## Phylogeny

DCLK2 (also called DCAMKL2, DCDC3B or DCK2) is a member of the doublecortin (DCX) family of serine/threonine kinases. Family members (DCLK1, DCLK2, DCLK3) share tandem DCX microtubule-binding domains fused to a CaMK-like kinase domain and are broadly conserved across vertebrates, with ancestry traceable to metazoan kinases (Reiner et al., 2006; Hu et al., 2024).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Hu et al., 2024).

## Cofactor Requirements

Mg²⁺ is required for catalytic activity; Ca²⁺/calmodulin dependence is greatly reduced compared with canonical CaMKs (Hu et al., 2024).

## Substrate Specificity

The kinase selectively phosphorylates TANK-binding kinase 1 (TBK1) on Ser172, a site essential for TBK1 activation. DCLK2 does not phosphorylate the related kinase IKKε at the equivalent site. Down-stream, activated TBK1 mediates phosphorylation of p62 on Ser366, highlighting a narrow substrate spectrum centred on the TBK1 pathway (Hu et al., 2024).

## Structure

• N-terminal tandem DCX domains – mediate microtubule binding and stabilization (Reiner et al., 2006).  
• C-terminal serine/threonine kinase domain – canonical CaMK fold. Lys423 is critical for ATP binding; K423A mutation abolishes activity (Hu et al., 2024).  
• Isoforms: the predominant cancer-associated isoform DCLK2^203 lacks an auto-inhibitory C-terminal Thr present in DCLK2^201, resulting in higher activity (Hu et al., 2024).  
Overall, the protein is modular, Ca²⁺/calmodulin-independent, and subject to isoform-specific structural regulation.

## Regulation

1. Alternative splicing – removal of the C-terminal auto-inhibitory Thr in DCLK2^203 confers elevated kinase activity (Hu et al., 2024).
2. Point mutation – K423A renders the enzyme catalytically inactive, blocking TBK1 phosphorylation and oncogenic functions (Hu et al., 2024).
3. Post-transcriptional control – reduced nonsense-mediated decay (e.g., lower UPF1) increases expression of the hyper-active isoform in clear cell renal cell carcinoma (Hu et al., 2024).

## Function

In clear cell renal cell carcinoma (ccRCC), DCLK2 is an oncogenic serine/threonine kinase that activates TBK1 (Ser172), leading to TBK1-dependent phosphorylation of p62 (Ser366) and promoting tumour cell growth, anchorage-independent colony formation and xenograft tumour progression. Its action is largely Ca²⁺/calmodulin-independent and is driven by elevated expression of the hyper-active DCLK2^203 isoform (Hu et al., 2024).

## Inhibitors

DCLK1-IN-1, originally developed for DCLK1, potently inhibits DCLK2 and serves as a selective chemical probe for the doublecortin-like kinase family (Ferguson et al., 2020).

## Other Comments

Family members, including DCLK2, participate in microtubule regulation and neuronal development, but the current experimental evidence emphasises its TBK1-centred oncogenic role in ccRCC. Selective inhibitors and isoform-specific regulation highlight therapeutic potential (Hu et al., 2024; Ferguson et al., 2020).

## 9. References

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