1. Phylogeny  
   UHMK1, also known as Kinase Interacting with Stathmin (KIS) or U2AF homology motif kinase 1, is classified as a non‐specific serine/threonine protein kinase under EC 2.7.11.1 and is part of the extensive repertoire of protein kinases conserved in the human genome (anti2009nonspecificserinethreonineprotein pages 19-22). Comparative analyses of the human kinome, as originally described by Manning and colleagues and expanded in later studies, reveal that many serine/threonine kinases share a conserved catalytic core; UHMK1 retains this canonical kinase domain while uniquely incorporating a U2AF homology motif (UHM) that is not commonly observed in other kinases (miranda‐saavedra2007classificationandfunctional pages 1-2, anti2009nonspecificserinethreonineprotein pages 27-29). Orthologs of UHMK1 have been identified across diverse eukaryotic species, indicating its evolutionary conservation from yeast to mammals; this conservation underscores its inclusion in the core set of kinases that emerged in the Last Eukaryotic Common Ancestor (anti2009nonspecificserinethreonineprotein pages 37-39, miranda‐saavedra2007classificationandfunctional pages 1-2). Phylogenetic analyses employing hidden Markov model (HMM) profiling and alignment of catalytic domains have positioned UHMK1 among non‐specific serine/threonine kinases that are broadly distributed, with the unique presence of the UHM domain suggesting an evolutionary specialization related to RNA processing functions (anti2009nonspecificserinethreonineprotein pages 19-22, miranda‐saavedra2007classificationandfunctional pages 1-2). Furthermore, sequence comparisons and domain architecture analyses reveal that while UHMK1 shares extensive homology with other members of the serine/threonine kinase complement, its ancillary UHM distinguishes it from conventional members of the CAMK and CMGC groups, even though similarities in the catalytic core suggest that it may be evolutionarily related to these families (anti2009nonspecificserinethreonineprotein pages 27-29, anti2009nonspecificserinethreonineprotein pages 37-39). Such phylogenetic placement not only reinforces its classification within the broad framework of eukaryotic protein kinases but also highlights the divergence in accessory domains that have allowed UHMK1 to acquire specialized functions in regulating cell cycle progression and RNA processing (miranda‐saavedra2007classificationandfunctional pages 1-2).
2. Reaction Catalyzed  
   UHMK1 functions by transferring a phosphate group from ATP to the hydroxyl group of serine or threonine residues in substrate proteins, thereby converting ATP into ADP and producing a phosphorylated substrate along with the release of a proton (anti2009nonspecificserinethreonineprotein pages 29-32). This catalytic reaction is characteristic of serine/threonine kinases and conforms to the general mechanism in which the gamma phosphate of ATP is used to phosphorylate target amino acid residues within protein substrates (anti2009nonspecificserinethreonineprotein pages 29-32).
3. Cofactor Requirements  
   The catalytic activity of UHMK1, like that of most serine/threonine kinases, requires the presence of divalent metal ions, with Mg²⁺ acting as an essential cofactor during the phosphoryl transfer reaction (anti2009nonspecificserinethreonineprotein pages 119-121). The binding of Mg²⁺ to the ATP molecule is critical for proper positioning of the phosphate groups within the active site, thereby facilitating the efficient transfer of the phosphoryl moiety (anti2009nonspecificserinethreonineprotein pages 119-121).
4. Substrate Specificity  
   UHMK1 phosphorylates serine/threonine residues in its target proteins and displays substrate specificity typical of non‐specific serine/threonine kinases, with a propensity toward phosphorylating proline‐directed serine residues within specific recognition motifs (anti2009nonspecificserinethreonineprotein pages 37-39). In particular, UHMK1 has been reported to phosphorylate substrates that are involved in RNA processing, such as components of the spliceosome, as well as cell cycle regulators like CDKN1B/p27Kip1, whose phosphorylation alters subcellular localization and modulates cell cycle progression in G1 phase (information provided, anti2009nonspecificserinethreonineprotein pages 37-39). The consensus substrate motif recognized by UHMK1 is less stringently defined than those of many highly specific kinases; however, its activity is preferentially directed toward serine residues positioned within proline‐rich or adjacent acidic regions that are common in proteins involved in RNA trafficking and splicing (anti2009nonspecificserinethreonineprotein pages 37-39).
5. Structure  
   UHMK1 is composed of a central catalytic kinase domain that conforms to the typical bilobal structure observed in serine/threonine kinases, with an N-terminal lobe primarily responsible for ATP binding and a larger C-terminal lobe that accommodates the protein substrate (anti2009nonspecificserinethreonineprotein pages 19-22). Critical catalytic residues, such as those implicated in ATP coordination and phosphate transfer, have been identified within this domain; for example, residues analogous to Lys233, along with other important amino acids, contribute to the formation of the active site (anti2009nonspecificserinethreonineprotein pages 19-22, anti2009nonspecificserinethreonineprotein pages 111-114). Uniquely, UHMK1 also contains a U2AF homology motif (UHM) that serves as a protein–protein interaction module and is primarily involved in mediating contacts with splicing factors such as SF1 and SF3B1 (information provided). This UHM is positioned adjacent to the kinase domain, thereby allowing UHMK1 to integrate catalytic function with substrate recruitment through its capacity to bind specific protein partners (anti2009nonspecificserinethreonineprotein pages 111-114). Although no high‐resolution crystal structure for UHMK1 is available in the literature referenced here, computational models and sequence homology indicate that its overall three‐dimensional organization is consistent with that of classical serine/threonine kinases, featuring an activation loop, a conserved catalytic loop, and a C-helix that are essential for its enzymatic activity (anti2009nonspecificserinethreonineprotein pages 19-22, anti2009nonspecificserinethreonineprotein pages 111-114).
6. Regulation  
   Regulation of UHMK1 occurs at multiple levels, including post‐translational modifications and protein–protein interactions that modulate its catalytic activity. Autophosphorylation events have been described as a common regulatory mechanism among non‐specific serine/threonine protein kinases, and UHMK1 is subject to similar modifications that may affect its conformation and functional state (anti2009nonspecificserinethreonineprotein pages 27-29). In addition, phosphorylation of UHMK1’s substrates, such as CDKN1B/p27Kip1, is critical for controlling their subcellular localization and, in turn, the progression of the cell cycle through the G1 phase; these substrate phosphorylation events indirectly reflect the regulatory output of UHMK1 activity (information provided, anti2009nonspecificserinethreonineprotein pages 37-39). Transcriptional regulation also plays a role in controlling UHMK1 levels, with evidence indicating that its expression is induced upon serum stimulation and during specific differentiation processes, thereby linking its activity to cellular proliferation and differentiation programs (information provided, anti2009nonspecificserinethreonineprotein pages 27-29). Overall, both the intrinsic catalytic properties of UHMK1 and its regulation by upstream signals converge to ensure appropriate modulation of its kinase activity within the cellular context (anti2009nonspecificserinethreonineprotein pages 37-39).
7. Function  
   UHMK1 has been demonstrated to phosphorylate the cyclin-dependent kinase inhibitor CDKN1B/p27Kip1 in response to serum stimulation, an event that is central to controlling the subcellular localization of p27Kip1 and regulating entry into the cell cycle during the G1 phase (information provided, anti2009nonspecificserinethreonineprotein pages 37-39). This phosphorylation event is critical for modulating cell cycle progression, as the redistribution of p27Kip1 influences the activity of cyclin-dependent kinases and thereby affects the timing of the G1 to S phase transition (information provided, anti2009nonspecificserinethreonineprotein pages 111-114). In addition to its role in cell cycle control, UHMK1 is implicated in the regulation of RNA processing and trafficking; its U2AF homology motif facilitates interactions with splicing factors, contributing to alterations in pre-mRNA splicing events that can have widespread effects on gene expression (information provided, anti2009nonspecificserinethreonineprotein pages 37-39). The kinase’s involvement in these processes suggests a dual functional role whereby UHMK1 coordinates cell cycle dynamics with post‐transcriptional regulation, a mechanism that has been conserved across multiple species (anti2009nonspecificserinethreonineprotein pages 27-29, anti2009nonspecificserinethreonineprotein pages 37-39). Expression studies have also revealed that UHMK1 activity is associated with cellular responses to extracellular signals, such as serum factors, further underscoring its significance in integrating proliferative signals with RNA metabolic processes (information provided, anti2009nonspecificserinethreonineprotein pages 19-22).
8. Other Comments  
   No specific inhibitors for UHMK1 have been characterized in the publications referenced here; however, its unique domain architecture—comprising a kinase catalytic domain and an appended U2AF homology motif—indicates that it may represent a novel target for future pharmacological intervention (anti2009nonspecificserinethreonineprotein pages 111-114). Disease associations for UHMK1 have been suggested by its role in modulating cell cycle progression via phosphorylation of CDKN1B/p27Kip1, a process with potential relevance to oncogenic transformation and uncontrolled cell proliferation (anti2009nonspecificserinethreonineprotein pages 37-39, anti2009nonspecificserinethreonineprotein pages 119-121). Although detailed studies on mutations or clinical correlations are not available in the current literature, the integration of cell cycle regulation with RNA processing implicates UHMK1 as a protein of interest in pathological conditions characterized by dysregulation of these fundamental processes (anti2009nonspecificserinethreonineprotein pages 37-39). Its categorization within the “Protein kinase, Other” group further highlights the need for additional research to elucidate its unique regulatory mechanisms and potential as a therapeutic target (miranda‐saavedra2007classificationandfunctional pages 1-2).
9. References
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