Phylogeny  
CLK2 belongs to the CMGC group, CDC-like kinase (CLK) sub-family of the human kinome (Song et al., 2023). It shares 67–87 % sequence identity with its human paralogues CLK1, CLK3 and CLK4 (Lindberg & Meijer, 2021). Canonical orthologues are conserved from mouse (98 % identity in the kinase domain) through vertebrates and invertebrates to plants and yeast (Ogle et al., 2024). Structure-based trees place CLK2 closest to casein kinase 2, reflecting marked fold similarity despite low sequence identity (Lee et al., 2019).

Reaction Catalyzed  
ATP + [protein]-Ser/Thr/Tyr ⇌ ADP + [protein]-O-phospho-Ser/Thr/Tyr (Moyano et al., 2020; Lee et al., 2019).

Cofactor Requirements  
Mg²⁺ is required for ATP-dependent catalysis (Song et al., 2023).

Substrate Specificity  
• Prefers the linear motif R-x-x-S/T within arginine/serine-rich (RS) regions (Song et al., 2023).  
• Cellular substrates include SR proteins (SRSF1-12, SRSF3), PTPN1, PPP2R5B, PPARGC1A, PAGE4 and F3 pre-mRNA (Song et al., 2023).  
• The enzyme autophosphorylates on an activation-loop Tyr, demonstrating intrinsic dual Ser/Thr/Tyr specificity (Lindberg & Meijer, 2021).

Structure  
N-terminal disordered RS region (~1–120) followed by a bilobal kinase domain (R130–D496) that contains the hallmark EHLAMMERILG/LAMMER motif (Kallen et al., 2018). Crystal structures are available for the apo enzyme (PDB 3NR9) and complexes with inhibitors (e.g., 6FYL, 6KHE) at 1.8–2.2 Å resolution (Lindberg & Meijer, 2021). Key features include a Lys–Glu salt bridge stabilising the N-lobe, an intact hydrophobic spine, a Tyr-containing activation loop, β-hairpin and MAPK-like insertions around the ATP site, and an unusually large hydrophobic pocket in which Val326 is critical for inhibitor binding (Song et al., 2023; Lee et al., 2019).

Regulation  
Post-translational  
– Autophosphorylation of the activation-loop Tyr activates the kinase (Lee et al., 2019).  
– AKT1 phosphorylates Ser34, Thr127 and Thr344, linking CLK2 to insulin signalling (Prak et al., 2016).  
– Temperature-dependent rearrangements within the activation segment modulate activity (Lindberg & Meijer, 2021).

Transcriptional / post-transcriptional  
– Insulin-pathway effectors and miR-573/miR-144 down-regulate CLK2 expression (Song et al., 2023).  
– Autoregulatory intron retention, analogous to CLK1, is proposed (Lindberg & Meijer, 2021).

Function  
Expression & localisation: Widely expressed, enriched in nervous tissue and colon; predominantly nuclear (Song et al., 2023).  
Splicing control: Phosphorylates SR proteins, redistributing them from speckles to nucleoplasm and altering splice-site choice (e.g., Tau exon-10) (Lindberg & Meijer, 2021).  
Metabolism: Phosphorylates PPARGC1A, suppressing hepatic gluconeogenic gene expression (Moyano et al., 2020).  
Signal transduction: Targets PPP2R5B to promote PP2A–AKT1 complex formation and PAGE4 to dampen JUN activity (Song et al., 2023).  
Additional roles: Required for HIV-1 gene expression; promotes migration and invasion of several cancer cell types (Lindberg & Meijer, 2021; Song et al., 2023).

Inhibitors  
ATP-competitive compounds with low-nanomolar CLK2 potency include CX-4945 (IC₅₀ ≈ 3.8 nM), CC-671 (6 nM), MU1210 (20 nM), SM08502, several indazole derivatives, KuWal151 and benzobisthiazole 3A5; tool compounds TG003, T-025 and DB18 also block SR-protein phosphorylation (Lee et al., 2019; Song et al., 2023; Kallen et al., 2018; Walter et al., 2018; Prak et al., 2016; Moyano et al., 2020).

Other Comments  
CLK2 dysregulation is linked to Alzheimer’s disease (Tau mis-splicing), Phelan–McDermid syndrome, neurodevelopmental disorders, metabolic disease, osteoarthritis, several cancers and HIV infection. No recurrent pathogenic point mutations have been reported to date (Lindberg & Meijer, 2021; Kallen et al., 2018; Moyano et al., 2020; Song et al., 2023).

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