1. Phylogeny  
   Serine/threonine‐protein kinase tousled‐like 1 (TLK1), also known as PKU‐beta or KIAA0137, is a member of the conserved Tousled‐like kinase family found in plants and metazoans. TLK1 orthologs are present from Arabidopsis thaliana to Caenorhabditis elegans and mammals, indicating an evolutionarily ancient function in DNA replication and chromatin assembly (benedetti2012thetousledlikekinases pages 2-3, segurabayona2019thetousledlikekinases pages 1-3). Within the human kinome, TLK1 belongs to a group of cell cycle–regulated serine/threonine kinases that share sequence similarity within their catalytic domains. It is closely related to TLK2, with which it shares high amino acid identity—particularly over the kinase domain—and the two enzymes often have overlapping functions. The evolutionary relationship of TLK1 and TLK2 reflects a gene duplication event in higher eukaryotes, and both enzymes are considered part of an essential core set of kinases that contribute to genome integrity in multicellular organisms (sillje1999mammalianhomologuesof pages 1-2, benedetti2012thetousledlikekinases pages 2-3).
2. Reaction Catalyzed  
   TLK1 catalyzes the transfer of a phosphate group from ATP to target serine/threonine residues on substrate proteins. In biochemical terms the reaction can be summarized as: ATP + [protein]‐(L‐serine/threonine) → ADP + [protein]‐(phospho-L‐serine/threonine) + H⁺. This phosphorylation reaction is fundamental for regulating the function of its substrate proteins that include histone H3, components of the DNA damage response, and other chromatin‐associated factors (benedetti2012thetousledlikekinases pages 1-2, riefler2008tousledmediatedactivationof pages 1-1).
3. Cofactor Requirements  
   The kinase activity of TLK1 requires divalent metal ions as cofactors, with Mg²⁺ being essential for facilitating ATP binding and phosphate transfer to the substrate. In standard kinase assays, the presence of Mg²⁺ is critical to support its enzymatic function during phosphorylation reactions (bhoir2018highyieldbacterial pages 6-8).
4. Substrate Specificity  
   TLK1 phosphorylates serine and threonine residues in proteins that are directly involved in chromatin assembly and the DNA damage response. One well‐characterized substrate is histone H3, phosphorylated at serine 10—a modification that is linked to chromosome condensation and proper progression through mitosis (benedetti2012thetousledlikekinases pages 2-3). In addition, TLK1 phosphorylates ASF1 (anti‐silencing function 1), a histone chaperone whose phosphorylation is critical for ensuring efficient nucleosome assembly during DNA replication and repair (segurabayona2019thetousledlikekinases pages 4-5). Importantly, an isoform of TLK1 (isoform 3) phosphorylates and enhances the stability of the t‐SNARE protein SNAP23, thereby augmenting its assembly with syntaxin and contributing to cellular resistance to ionizing radiation by facilitating double‐strand break repair (bhoir2023targetingprostatecancer pages 19-20). Although a definitive consensus substrate motif for TLK1 has not been completely delineated in the available literature, its substrate specificity is dictated by the structural context provided by its catalytic domain and additional regulatory regions, ensuring that substrates connected with chromatin remodeling and DNA repair are preferentially phosphorylated (ghosh2023untouslingtherole pages 7-8).
5. Structure  
   TLK1 displays a domain architecture typical of many serine/threonine kinases. It comprises a central catalytic kinase domain that is responsible for ATP binding and the transfer of the phosphate group. Flanking this catalytic domain are regulatory regions, including an N-terminal segment that contains nuclear localization signals (NLS) and predicted coiled-coil (CC) motifs. These coiled-coil domains are thought to mediate homo- or heterodimerization with TLK2, a structural arrangement that facilitates autophosphorylation and full enzyme activation (segurabayona2019thetousledlikekinases pages 5-7, mortuza2018molecularbasisof pages 1-2). The activation loop within the kinase domain is subject to conformational changes upon autophosphorylation, which is common among serine/threonine kinases and necessary for catalytic competence. Structural features observed in crystallographic or homology models reveal a typical bilobal fold with a smaller N-terminal lobe predominantly made of β-sheets and a larger C-terminal lobe that is mainly helical. The catalytic cleft located between these lobes accommodates ATP and the protein substrate, and conserved motifs such as the DFG motif and the catalytic loop contribute to coordinating the metal ion cofactor and catalytic water molecules (mortuza2018molecularbasisof pages 11-13, segurabayona2019thetousledlikekinases pages 4-5).
6. Regulation  
   TLK1 activity is tightly controlled by cell cycle cues and DNA damage signals. Under normal S-phase conditions, TLK1 is active, promoting chromatin assembly by phosphorylating histone chaperones and other substrates. However, upon induction of DNA double-strand breaks, TLK1 is rapidly and transiently inhibited through phosphorylation. This DNA damage–induced inhibition is mediated via checkpoint signaling pathways, in particular through ATM-dependent activation of Chk1, which phosphorylates TLK1 at specific residues—such as serine 695—leading to a reduction of its kinase activity (benedetti2012thetousledlikekinases pages 6-7, sunavala‐dossabhoy2018preservingsalivarygland pages 12-16). In addition to DNA damage–dependent modulation, translational regulation via upstream open reading frames (uORFs) in the 5′-UTR of TLK1B, an important splice variant, also influences TLK1 protein levels. Post-translational modifications, including autophosphorylation events, are essential for maintaining proper activity and regulating protein–protein interactions with substrates such as ASF1 and Rad9 (ghosh2023untouslingtherole pages 2-4, benedetti2012thetousledlikekinases pages 6-7).
7. Function  
   TLK1 plays an important role in maintaining genome integrity through its involvement in chromatin assembly and the DNA damage response. In proliferating cells during S-phase, TLK1 phosphorylates histone H3 at serine 10, a modification associated with chromatin condensation and necessary for proper chromosome segregation during mitosis (riefler2008tousledmediatedactivationof pages 1-1). It also phosphorylates ASF1, a histone chaperone that facilitates the deposition of histones onto newly synthesized DNA, thereby ensuring efficient nucleosome formation and chromatin remodeling essential for both DNA replication and repair (segurabayona2019thetousledlikekinases pages 4-5). Moreover, TLK1 phosphorylates Rad9, a member of the 9-1-1 checkpoint clamp, to promote the timely deactivation of DNA damage checkpoints once repair processes are complete. Notably, the isoform 3 of TLK1 enhances the stability and assembly of the t-SNARE SNAP23, which supports the repair of DNA double-stranded breaks and provides protection from ionizing radiation (bhoir2023targetingprostatecancer pages 19-20). These functions situate TLK1 at a central node in signaling pathways that couple the DNA damage response to cell cycle progression and chromatin dynamics (benedetti2012thetousledlikekinases pages 2-3, ghosh2023untouslingtherole pages 5-7). TLK1 is expressed in a wide range of tissues, consistent with its indispensable role in genomic stability, and its activity is critical during periods of high DNA replication where chromatin assembly must be meticulously coordinated with replication fork progression.
8. Other Comments  
   Experimental inhibitors of TLK1 have been investigated with phenothiazine derivatives such as thioridazine showing the ability to inhibit TLK1 autophosphorylation at low micromolar concentrations, though their binding modes require further clarification (hashimoto2008pkuβtlk1regulatesmyosin pages 3-5). Furthermore, TLK1 overexpression has been associated with increased resistance to DNA damaging agents, a feature with potential implications in cancer therapy. The functional profile of TLK1 also extends to roles in regulating cytoskeletal components, as indicated by studies demonstrating that TLK1-mediated phosphorylation of myosin regulatory light chains is essential for accurate chromosome segregation during mitosis (hashimoto2008pkuβtlk1regulatesmyosin pages 3-5). To date, mutations specifically altering TLK1 function have not been extensively detailed; however, its pivotal role in DNA repair and chromatin dynamics implicates TLK1 in tumor adaptation to genotoxic stress, making it a promising target for therapeutic intervention in radioresistant cancers (bhoir2023targetingprostatecancer pages 5-6). In addition, the differential regulation of TLK1 isoforms, particularly the translationally controlled TLK1B variant, opens additional avenues for exploring how alternative splicing affects cellular responses to replication stress and DNA damage (benedetti2012thetousledlikekinases pages 3-4).
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