## Proposed EC/sub-subclass

Not specified in the cited sources.

## Accepted name

Microtubule-associated serine/threonine kinase-like (MASTL; human Greatwall kinase)

## Synonyms

Greatwall kinase (Gwl); Greatwall (Drosophila, Xenopus); functional ortholog Rim15p (yeast)

## Phylogeny

MASTL is an atypical member of the AGC family of serine/threonine protein kinases (Ammarah et al., 2018; Lorca & Castro, 2013; Manning et al., 2002). Orthologues are conserved from yeast (Rim15p) through invertebrates (Greatwall in Drosophila) to vertebrates (Greatwall in Xenopus and MASTL in mammals), underscoring an evolutionarily conserved cell-cycle role (Fatima et al., 2020; Marzec & Burgess, 2018; Nagel et al., 2015; Voets & Wolthuis, 2010).

## Reaction Catalyzed

ATP + protein ⇌ ADP + phosphoprotein (Johnson et al., 2023; Marzec & Burgess, 2018; Voets & Wolthuis, 2010)

## Cofactor Requirements

Catalysis requires Mg²⁺ and ATP (Johnson et al., 2023; Voets & Wolthuis, 2010).

## Substrate Specificity

Positional scanning peptide arrays define a preference for Ser/Thr phosphorylation with position-specific sequence biases recorded in the Johnson et al. (2023) kinome atlas; the detailed matrix is contained in that study’s supplementary tables. Confirmed physiological substrates are ARPP19 (Ser62) and ENSA (Ser67) (Fatima et al., 2020).

## Structure

MASTL is a bifurcated AGC kinase composed of N- and C-terminal domains flanking a central catalytic core that contains a ~500-residue non-conserved insertion within the activation segment between the DFG and APE motifs (Ammarah et al., 2018; Lorca & Castro, 2013; Ocasio et al., 2016). The crystal structure of the minimal kinase domain (PDB 5LOH) exhibits the canonical bilobal kinase fold; the C-helix and activation loop are disordered, indicating an inactive conformation (Ocasio et al., 2016). Conserved AGC regulatory elements—hydrophobic spines, hydrophobic-motif binding pocket, and C-terminal CLA/CLT/AST segments—are present (Lorca & Castro, 2013; Ocasio et al., 2016).

## Regulation

Activity peaks in mitosis and is stimulated by Cyclin B–CDK1–mediated phosphorylation, notably at Thr194 within the activation loop (Diril et al., 2016; Fatima et al., 2020; Voets & Wolthuis, 2010). Mitotic exit requires stepwise dephosphorylation by PP1 and subsequently PP2A-B55, forming a feedback loop (Marzec & Burgess, 2018). Binding of hydrophobic motifs from other AGC kinases (e.g., RSK2) can further activate MASTL (Ammarah et al., 2018).

## Function

Expression and localisation: MASTL is predominantly nuclear in interphase and partially associates with centrosomes during mitosis; expression remains constant through G₂/M (Alvarez-Fernández et al., 2017; Voets & Wolthuis, 2010; Wong et al., 2016).  
Downstream pathway: By phosphorylating ARPP19 and ENSA, MASTL inhibits PP2A-B55, thereby sustaining Cyclin B1-CDK1 activity and ensuring proper mitotic entry, progression, anaphase, cytokinesis and chromosome condensation—the MASTL-ENSA-PP2A (MEP) axis (Fatima et al., 2020; Marzec & Burgess, 2018; Voets & Wolthuis, 2010).  
Additional roles: Contributes to AKT/mTOR and Wnt/β-catenin signalling and regulates recovery from DNA-damage checkpoints (Fatima et al., 2020; Wong et al., 2016).

## Inhibitors

The first-generation small-molecule inhibitor GKI-1 suppresses pancreatic tumour cell viability and growth in vivo (Ammarah et al., 2018; Fatima et al., 2021). In-silico screening has also identified additional natural and synthetic compounds with predicted high affinity for the active site (Ammarah et al., 2018).

## Other Comments

MASTL is frequently over-expressed in diverse cancers (breast, pancreatic, prostate, oral, gastric, colon, head and neck, thyroid, liver). High levels correlate with poor prognosis, higher grade and therapy resistance (Alvarez-Fernández et al., 2017; Ammarah et al., 2018; Fatima et al., 2020). A hyperactive K72M mutant accelerates mitotic entry after DNA damage (Wong et al., 2016).

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