MKK4→JNK cascade but not ERK or p38 (chuang2016map4kfamilykinases pages 14-18). Ser170 phosphorylation links amino-acid sufficiency to mTORC1 and phosphorylates TFEB Ser3, suppressing autophagy (chuang2019map4k3glkinautoimmune pages 1-2). The kinase phosphorylates LATS1/2 to activate Hippo signalling, an effect antagonised by STRIPAK (seo2020map4kinteractomereveals pages 1-4). Phosphorylation of IQGAP1 Ser480 promotes Cdc42-mediated cell migration (chuang2019map4k3glkinautoimmune pages 4-6). GLK also stabilises BH3-only proteins and phosphorylates BIM via JNK, driving apoptosis (lam2009map4k3modulatescell pages 1-1).

Inhibitors  
Verteporfin inhibits MAP4K3 with IC₅₀ ≈ 1.15 nM and reduces IL-17A production (chuang2019map4k3glkinautoimmune pages 4-6). Crizotinib analogues show enzymatic inhibition but limited exposure in vivo (chuang2019map4k3glkinautoimmune pages 4-6). A co-crystallised pyrrolo-pyridinylamine (“Compound 1”) yields IC₅₀ ≈ 110 nM and is selective within the GCK-I family (marcotte2017germinal‐centerkinase‐likekinase pages 25-30). Astragalus polysaccharide and 10-hydroxycamptothecin also suppress kinase activity and downstream mTORC1 signalling (chuang2019map4k3glkinautoimmune pages 4-6).

Other Comments  
GLK-null mice show defective antibody responses and resistance to experimental autoimmune encephalomyelitis (chuang2016map4kfamilykinases pages 18-21). T-cell MAP4K3 levels correlate with disease activity in systemic lupus erythematosus, rheumatoid arthritis and adult-onset Still’s disease (chuang2019map4k3glkinautoimmune pages 2-4). High MAP4K3-IQGAP1 Ser480 complex abundance predicts metastasis and poor survival in non-small-cell lung carcinoma (chuang2019map4k3glkinautoimmune pages 4-6). A pancreatic cancer mutation, E351K, increases kinase activity (chuang2019map4k3glkinautoimmune pages 4-6).

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