## Phylogeny

Megakaryocyte-associated tyrosine-protein kinase (MATK; CSK-homologous kinase) is a non-receptor tyrosine kinase most closely related to C-terminal Src kinase (CSK). Orthologues have been detected almost exclusively in vertebrates and show enriched expression in hematopoietic lineages and the nervous system (Chong et al., 2005; Grgurevich et al., 1997). Sequence comparisons place MATK on the CSK evolutionary branch that emerged from the core kinase repertoire of the last eukaryotic common ancestor and co-evolved with Src family kinases. While its catalytic domain is highly conserved relative to CSK, its SH2 (and other regulatory) regions display lineage-specific adaptations that underpin tissue-restricted functions (Grgurevich et al., 1997).

## Reaction Catalyzed

ATP + [protein]-Tyr ⇌ ADP + [protein]-pTyr + H⁺  
MATK phosphorylates the conserved C-terminal regulatory tyrosine of Src family kinases, locking them into an inactive conformation (Chong et al., 2005).

## Cofactor Requirements

Mg²⁺ is essential for ATP binding and catalysis (Ia et al., 2010).

## Substrate Specificity

MATK targets the C-terminal Tyr of Src family kinases and recognises optimal motifs such as EEIYFFF; fidelity depends on local sequence determinants plus distal docking via the SH2/SH3 domains (Chong et al., 2005; Ia et al., 2010). In addition to catalytic phosphorylation, MATK can bind active Src kinases to form non-catalytic inhibitory complexes (Chong et al., 2005).

## Structure

The protein comprises an N-terminal region followed by SH3, SH2 and catalytic kinase domains. Canonical kinase motifs (glycine-rich loop, catalytic and activation loops, hydrophobic spine) are present, but MATK lacks the C-terminal inhibitory Tyr and autophosphorylation sites seen in Src kinases. Inter-domain contacts between SH2/SH3 and the kinase core modulate activity and substrate selection, mirroring mechanisms defined for CSK (Chong et al., 2005; Ia et al., 2010). No MATK-specific structural elements beyond these CSK-family features have been reported.

## Regulation

1. Catalytic action: phosphorylation of Src family kinases at the C-terminal Tyr switches them off (Chong et al., 2005).
2. MATK phosphorylation: PKA-mediated modification of residues equivalent to CSK Ser-364 stimulates full activity (Ia et al., 2010; Chong et al., 2005).
3. Localization: the SH2 domain recruits MATK to phospho-Tyr–containing adaptors (e.g., Cbp/PAG) at the plasma membrane; in platelets, thrombin triggers translocation from cytosol to cytoskeleton (Hirao et al., 1997).
4. Non-catalytic inhibition: stable MATK–Src complexes further restrain Src signalling (Chong et al., 2005).

## Function

MATK serves as a negative regulator of Src family kinase signalling.  
• Hematopoietic system: abundant in megakaryocytes, T lymphocytes and natural killer cells where it restrains proliferation/differentiation by suppressing Lyn, Lck and related kinases (Kim et al., 2004; Grgurevich et al., 1997).  
• Nervous system: neuronal expression links MATK to control of neurite outgrowth, axonal guidance and differentiation via local Src modulation (Chong et al., 2005).

## Inhibitors

No inhibitors selective for MATK are currently available. CSK-directed compounds or strategies that enhance MATK activity/mimic its Src-inhibitory interaction are being explored as potential approaches to curb aberrant Src signalling in cancer (Chong et al., 2005; Boubeva, 2011).

## Other Comments

Epigenetic silencing of the MATK gene has been documented in colorectal cancer, supporting a putative tumour-suppressor role (Chueh et al., 2021). Its restricted expression pattern makes MATK an attractive target for studies of immune dysregulation and neurological disorders.

## 9. References

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