## Phylogeny

MATK is a member of the tyrosine kinase (TK) group, CSK family (Manning et al., 2002). It shares ~50 % sequence identity with CSK and forms a distinct non-receptor TK sub-branch possessing SH3–SH2–kinase topology (Csk-homologous kinase (Chk/Matk), 2015, pp. 12–18). Orthologous genes in mouse (Chr 8), chicken and zebrafish cluster with human MATK within the CSK lineage (Csk-homologous kinase (Chk/Matk), 2015, pp. 1–5). Proteins previously named LSK and HYL originate from the same MATK locus on 19q13.3 (Grgurevich et al., 1997). Multiple-sequence alignment confirms conservation of catalytic HRD and DFG motifs across MATK orthologs (McSkimming et al., 2016).

## Reaction Catalyzed

ATP + Src-family kinase [C-terminal Tyr] ⇌ ADP + Src-family kinase [C-terminal phospho-Tyr] (Csk-homologous kinase (Chk/Matk), 2015, pp. 1–5).

## Cofactor Requirements

Catalysis requires divalent Mg²⁺ coordinated by Asp-370 in the DFG motif (Csk-homologous kinase (Chk/Matk), 2015, pp. 22–24).

## Substrate Specificity

Primary substrates are the conserved C-terminal regulatory tyrosines of Src, Lyn and Lck (Csk-homologous kinase (Chk/Matk), 2015, pp. 12–18). β-Synuclein is an additional validated substrate in neuronal tissue (Csk-homologous kinase (Chk/Matk), 2015, pp. 9–12). Efficient phosphorylation requires a C-terminal tail bearing the inhibitory Tyr preceded by hydrophobic residues; no broader linear consensus has been reported (Csk-homologous kinase (Chk/Matk), 2015, pp. 12–18).

## Structure

MATK consists of an N-terminal SH3 domain (residues 1–60), SH2 domain (~61–150), a flexible linker and a C-terminal bilobed kinase domain (~170–510). The p56 isoform carries an additional 41-residue N-terminal extension not present in the neuronal p52 isoform (Csk-homologous kinase (Chk/Matk), 2015, pp. 5–7; Grgurevich et al., 1997). Homology modelling using the CSK crystal structure positions the glycine-rich loop (Gly 241–246), Lys 262–Glu 276 ion pair, catalytic HRDLAARN, DFG motif (Asp 370–Gly 372) and activation loop (Asp 370–Glu 390) in canonical orientations (Csk-homologous kinase (Chk/Matk), 2015, pp. 22–24). A unique non-catalytic interface on the N-lobe and αD/αF-αG regions confers high-affinity binding to active Src-family kinases, a feature absent in CSK (Csk-homologous kinase (Chk/Matk), 2015, pp. 12–18). The p56 extension contains a nuclear localisation signal (Csk-homologous kinase (Chk/Matk), 2015, pp. 5–7).

## Regulation

• Transcription is up-regulated by stem cell factor (50–100 ng mL⁻¹) and PMA in MO7e megakaryoblastic cells, peaking at 6 h (mRNA) and 12 h (protein) (Grgurevich et al., 1997).  
• Promoter hypermethylation silences MATK in colorectal cancer, glioma and acute lymphoblastic leukaemia (Csk-homologous kinase (Chk/Matk), 2015, pp. 18–22).  
• The kinase lacks activating autophosphorylation; ATP binding alone permits adoption of the inhibitory conformation that engages active Src-family kinases (Csk-homologous kinase (Chk/Matk), 2015, pp. 7–9).  
• Subcellular targeting is mediated by SH2-dependent binding to phosphotyrosine motifs on receptors such as c-Kit and TrkA; absence of N-terminal myristoylation keeps MATK predominantly cytosolic until engagement (Csk-homologous kinase (Chk/Matk), 2015, pp. 5–7; Radhakrishnan et al., 2011).

## Function

MATK is highly expressed in neurons and haematopoietic cells, with moderate levels in small intestine, colon, lung and stomach (Csk-homologous kinase (Chk/Matk), 2015, pp. 1–5). Recruitment by SCF/c-Kit, IGF-I receptor or TrkA brings MATK to signalling complexes (Grgurevich et al., 1997; Radhakrishnan et al., 2011). Catalytic phosphorylation together with non-catalytic binding suppresses Src, Lyn and Lck activities, attenuating MAPK and Akt pathways and thereby limiting T-cell proliferation and haematopoietic cell spreading (Csk-homologous kinase (Chk/Matk), 2015, pp. 12–18; Radhakrishnan et al., 2011).

## Other Comments

MATK is frequently down-regulated or mutated in colorectal, lung, gastric, breast, skin, endometrial and ovarian cancers. Missense mutations within the glycine-rich loop (E243A), αC helix (T277M), catalytic loop (R356H) and activation loop (D370N, R385Q) abolish kinase activity or disrupt Src-family kinase binding (Csk-homologous kinase (Chk/Matk), 2015, pp. 18–24). Nuclear localisation of the p52 isoform serves as a marker for type II enteropathy-associated T-cell lymphoma (Csk-homologous kinase (Chk/Matk), 2015, pp. 12–18).

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