1. Phylogeny  
   CDK14 belongs to the CDK14–18 subfamily of atypical cyclin‐dependent kinases, which are characterized by unique motifs such as the PFTAIRE sequence that distinguishes them from canonical CDKs involved in classical cell cycle control (alonso2021caracterizacióndecdk1418 pages 32-35, ferguson2019discoveryofcovalent pages 1-3). It is evolutionarily conserved across metazoans and is most prominently expressed in brain tissue and specific postmitotic cells, with additional expression detected in testis, heart, kidney, pancreas, and ovary (alonso2021caracterizacióndecdk1418 pages 41-44, mikolcevic2012orphankinasesturn pages 1-2). Phylogenetic analyses place CDK14 alongside related PFTAIRE family members, showing conserved catalytic domains and extended regulatory regions; these characteristics imply that CDK14 shares a common ancestor with kinases such as CDK5 and CDK16 and belongs to the broader CMGC kinase group (malumbres2009cyclindependentkinasesa pages 1-2, mikolcevic2012orphankinasesturn pages 1-2).
2. Reaction Catalyzed  
   CDK14 catalyzes the phosphorylation reaction in which a phosphate group is transferred from ATP to a serine or threonine residue on a protein substrate, resulting in the formation of ADP, a phosphorylated protein, and the release of a proton (alonso2021caracterizacióndecdk1418 pages 32-35, ferguson2019discoveryofcovalent pages 1-3).
3. Cofactor Requirements  
   The catalytic activity of CDK14 is dependent on the binding of ATP as the phosphoryl donor, and like other serine/threonine kinases, its activity requires the presence of divalent cations, typically Mg²⁺, which facilitate proper ATP coordination within the active site (alonso2021caracterizacióndecdk1418 pages 29-32, ferguson2019discoveryofcovalent pages 20-21).
4. Substrate Specificity  
   CDK14 phosphorylates target proteins on serine/threonine residues within specific consensus motifs. Experimentally, one well‐characterized substrate is the WNT co‐receptor LRP6, which is phosphorylated at Ser1490 by the CDK14–cyclin Y complex during the G2/M phase (alonso2021caracterizacióndecdk1418 pages 32-35, ferguson2019discoveryofcovalent pages 1-3). In addition, in vitro studies have demonstrated that CDK14 can phosphorylate retinoblastoma protein (RB1); however, the in vivo relevance of RB1 phosphorylation remains to be confirmed (alonso2021caracterizacióndecdk1418 pages 35-38). As a member of the CMGC kinase group, CDK14 is expected to exhibit proline-directed substrate specificity, favoring phosphorylatable serine/threonine residues followed by a proline, and additional amino acid preferences resembling the general S/T–P consensus motif (johnson2023anatlasof pages 4-4, janackova2023mechanismusregulacecyklindependentní pages 20-24).
5. Structure  
   CDK14 contains a conserved serine/threonine kinase domain of approximately 300 amino acids that is organized into a bilobal fold with a small N-terminal lobe composed mainly of β-sheets and a larger C-terminal lobe predominantly α-helical. The kinase domain harbors the critical ATP-binding pocket defined by conserved motifs such as the DFG motif responsible for Mg²⁺ coordination and a catalytic loop that includes key residues for phosphate transfer (kamkar2015pftaire1(cyclindependent pages 29-34, korolchuk2018structuralandfunctional pages 35-40). A distinctive feature of CDK14 is the presence of the PFTAIRE motif, which, unlike the classical PSTAIRE sequence found in many cell cycle CDKs, confers unique cyclin-binding specificity. CDK14 associates with cyclin Y, which itself possesses an N-myristoylation signal that facilitates targeting of the complex to cellular membranes (alonso2021caracterizacióndecdk1418 pages 32-35, ferguson2019discoveryofcovalent pages 4-5). AlphaFold‐predicted models and structural alignments with other CDKs indicate that CDK14 also contains an activation loop (T-loop), hydrophobic spines, and a C-helix, which are essential for stabilization of the active conformation upon cyclin binding (kamkar2015pftaire1(cyclindependent pages 34-40, mikolcevic2012orphankinasesturn pages 3-4).
6. Regulation  
   CDK14 regulation is mediated primarily through its interaction with cyclin Y, which is required for both activating the kinase and directing its subcellular localization to the plasma membrane. This interaction is facilitated by the unique PFTAIRE motif within CDK14 and the cyclin box domain of cyclin Y (alonso2021caracterizacióndecdk1418 pages 32-35, mikolcevic2012orphankinasesturn pages 1-2). Phosphorylation events play a significant role in regulating CDK14 activity; for example, phosphorylation of specific residues on cyclin Y, such as S71 and S73, has been linked to cyclin Y stability via a negative feedback loop (alonso2021caracterizacióndecdk1418 pages 32-35, ferguson2019discoveryofcovalent pages 13-14). Additionally, CDK14 itself can be phosphorylated, a modification that is typical for CDKs and is thought to contribute to the conformational adjustments necessary for catalytic activity. CDK14 also phosphorylates downstream targets, including LRP6 at Ser1490, which ties its activity to the regulation of the Wnt signaling cascade during critical cell cycle phases such as G2/M (alonso2021caracterizacióndecdk1418 pages 32-35, ferguson2019discoveryofcovalent pages 1-3). Other regulatory interactions, including potential engagement with 14-3-3 proteins, have been observed in studies of related kinases, although detailed mechanisms in CDK14 remain to be fully elucidated (alonso2021caracterizacióndecdk1418 pages 114-118, mikolcevic2012orphankinasesturn pages 2-3).
7. Function  
   CDK14 functions as a serine/threonine kinase involved in the regulation of the eukaryotic cell cycle and cellular proliferation. One of its best-characterized roles is in the Wnt signaling pathway, where the CDK14–cyclin Y complex phosphorylates the Wnt co-receptor LRP6 at Ser1490 during the G2/M phase, thereby priming LRP6 for further activation and contributing to cell cycle regulation (alonso2021caracterizacióndecdk1418 pages 32-35, ferguson2019discoveryofcovalent pages 1-3). In vitro, CDK14 has been shown to phosphorylate RB1, suggesting a role in cell cycle progression; however, the physiological importance of this reaction remains to be validated in vivo (alonso2021caracterizacióndecdk1418 pages 35-38). Furthermore, CDK14 is expressed predominantly in the brain and other postmitotic tissues, indicating functions in neuronal differentiation and possibly in meiosis. In addition to its role in cell cycle control and developmental signaling, CDK14 is implicated as a negative regulator of insulin-responsive glucose transport, thereby potentially influencing metabolic processes (alonso2021caracterizacióndecdk1418 pages 114-118). Altered expression of CDK14 has been associated with cancer phenotypes, with studies linking its dysregulation to hepatocellular carcinoma, colorectal cancer, and other tumor types through its effects on cell proliferation, migration, and cytoskeletal dynamics (alonso2021caracterizacióndecdk1418 pages 41-44, ferguson2019discoveryofcovalent pages 1-3).
8. Other Comments  
   Recent chemical biology studies have led to the development of covalent inhibitors such as FMF-04-159-2 that target CDK14 and other TAIRE kinases with pan-specificity. These inhibitors irreversibly bind to a non-conserved cysteine (Cys218) in the ATP-binding pocket, thus providing useful chemical probes for dissecting the biological functions of CDK14 and its related kinases (ferguson2019discoveryofcovalent pages 5-8, ferguson2019discoveryofcovalent pages 25-27). Although no inhibitor is currently approved specifically for CDK14, these chemical tools are instrumental in linking alterations in CDK14 activity to cancer biology and other cellular processes. In addition, altered regulatory mechanisms and mutations within the CDK14 signaling pathway have been reported in various oncological studies, though detailed mutation profiles remain to be fully characterized (alonso2021caracterizacióndecdk1418 pages 38-41, mikolcevic2012orphankinasesturn pages 3-4).
9. References  
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