1. Phylogeny  
   CLK4 is an evolutionarily conserved member of the CDC2‐like kinase family, which belongs to the CMGC group of protein kinases that also includes cyclin‐dependent kinases (CDKs), mitogen‐activated protein kinases (MAPKs) and glycogen synthase kinases (GSKs). Early phylogenetic analyses have demonstrated that the CLK family, originally described in the early 1990s, emerged from a common ancestral kinase present in the Last Eukaryotic Common Ancestor (LECA), and gene duplication events during metazoan evolution led to the establishment of four paralogous isoforms—CLK1, CLK2, CLK3, and CLK4—in vertebrates (moyano2020cdclikekinases(clks) pages 1-3). Comparative studies using orthologous sequences from yeast, plants and animals reveal that the central catalytic domain of CLK4, including the ATP‐binding motif LGEGAFGKV, is highly conserved across species, underscoring its critical functional role. In mouse, for example, the orthologous kinase (mCLK4) exhibits similar biochemical and regulatory properties as those observed in the human protein, indicating that the core functions of CLK4 have been preserved over millions of years (nayler1997characterizationandcomparison pages 6-7). Moreover, the structural features shared by all CDC2‐like kinases—including the presence of regulatory motifs such as the LAMMER sequence—establish CLK4 within a distinct phylogenetic subgroup characterized by dual‐specificity catalytic activity, and these evolutionary relationships are supported by both sequence alignments and phylogenetic mapping studies (moyano2020cdclikekinases(clks) pages 1-3, mott…2011aninhibitorof pages 1-6).
2. Reaction Catalyzed  
   CLK4 catalyzes the transfer of a phosphate group from ATP to specific amino acid residues on substrate proteins. The general reaction follows the canonical kinase mechanism: ATP + [protein]-(L‑serine or L‑threonine) yields ADP + [protein]-(L‑serine/threonine)-phosphate + H⁺. Although CLK4 is classified as a dual-specificity kinase capable of acting on serine/threonine as well as tyrosine residues, its primary in vivo substrates are the serine/arginine-rich (SR) proteins, where phosphorylation predominantly occurs on serine residues localized within their RS (arginine-serine) domains (elhady2017developmentofselective pages 13-14, song2023cdc2likekinasesstructure pages 3-3).
3. Cofactor Requirements  
   As with most kinases, CLK4 requires ATP as a phosphate donor for its catalytic activity, and its function is significantly enhanced in the presence of divalent cations. Magnesium ions (Mg²⁺) are essential cofactors that stabilize the binding of ATP within the kinase’s active site, thereby facilitating efficient phosphate transfer during the catalytic cycle. The need for Mg²⁺ is consistent with the biochemical behavior of the CMGC family of kinases and is fundamental for CLK4’s activity during phosphorylation reactions (elhady2017developmentofselective pages 13-14, moyano2020cdclikekinases(clks) pages 1-3).
4. Substrate Specificity  
   The substrate specificity of CLK4 is defined by its ability to recognize and phosphorylate serine/arginine-rich (SR) proteins that are integral components of the spliceosomal machinery. CLK4 preferentially phosphorylates key splicing factors such as SRSF1 and SRSF3, targeting multiple serine residues clustered within the RS domains of these proteins. This phosphorylation event alters the conformation and charge characteristics of SR proteins, thereby modulating their intranuclear distribution, their assembly into the spliceosome, and ultimately splice site selection during pre-mRNA processing. In addition to its well‐established role in modulating the splicing of genes such as MAPT (TAU) and tissue factor (F3) within endothelial cells, CLK4’s substrate specificity further extends to the regulation of alternative splicing events by fine-tuning the activity and nuclear dynamics of multiple SR protein family members (elhady2017developmentofselective pages 13-14, hogg2023functionsofsrpkclkanddyrkkinasesin pages 7-8, song2023cdc2likekinasesstructure pages 1-3).
5. Structure  
   CLK4 contains a well‐defined central kinase domain, which is characteristic of the CMGC group, and is flanked by regulatory regions that include an intrinsically disordered N-terminal extension enriched in arginine/serine sequences. The catalytic domain adopts the canonical bi-lobed architecture with an N-terminal lobe composed mainly of β-sheets and a C-terminal lobe that is predominantly α-helical; these lobes are connected by a flexible hinge region that contributes to the formation of the ATP-binding pocket. Within this pocket, a conserved motif—LGEGAFGKV—is critical for coordinating ATP binding and subsequent phosphate transfer (moyano2020cdclikekinases(clks) pages 1-3).  
   Crystal structure data, as exemplified by high-resolution X-ray structures of CLK isoforms, reveal additional structural elements that regulate function. CLK4, like other family members, features a regulatory insertion that includes the LAMMER motif, a signature sequence that contributes to substrate recognition through interactions with the RS domains of target splicing factors. Structural studies have further delineated key catalytic elements such as the activation loop, which adopts a conformation that enables efficient substrate binding, the hydrophobic spine that stabilizes the active conformation, and the C-helix that is essential for the proper positioning of catalytic residues (kallen2018x‐raystructuresand pages 11-12, aubol2014nterminusofthe pages 1-3). These studies confirm that CLK4’s overall structural organization is optimized for its dual-specificity catalytic mechanism while also providing the molecular basis for its inhibitor binding properties, as demonstrated by co-crystallization with selective small-molecule inhibitors (moyano2020cdclikekinases(clks) pages 3-6).
6. Regulation  
   The activity of CLK4 is finely tuned by multiple regulatory mechanisms that ensure its proper function in cellular RNA processing. One of the primary modes of regulation is autophosphorylation, in which CLK4 phosphorylates itself on critical serine, threonine, and tyrosine residues. This autophosphorylation not only modulates its enzymatic activity but also influences its substrate affinity and overall conformation. In addition to autophosphorylation, CLK4 is subject to regulation by upstream signaling pathways; for instance, kinases such as AKT can phosphorylate CLK family members, thereby integrating external growth factor signals with splicing regulation (mott…2011aninhibitorof pages 1-6, song2023cdc2likekinasesstructure pages 7-7).  
   Redox-based modifications also play a role in the regulation of CLK4. Specific oxidation events, such as the oxidation of a methionine residue (Met307), have been shown to impair its kinase activity, representing a mechanism by which cellular oxidative stress may modulate splicing events through CLK4-dependent pathways (song2023cdc2likekinasesstructure pages 15-15, song2023cdc2likekinasesstructure pages 15-16). Furthermore, the nuclear localization of CLK4 is largely determined by its disordered N-terminal region, which facilitates interactions with nuclear transport receptors and splicing components; precise subnuclear localization is essential for the regulation of pre-mRNA splicing and is subject to modulation in response to cellular stress or developmental signals (hogg2023functionsofsrpkclkanddyrkkinasesin pages 7-8, moyano2020cdclikekinases(clks) pages 6-8).
7. Function  
   CLK4 serves a pivotal role in orchestrating alternative pre-mRNA splicing by phosphorylating key serine/arginine-rich splicing factors. In doing so, it exerts control over the assembly and reorganization of the spliceosome, thereby directly influencing splice site selection and the generation of alternatively spliced mRNA isoforms. Among its substrates, CLK4 phosphorylates SRSF1 and SRSF3, facilitating their release from nuclear speckles and enhancing their association with the splicing machinery. This mechanism is essential for regulating the alternative splicing of genes implicated in crucial cellular functions; for example, CLK4 activity is required for the proper splicing of the MAPT/TAU pre-mRNA, a process that is paramount to neuronal function, as well as for the alternative splicing of tissue factor (F3) pre-mRNA, which has implications in the regulation of blood coagulation in endothelial cells (elhady2017developmentofselective pages 13-14, Information).  
   Beyond its canonical role in splicing regulation, CLK4 has been implicated in disease-relevant processes. Altered expression or dysfunctional regulation of CLK4 is associated with oncogenic pathways; indeed, several studies have demonstrated that dysregulation of CLK isoforms can promote cancer cell proliferation, invasion, and metastasis by altering alternative splicing patterns of genes involved in cell cycle progression and apoptosis. For instance, selective inhibition of CLK4 has been shown to impact the splicing of cancer-relevant proteins, suggesting that its activity may contribute to tumor progression in certain cancer types. In addition, CLK4 has been linked to the regulation of cardiac function; its phosphorylation of substrates such as NEXN at Ser437 is critical for maintaining myocardial architecture, and deletion or inhibition of CLK4 has been observed to trigger pathological cardiac hypertrophy and heart failure in model systems (song2023cdc2likekinasesstructure pages 9-10). Tissue-specific expression data indicate that CLK4 is highly expressed in the retina, brain, and specific germ and neuronal cell clusters, consistent with its roles in neural differentiation and stress-responsive splicing regulation (hogg2023functionsofsrpkclkanddyrkkinasesin pages 14-16).
8. Other Comments  
   The therapeutic potential of targeting CLK4 has driven considerable interest in the development of small-molecule inhibitors that can modulate its activity. Several selective inhibitors have been reported—including ML167, TG003, and KH-CB19—that demonstrate potent inhibition of CLK4 with nanomolar IC50 values. These chemical probes have proven useful in cellular depletion studies, offering insights into the oncogenic and splicing regulatory roles of CLK4 in various cancer models (mott…2011aninhibitorof pages 1-6, moyano2020cdclikekinases(clks) pages 13-16). In addition, pyrido[3,4-g]quinazoline derivatives and indazole-based inhibitors have been identified as selective agents that target CLK4’s ATP-binding pocket, thereby perturbing its activity and inducing widespread alterations in RNA splicing that contribute to cytotoxic effects in cancer cells (borisevich2024thenitrogroup pages 19-21, fedorov2011specificclkinhibitors pages 1-2).  
   Disease associations of CLK4 extend to several pathological conditions where aberrant splicing plays a central role. Increased expression or abnormal activity of CLK4 has been observed in various malignancies, including breast cancer and glioblastoma, where it is thought to contribute to tumorigenesis by promoting the production of pro-oncogenic splice variants. Moreover, the role of CLK4 in cardiac tissue is highlighted by its involvement in phosphorylating NEXN, a protein whose proper regulation is critical for preventing pathological myocardial hypertrophy. Thus, modulators of CLK4 activity are currently being investigated not only as anticancer agents but also as potential therapeutics for cardiovascular and neurodegenerative disorders characterized by splicing defects (elhady2017developmentofselective pages 13-14, song2023cdc2likekinasesstructure pages 9-10, song2023cdc2likekinasesstructure pages 17-18).
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