## Phylogeny

• Kinome placement: CMGC group, Ime2/MAK/ICK subfamily; catalytic domain most similar to CDK2 and ERK2 (fu2006identificationofyinyang pages 1-2, hanks2003genomicanalysisof pages 5-6).  
• Human paralogs: ICK/MRK (>90 % identity in kinase core) and the related CDKL5; MAK and ICK exhibit functional overlap in ciliary regulation (fu2006identificationofyinyang pages 14-15, chaya2024ccrkmakickkinasesignaling pages 5-8).  
• Documented orthologs: Saccharomyces cerevisiae Ime2p, Schizosaccharomyces pombe Mde3/Pit1, Caenorhabditis elegans DYF-5, Chlamydomonas reinhardtii and Leishmania mexicana MAK homologs, and Mus musculus Mak (fu2006identificationofyinyang pages 1-2, ozgul2011exomesequencingand pages 7-9).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-Ser/Thr-phosphate (fu2006identificationofyinyang pages 1-2).

## Cofactor Requirements

Mg²⁺ is required for phosphotransfer activity; in-vitro kinase assays were carried out in Mg²⁺-containing buffers (fu2006identificationofyinyang pages 1-2).

## Substrate Specificity

• Consensus motif: R-P-X-S/T-P, with an obligatory Arg at −3 and preferred Pro at −2/−1; Pro at +2 is tolerated but not essential (fu2006identificationofyinyang pages 14-15).  
• Verified protein substrates:  
– CDH1/FZR1, multiple RPX-S/T sites in its N-terminus (wang2012malegermcellassociated pages 3-4).  
– Scythe/BAT3 Thr1080 (fu2006identificationofyinyang pages 14-15).

## Structure

• Domain organisation: N-terminal protein kinase domain (~1-300) harbouring the TDY activation motif; C-terminal Pro/Gln-rich regulatory tail (~301-622) (matsushime1990anovelmammalian pages 4-5, wang2012malegermcellassociated pages 3-4).  
• Key catalytic motifs: VAIK Lys essential for ATP anchoring, HRD catalytic triad, and TDY activation loop (Thr157-Asp158-Tyr159) (wang2012malegermcellassociated pages 2-3).  
• 3-D information: AlphaFold model AF-P20794-F1 predicts a canonical bilobed CMGC fold with an ordered activation segment; no experimental crystal structure is available (chaya2024ccrkmakickkinasesignaling pages 42-45).  
• Regulatory elements: Activation loop phosphorylation of Thr157 and Tyr159 is obligatory for catalytic activity; additional regulatory domains have not been described (fu2006identificationofyinyang pages 1-2).

## Regulation

• Activation loop dual phosphorylation – Thr157 by CCRK and Tyr159 by MAK autophosphorylation – activates the kinase (fu2006identificationofyinyang pages 1-2).  
• Dephosphorylation: PP5 removes the Thr157 phosphate, antagonising CCRK-mediated activation (fu2006identificationofyinyang pages 1-2).  
• Cell-cycle dynamics: TDY phosphorylation peaks at G2/early M and declines at mitotic exit (wang2012malegermcellassociated pages 2-3).  
• Subcellular redistribution: Nuclear in interphase, associates with spindle poles, centrosomes and midbody during mitosis, and accumulates at ciliary tips in photoreceptors (wang2012malegermcellassociated pages 1-2, chaya2024ccrkmakickkinasesignaling pages 5-8).

## Function

• Expression: Highly expressed in pachytene and later testicular germ cells, retinal photoreceptors (long isoform with exon 13), and over-expressed in prostate cancer cells (matsushime1990anovelmammalian pages 1-2, ozgul2011exomesequencingand pages 7-9, wang2012malegermcellassociated pages 6-7).  
• Ciliogenesis: Localises to ciliary tips, constrains axonemal length and governs IFT turnaround downstream of CCRK, critical for long-term photoreceptor survival (chaya2024ccrkmakickkinasesignaling pages 5-8, chaya2024ccrkmakickkinasesignaling pages 42-45).  
• Cell-cycle control: Phosphorylates CDH1/FZR1, suppresses APC/C^CDH1 activity, stabilises Aurora A and PLK1, promoting centrosome amplification and chromosome lagging (wang2012malegermcellassociated pages 3-4, wang2012malegermcellassociated pages 6-7).  
• Transcriptional signalling: Acts as a co-activator of androgen receptor to enhance androgen-dependent proliferation (wang2012malegermcellassociated pages 1-2).  
• Germ-cell survival: Phosphorylates Scythe/BAT3 at Thr1080, a modification linked to anti-apoptotic regulation (fu2006identificationofyinyang pages 14-15).

## Other Comments

• Retinitis pigmentosa: Recessive loss-of-function mutations within the kinase domain (e.g., Gly52, Asn171) abolish activity and cause progressive photoreceptor degeneration (ozgul2011exomesequencingand pages 7-9).  
• Oncology: MAK over-expression is frequent in primary and castration-resistant prostate cancer and contributes to chromosomal instability via APC/C^CDH1 inhibition (wang2012malegermcellassociated pages 6-7).

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