## Phylogeny

Male germ cell-associated kinase (MAK) belongs to the CMGC group, Ime2/MAK/ICK subfamily, and its catalytic core is most closely related to CDK2 and ERK2 (Fu et al., 2006; Hanks, 2003). Two human paralogues exist—intestinal cell kinase (ICK/MRK, > 90 % identity within the kinase domain) and CDKL5—and MAK and ICK show overlapping roles in ciliary regulation (Fu et al., 2006; Chaya et al., 2024). Documented orthologues include S. cerevisiae Ime2p, S. pombe Mde3/Pit1, C. elegans DYF-5, C. reinhardtii and L. mexicana MAK homologues, and mouse Mak (Fu et al., 2006; Özgül et al., 2011).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-Ser/Thr-phosphate (Fu et al., 2006).

## Cofactor Requirements

Mg²⁺ is required for phosphotransfer activity; in-vitro assays were performed in Mg²⁺-containing buffers (Fu et al., 2006).

## Substrate Specificity

MAK prefers the consensus sequence R-P-X-S/T-P, demanding an Arg at –3 and generally a Pro at –2/–1; a Pro at +2 is tolerated (Fu et al., 2006). Verified cellular substrates include the APC/C activator CDH1/FZR1 (multiple RPX-S/T sites) and Scythe/BAT3 at Thr1080 (Fu et al., 2006; Wang & Kung, 2012).

## Structure

The protein comprises an N-terminal kinase domain (~ residues 1–300) bearing the TDY activation motif and a Pro/Gln-rich C-terminal tail (~ 301–622) (Matsushime et al., 1990; Wang & Kung, 2012). Conserved catalytic elements include the VAIK Lys, HRD triad and activation-loop Thr157-Asp158-Tyr159 (Wang & Kung, 2012). An AlphaFold model (AF-P20794-F1) predicts a canonical bilobed CMGC fold with an ordered activation segment; no experimental structure is yet available (Chaya et al., 2024).

## Regulation

Activity requires dual activation-loop phosphorylation: Thr157 is added by CCRK, whereas Tyr159 is autophosphorylated by MAK (Fu et al., 2006). PP5 removes the Thr157 phosphate, counteracting CCRK-mediated activation (Fu et al., 2006). TDY phosphorylation peaks in G2/early M phase and wanes at mitotic exit; the kinase is nuclear during interphase, relocates to spindle poles, centrosomes and the midbody during mitosis, and accumulates at ciliary tips in photoreceptors (Wang & Kung, 2012; Chaya et al., 2024).

## Function

Expression is high in pachytene and later testicular germ cells, retinal photoreceptors (long isoform containing exon 13) and is up-regulated in prostate cancer cells (Matsushime et al., 1990; Özgül et al., 2011; Wang & Kung, 2012).  
• Ciliogenesis: MAK localises to ciliary tips, restricts axonemal length, governs IFT turnaround downstream of CCRK and is essential for long-term photoreceptor survival (Chaya et al., 2024).  
• Cell-cycle control: Phosphorylation of CDH1/FZR1 suppresses APC/C^CDH1, stabilising Aurora A and PLK1 and promoting centrosome amplification and chromosome lagging (Wang & Kung, 2012).  
• Transcriptional signalling: Acts as an androgen-receptor co-activator, enhancing androgen-dependent proliferation (Wang & Kung, 2012).  
• Germ-cell survival: Phosphorylates Scythe/BAT3 Thr1080, contributing to anti-apoptotic signalling (Fu et al., 2006).

## Other Comments

Loss-of-function mutations within the kinase domain (e.g., Gly52, Asn171) abolish activity and cause autosomal-recessive retinitis pigmentosa (Özgül et al., 2011). Over-expression is common in primary and castration-resistant prostate cancer and drives chromosomal instability via APC/C^CDH1 inhibition (Wang & Kung, 2012).

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