## Phylogeny

Integrin-linked kinase (ILK; gene ILK, isoforms ILK-1 and ILK-2) is conserved across Metazoa, with orthologues in Homo sapiens, Mus musculus, Drosophila melanogaster and Caenorhabditis elegans (~55 % identity to human) (Dedhar et al., 1999; Widmaier et al., 2012). No homologue is found in budding yeast, indicating metazoan-specific emergence (Dagnino, 2011; Qin & Wu, 2012). Kinome surveys place ILK in a small clade of atypical pseudokinases (“ILK family”) outside the canonical AGC and CAMK groups (Górska & Mazur, 2022; Qin & Wu, 2012).

## Reaction Catalyzed

Physiologically relevant phosphoryl-transfer has not been demonstrated; ILK acts as a scaffold pseudokinase (Qin & Wu, 2012; Wickström et al., 2010). Historic, now considered artefactual, assays reported:  
ATP + [protein] Ser/Thr ⇌ ADP + [protein]-P Ser/Thr (Maydan et al., 2010).

## Cofactor Requirements

No obligatory metal ion is required for scaffold function. Early in-vitro assays that claimed activity suggested Mn²⁺ > Mg²⁺ preference (Maydan et al., 2010).

## Substrate Specificity

High-throughput profiling and structural studies detect no intrinsic kinase activity and define no consensus phosphorylation motif (Górska & Mazur, 2022). Earlier reports of direct phosphorylation of Akt Ser473, GSK-3β Ser9, integrin-β1 Ser790 and myelin basic protein are attributable to indirect effects or contaminating kinases (Dedhar et al., 1999; Qin & Wu, 2012).

## Structure

Modular organisation:  
• Ankyrin-repeat domain (aa 33–164) binds PINCH and ILK-associated phosphatase (ILKAP).  
• PH-like segment (aa 180–212) engages PtdIns(3,4,5)P₃.  
• Catalytically deficient kinase-like domain (aa 293–451) interfaces with integrin-β cytoplasmic tails, α/β-parvin, kindlin-2 and paxillin LD1 (Fukuda et al., 2014; Nikolopoulos & Turner, 2001).

Crystal structure (PDB 3KMW) reveals a bilobal kinase fold with a mis-oriented ATP γ-phosphate; key catalytic motifs are degenerate (HRD→HCD, DFG→DVK) and the activation segment is truncated and rigid (Qin & Wu, 2012). The pseudo-active site forms high-affinity contacts with α-parvin CH2, stabilising the ILK–PINCH–parvin (IPP) complex (Fukuda et al., 2014). Mutations E359K (APE region) or S343A (activation segment) abolish signalling competence (Dedhar et al., 1999; Hannigan et al., 2005).

## Regulation

Post-translational modifications: Ser343 phosphorylation is required for downstream signalling; ubiquitylation has been reported, but sites and enzymes remain undefined (Górska & Mazur, 2022; Hannigan et al., 2005).  
Protein/lipid modulators: PtdIns(3,4,5)P₃ binding to the PH-like domain promotes focal-adhesion recruitment, opposed by PI3-kinase inhibitors or PTEN activity (Dedhar et al., 1999; Hannigan et al., 2005). ILKAP negatively regulates signalling via the ankyrin repeats, whereas formation of the heterotrimeric IPP complex is essential for stability and localisation. Paxillin LD1 and kindlin-2 further modulate spatial distribution and adhesion assembly (Fukuda et al., 2014; Nikolopoulos & Turner, 2001).

## Function

Expression: ILK is ubiquitously expressed, with highest levels in cardiac and skeletal muscle (Dedhar et al., 1999).  
Upstream signals: PI3-kinase products generated downstream of growth-factor receptors such as EGFR and PDGFR (Dedhar et al., 1999).  
Interacting partners/core complexes: PINCH, α/β-parvin, kindlin-2, paxillin, Nck-2 (Dedhar et al., 1999; Fukuda et al., 2014).  
Downstream effectors scaffolded: Akt, GSK-3β, β-catenin, myosin light chain and Rho GTPases (Hannigan et al., 2005; Persad & Dedhar, 2003).  
Cellular/physiological roles: focal-adhesion assembly, F-actin bundling, cell spreading and migration (Widmaier et al., 2012); regulation of epithelial–mesenchymal transition, extracellular-matrix deposition and invasion in cancers (Hannigan et al., 2005; McDonald & Dedhar, 2022); muscle attachment during embryogenesis and epiblast polarity (Sakai et al., 2003); modulation of cardiac contractility and hypertrophy signalling (Hannigan et al., 2007); facilitation of metastatic processes including invadopodia formation and therapy resistance (McDonald & Dedhar, 2022).

## Inhibitors

QLT0267 and Cpd22 inhibit ILK-dependent signalling with low-micromolar cellular IC₅₀ values and are used as chemical probes; QLT0267 additionally suppresses tumour growth and angiogenesis in vivo (Górska & Mazur, 2022; Hannigan et al., 2005).

## Other Comments

The ILK gene maps to chromosome 11p15.5-p15.4, a region frequently altered in human cancers (Dedhar et al., 1999). Three transcript variants encode at least two protein isoforms; ILK-2 is up-regulated in metastatic melanoma (Nikolopoulos & Turner, 2001; Górska & Mazur, 2022). Loss-of-function mutations are linked to dilated cardiomyopathy and muscular dystrophy (Górska & Mazur, 2022). Current structural and genetic data support classification of ILK as a scaffold pseudokinase (Qin & Wu, 2012; Wickström et al., 2010; Dagnino, 2011).

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