## Phylogeny

Integrin-linked kinase (ILK; gene ILK, isoforms ILK-1 and ILK-2) is conserved throughout Metazoa, with orthologs reported in Homo sapiens, Mus musculus, Drosophila melanogaster and Caenorhabditis elegans (≈55 % identity to human) (dedhar1999integrinlinkedkinase(ilk) pages 2-3, widmaier2012integrinlinkedkinaseat pages 1-2).  
No ortholog exists in budding yeast, indicating a metazoan-specific emergence (dagnino2011integrinlinkedkinasea pages 1-2, qin2012ilkapseudokinase pages 5-6).  
Kinome analyses place ILK in a small pseudokinase clade outside the conventional AGC and CAMK groups; it is classified within the “ILK family / atypical pseudokinases” in the Manning human kinome framework (gorska2022integrinlinkedkinase(ilk) pages 19-20, qin2012ilkapseudokinase pages 1-2).

## Reaction Catalyzed

Consensus view: no physiologically relevant phosphoryl-transfer has been demonstrated; ILK functions predominantly as a scaffold pseudokinase (qin2012ilkapseudokinase pages 5-6, wickstrom2010theilkpinchparvincomplex pages 11-11).  
Historic in-vitro reports (now considered artefactual) described:  
ATP + [protein] Ser/Thr → ADP + [protein]-P Ser/Thr (maydan2010integrinlinkedkinaseis pages 10-10).

## Cofactor Requirements

No obligatory metal ion is required for scaffold function. Early kinase assays that reported activity indicated Mn²⁺ > Mg²⁺ preference (maydan2010integrinlinkedkinaseis pages 10-10).

## Substrate Specificity

High-throughput profiling and structural data assign ILK to the “no activity detected” category; no intrinsic consensus motif is defined (gorska2022integrinlinkedkinase(ilk) pages 19-20).  
Earlier claims of direct phosphorylation of Akt Ser473, GSK-3β Ser9, integrin-β1 Ser790 and myelin basic protein are attributed to indirect effects or contaminating kinases (dedhar1999integrinlinkedkinase(ilk) pages 1-2, qin2012ilkapseudokinase pages 1-2).

## Structure

Domain organisation  
• Ankyrin-repeat domain (aa 33–164): binds PINCH LIM domains and ILK-associated phosphatase (ILKAP) (dedhar1999integrinlinkedkinase(ilk) pages 1-2, hannigan2005integrinlinkedkinasea pages 3-4).  
• Pleckstrin-homology-like segment (aa 180–212): engages PtdIns(3,4,5)P₃ (dedhar1999integrinlinkedkinase(ilk) pages 1-2).  
• Kinase-like domain (aa 293–451): catalytically deficient; provides binding sites for integrin-β cytoplasmic tails, α/β-parvin, kindlin-2 (Leu-rich helix 339–358) and paxillin LD1 (fukuda2014molecularbasisof pages 1-2, nikolopoulos2001integrinlinkedkinase(ilk) pages 1-1).

3-D structural features  
Crystal structure PDB 3KMW shows a bilobal kinase fold with bound ATP whose γ-phosphate is mis-oriented; catalytic motifs are disrupted: VAIK Lys220 intact, HRD → HCD, DFG replaced by DVK, activation segment truncated and rigid (qin2012ilkapseudokinase pages 2-4, dagnino2011integrinlinkedkinasea pages 2-3).  
The pseudo-active site mediates high-affinity binding to α-parvin CH2, stabilising the IPP complex (fukuda2014molecularbasisof pages 1-2).  
Mutation E359K in the degenerate APE motif or S343A within the activation segment abolishes signalling competence (dedhar1999integrinlinkedkinase(ilk) pages 1-2, hannigan2005integrinlinkedkinasea pages 4-5).

## Regulation

Post-translational modifications  
• Ser343 phosphorylation within the activation segment is required for downstream signalling (hannigan2005integrinlinkedkinasea pages 4-5).  
• Ubiquitylation of ILK has been reported, although sites and enzymes remain undefined (gorska2022integrinlinkedkinase(ilk) pages 1-2).

Protein and lipid modulators  
• PtdIns(3,4,5)P₃ binding to the PH-like domain enhances recruitment to focal adhesions; PI3-kinase inhibitors or PTEN antagonise this interaction (dedhar1999integrinlinkedkinase(ilk) pages 1-2, hannigan2005integrinlinkedkinasea pages 3-4).  
• ILKAP binds the ankyrin repeats and negatively regulates signalling output (hannigan2005integrinlinkedkinasea pages 3-4).  
• Formation of the heterotrimeric IPP complex (ILK–PINCH–parvin) is essential for protein stability and focal-adhesion localisation (fukuda2014molecularbasisof pages 1-2).  
• Paxillin LD1 and kindlin-2 interactions modulate spatial distribution and adhesion assembly (nikolopoulos2001integrinlinkedkinase(ilk) pages 1-1, fukuda2014molecularbasisof pages 1-2).

## Function

Expression  
ILK is ubiquitously expressed, with highest levels in cardiac and skeletal muscle tissues (dedhar1999integrinlinkedkinase(ilk) pages 1-2).

Signalling context  
Upstream activators: PI3-kinase products downstream of growth-factor receptors such as EGFR and PDGFR (dedhar1999integrinlinkedkinase(ilk) pages 2-3).  
Core complexes and partners: PINCH, α/β-parvin, kindlin-2, paxillin, Nck-2 (dedhar1999integrinlinkedkinase(ilk) pages 2-3, fukuda2014molecularbasisof pages 1-2).  
Downstream effectors reached by scaffolding: Akt, GSK-3β, β-catenin, myosin light chain, Rho family GTPases (hannigan2005integrinlinkedkinasea pages 3-4, persad2003theroleof pages 1-3).

Cellular and physiological roles  
• Focal adhesion assembly, F-actin bundling, cell spreading and migration (widmaier2012integrinlinkedkinaseat pages 1-2, fukuda2014molecularbasisof pages 1-2).  
• Regulation of epithelial-mesenchymal transition, extracellular matrix deposition and invasion in diverse cancers (hannigan2005integrinlinkedkinasea pages 13-13, mcdonald2022newperspectiveson pages 1-2).  
• Muscle attachment during embryogenesis and epiblast polarity (sakai2003integrinlinkedkinase(ilk) pages 15-16).  
• Modulation of cardiac contractility and hypertrophic signalling pathways (hannigan2007integrinlinkedkinaseat pages 7-8).  
• Facilitation of metastatic steps including invadopodia formation and therapy resistance (mcdonald2022newperspectiveson pages 1-2).

## Inhibitors

QLT0267: low-micromolar IC₅₀ in cell-based assays; suppresses tumour growth and angiogenesis (hannigan2005integrinlinkedkinasea pages 1-2, gorska2022integrinlinkedkinase(ilk) pages 19-20).  
Cpd22: low-micromolar IC₅₀ against ILK-dependent signalling; used as a chemical probe (gorska2022integrinlinkedkinase(ilk) pages 19-20).

## Other Comments

The ILK gene maps to chromosome 11p15.5-p15.4, a region frequently altered in human cancers (dedhar1999integrinlinkedkinase(ilk) pages 2-3).  
Three transcript variants encode at least two protein isoforms; ILK-2 is up-regulated in metastatic melanoma (nikolopoulos2001integrinlinkedkinase(ilk) pages 1-1, gorska2022integrinlinkedkinase(ilk) pages 1-2).  
Loss-of-function mutations are linked to dilated cardiomyopathy and muscular dystrophy phenotypes (gorska2022integrinlinkedkinase(ilk) pages 19-20).  
Current structural and genetic evidence supports designation of ILK as a scaffold pseudokinase rather than an active enzyme (qin2012ilkapseudokinase pages 1-2, wickstrom2010theilkpinchparvincomplex pages 11-11, dagnino2011integrinlinkedkinasea pages 1-2).

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