## Phylogeny

Tyrosine-protein kinase HCK is a member of the Src family of non-receptor tyrosine kinases. Orthologs occur throughout vertebrates and the catalytic domain is highly conserved, reflecting an evolutionary origin in early metazoans. Within the human kinome, HCK clusters with c-Src, Lyn, Fgr, Fyn, Blk, Lck and Yes (Ayrapetov, 2006; Lin, 2005; Kwon, 2019).

## Reaction Catalyzed

ATP + [protein]-tyrosine ⇌ ADP + H⁺ + [protein]-phosphotyrosine (Ayrapetov, 2006; Corwin, 2016).

## Cofactor Requirements

Mg²⁺ is required for ATP coordination and phosphoryl transfer (Ayrapetov, 2006; Lin, 2005).

## Substrate Specificity

Substrate recognition involves both the catalytic pocket and the SH2/SH3 docking modules. HCK phosphorylates adaptor and signaling proteins such as CBL, ADAM15, BCR, ELMO1, FCGR2A, GAB1/2, RAPGEF1, STAT5B, TP73, VAV1 and WAS. No simple linear consensus is apparent; specificity is dictated by residues flanking the target tyrosine together with SH2-mediated docking to phosphotyrosine motifs generated during signaling (Bhanumathy et al., 2021; Corwin, 2016).

## Structure

HCK comprises:  
• SH4 domain—myristoylated (and sometimes palmitoylated) for membrane association.  
• Unique region—isoform-specific interactions.  
• SH3 domain—binds proline-rich ligands and participates in autoinhibition.  
• SH2 domain—recognises phosphotyrosine motifs.  
• Bilobal kinase domain—contains the activation loop, hydrophobic spine and C-helix essential for activity.  
• C-terminal tail—phosphorylation of a regulatory tyrosine promotes SH2 binding and autoinhibition.  
This modular architecture underlies localization, substrate docking and regulated catalytic output (Ayrapetov, 2006; Lin, 2005; Corwin, 2016).

## Regulation

Activity is controlled by multiple phosphorylation events and intramolecular interactions. Autophosphorylation within the activation loop activates the enzyme, whereas C-terminal tail phosphorylation by Csk enforces a closed, inactive conformation. Displacement of SH3/SH2 contacts by competing ligands or engineered insertions can trigger activation; for example, the HckFL-Bad variant is reversibly activated by the small-molecule disruptor A-1155463 (Ayrapetov, 2006; Lin, 2005; Bienick, 2019; Corwin, 2016).

## Function

HCK is predominantly expressed in hematopoietic cells (neutrophils, monocytes, macrophages, mast cells). It transduces signals from Fcγ receptors, CSF3R, IFNG, IL-2/6/8 receptors and integrins. Downstream phosphorylation of CBL, ADAM15, BCR, ELMO1, GAB1/2, RAPGEF1, STAT5B, TP73, VAV1 and WAS coordinates:  
• Secretory lysosome mobilization, degranulation and NADPH oxidase activation during phagocytosis.  
• Actin cytoskeleton remodeling, podosome formation and cell migration.  
• Negative regulation of TP73-driven transcription and apoptosis (Bhanumathy et al., 2021; Corwin, 2016; Ubau, 2013).

## Inhibitors

Selective small-molecule inhibitors and engineered control systems have been developed. The SH3/SH2-disrupting compound A-1155463 potently activates an engineered HCK variant; additional ATP-competitive inhibitors are being explored, guided by principles established for Src family kinases (Bienick, 2019; Ayrapetov, 2006).

## Other Comments

Aberrant HCK activity contributes to leukemogenesis and other hematological malignancies, making the kinase a therapeutic target. Mutations in catalytic or regulatory domains and network connectivity with upstream receptors highlight the need for refined pharmacological strategies (Bhanumathy et al., 2021; Corwin, 2016).

## 9. References

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