1. Phylogeny  
   MAST1 (Microtubule‐associated serine/threonine‐protein kinase 1, gene KIAA0973, also known as SAST) is a member of the MAST kinase family, which forms a distinct subgroup within the AGC kinase superfamily. MAST kinases are evolutionarily conserved proteins found in a wide range of metazoans, including vertebrates, insects, and nematodes, indicating that this family arose early in animal evolution and has been maintained throughout development and diversification of the eukaryotic lineage (rumpf2023microtubuleassociatedserinethreonine(mast) pages 11-13). Members of this family share a common modular organization that distinguishes them from other AGC kinase subfamilies. Phylogenetic analyses based on primary amino acid sequences support that MAST1, along with its paralogs MAST2, MAST3, and MAST4, originated from gene duplication events in early metazoans, maintaining a core set of conserved domains such as a DUF1908 region, a catalytic serine/threonine kinase domain, and a C-terminal PDZ domain (tripathy2018mutationsinmast1 pages 3-5). The substantial conservation of both sequence and domain architecture across species implies that MAST kinases perform fundamental and critical cellular functions that have been preserved during evolution (rumpf2023microtubuleassociatedserinethreonine(mast) pages 11-13).
2. Reaction Catalyzed  
   MAST1 catalyzes the transfer of a phosphate group from ATP to the hydroxyl group on the serine or threonine residue of a protein substrate. In biochemical terms, the reaction may be represented as:  
     ATP + [protein]–(L‐serine or L‐threonine) → ADP + [protein]–(L‐serine/threonine)‐phosphate + H⁺ (anti2009nonspecificserinethreonineprotein pages 19-22).  
   This reaction, common to all serine/threonine kinases, underlies the enzyme’s role in modulating the function, localization, and interactions of its protein substrates by altering their phosphorylation state.
3. Cofactor Requirements  
   The catalytic activity of MAST1, similar to other serine/threonine protein kinases, is dependent upon the presence of divalent metal ions. In most instances, the kinase activity requires Mg²⁺ as a cofactor to coordinate the binding of ATP to the active site and facilitate the transfer of the phosphate group (anti2009nonspecificserinethreonineprotein pages 19-22). This requirement for Mg²⁺ is consistent with the mechanistic attributes shared by the AGC family of protein kinases.
4. Substrate Specificity  
   MAST1 is thought to phosphorylate serine/threonine residues on a variety of protein substrates, although a definitive consensus phosphorylation motif for MAST1 has not been fully characterized. The enzyme’s substrate specificity appears to be determined by the inherent selectivity of its catalytic domain as well as by the additional substrate‐targeting functions of its C‐terminal PDZ domain, which mediates protein–protein interactions by recognizing specific C‐terminal sequences in partner proteins (rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5). By similarity to other AGC kinases and based on its cellular interactions, potential substrates include components of the dystrophin/utrophin network – such as dystrophin (DMD) and utrophin (UTRN) – where phosphorylation may modulate their binding affinities for associated proteins (Information; sun2006identificationofa pages 1-4). In addition, studies employing large-scale peptide library screening for serine/threonine kinases suggest that kinase substrate specificity is influenced by the amino acid environment surrounding the target residue; however, for MAST1 the exact amino acid preferences remain to be fully defined (mok2010decipheringproteinkinase pages 15-19, rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5).
5. Structure  
   MAST1 exhibits a modular domain organization that is characteristic of the MAST kinase family. The N-terminal region contains a domain of unknown function (DUF1908), approximately 275 amino acids in length, which is divided into an unstructured segment enriched in serine, threonine, and tyrosine residues (potential phosphorylation sites) and a structured region containing several alpha-helices (rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5). This DUF1908 segment is conserved among MAST kinases and may play a role in regulatory interactions, although its precise function has not been elucidated.  
   The central region of MAST1 houses the serine/threonine kinase domain, which adopts a bi-lobal fold typical of AGC kinases. The N-lobe, predominantly composed of beta-strands, and the predominantly alpha-helical C-lobe together form an ATP-binding cleft where critical catalytic motifs such as the DFG, APE, and HRD sequences are located. A unique structural feature of MAST kinases is the substitution of the first glycine in the conserved glycine-rich loop (GXGXXG) with a serine residue, a change that potentially permits regulatory phosphorylation at this position and might modulate kinase activity (rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5, pages 5-7).  
   At the C-terminus, MAST1 contains a PDZ domain, a well‐characterized structural module that mediates interactions with specific C-terminal motifs of partner proteins. High-resolution structural studies, including X-ray crystallography and AlphaFold predictions for related MAST family members, have demonstrated that the PDZ domain of MAST kinases exhibits minimal structural deviation among family members, supporting its conserved role in substrate and partner recruitment (rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5). This PDZ domain is especially relevant for linking the kinase to components of the dystrophin/utrophin network via syntrophin interaction.  
   Overall, the three-domain architecture – DUF1908, central catalytic kinase domain, and C-terminal PDZ domain – provides MAST1 with both enzymatic activity and the precise subcellular targeting necessary for its role in complex signaling and structural networks within the cell (rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5, sun2006identificationofa pages 1-4).
6. Regulation  
   The regulation of MAST1 involves multiple post‐translational modifications and protein–protein interactions that together modulate its stability and kinase activity. Phosphorylation within the kinase domain and its regulatory tails is believed to govern its catalytic activity, though exact phosphorylation sites on MAST1 have not been comprehensively mapped. In addition to phosphorylation, MAST1 undergoes ubiquitin‐dependent regulation. A genome-wide CRISPR/Cas9-based screening in cisplatin-resistant cells has identified the deubiquitinase USP1 as a critical regulator that interacts with and stabilizes MAST1 by removing ubiquitin chains, thereby preventing its proteasomal degradation (tyagi2022crisprcas9basedgenomewidescreening pages 11-14). Conversely, the E3 ubiquitin ligase Cdh1 has been shown to bind MAST1 and promote its ubiquitination, leading to reduced protein levels. These opposing regulatory mechanisms help maintain appropriate cellular levels of MAST1 and likely influence its activity under various physiological conditions.  
   Furthermore, mutations in MAST1, such as the deletion mutant L278del, have been shown to alter its binding to microtubules and interfere with proper signaling in neurons, underscoring the importance of precise regulatory modification for normal protein function (tripathy2018mutationsinmast1 pages 8-9). Such modifications, whether occurring through phosphorylation or ubiquitination, have functional consequences in terms of kinase activity, substrate recognition, and ultimately cellular signaling, although the complete mechanistic details remain an active area of investigation (rumpf2023microtubuleassociatedserinethreonine(mast) pages 16-17).
7. Function  
   MAST1 plays an essential role in brain development and neuronal function. It is classified as a microtubule-associated protein and is critical for the correct formation of brain structures. MAST1 exerts its function in part by linking the dystrophin/utrophin network with microtubule filaments, a connection that is mediated via its interaction with syntrophins, particularly β2-syntrophin (sun2006identificationofa pages 1-4). This scaffolding function facilitates the proper organization of cytoskeletal elements and signaling complexes in neurons.  
   In addition to its structural role, MAST1 participates in intracellular signaling cascades. There is evidence that MAST1 associates with components of the MAPK pathway wherein it may phosphorylate downstream kinases such as MEK1 on serine residues, thereby modulating signaling events that control cell proliferation and survival. Such activities are critical for both the development and maintenance of neuronal networks (rumpf2023microtubuleassociatedserinethreonine(mast) pages 8-10).  
   Dysregulation of MAST1, as evidenced by mutations that alter its microtubule binding or affect its stability, is linked to severe neurodevelopmental disorders characterized by abnormal brain morphology, including mega-corpus-callosum syndrome with cerebellar hypoplasia and cortical malformations (tripathy2018mutationsinmast1 pages 3-5, pages 8-9). Moreover, aberrant expression or gene fusions involving MAST1 have been observed in certain cancers, such as invasive breast carcinomas, where they may contribute to dysregulated signaling and chemoresistance (rumpf2023microtubuleassociatedserinethreonine(mast) pages 8-10, tyagi2022crisprcas9basedgenomewidescreening pages 11-14).  
   MAST1 is predominantly expressed in the central nervous system, consistent with its critical role in neurodevelopment, and its interactions with proteins involved in cytoskeletal dynamics underscore its importance in maintaining cellular architecture and signaling integrity in neurons (Information; tripathy2018mutationsinmast1 pages 3-5).
8. Other Comments  
   Beyond its established roles in brain development and synaptic organization, MAST1 has emerged as an important mediator in various pathological contexts. Gene fusions involving MAST1 and its overexpression have been documented in certain malignancies, including breast cancer, where they are associated with enhanced cell proliferation and cisplatin resistance (rumpf2023microtubuleassociatedserinethreonine(mast) pages 8-10, tyagi2022crisprcas9basedgenomewidescreening pages 11-14).  
   Additionally, mutations in MAST1, such as specific amino acid deletions within the DUF1908 domain, have been linked to neurodevelopmental syndromes characterized by structural brain abnormalities. These mutations typically exert dominant-negative effects that compromise the normal function of MAST kinase signaling in neurons (tripathy2018mutationsinmast1 pages 3-5, pages 8-9).  
   Although no MAST1-specific inhibitors have been widely validated in clinical settings to date, the interest in targeting kinases within the AGC family, combined with the unique structural features of MAST1—particularly the distinctive residues in its ATP-binding and substrate recognition regions—presents potential avenues for the development of selective therapeutic agents. In this regard, further studies aimed at elucidating the precise consensus phosphorylation motifs and regulatory mechanisms of MAST1 will be essential (karpov2024predictionofproteinligand pages 1-2).
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