## Phylogeny

ABL1 (c-Abl) is one of two ubiquitously expressed Abl family kinases in mammals (the other is ABL2/Arg). A single ortholog functions in Drosophila, illustrating conservation of Abl kinases throughout metazoans (Hantschel, 2012; Rogers et al., 2020). Phylogenetic analyses place ABL1 within the tyrosine kinase group alongside Src-related families, indicating an origin early in eukaryotic evolution (Superti-Furga & Courtneidge, 1995).

## Reaction Catalyzed

ATP + protein-(L-tyrosine) ⇌ ADP + protein-(L-tyrosine)-phosphate + H⁺ (Roskoski, 2003)

## Cofactor Requirements

Mg²⁺ is essential for ATP coordination and catalysis (Roskoski, 2003).

## Substrate Specificity

ABL1 phosphorylates tyrosine residues on diverse targets that regulate the actin cytoskeleton, receptor endocytosis, and DNA damage responses. Substrate recognition is refined by its SH3 domain, which binds proline-rich motifs, and its SH2 domain, which engages phosphotyrosine sequences, promoting multisite phosphorylation. Reported substrates include WASF3, CBL, CRK/CRKL, EGFR and RIN1 (Hantschel, 2012; Roskoski, 2003; Tse & Verkhivker, 2015).

## Structure

ABL1 displays a modular architecture: N-terminal myristoylation signal and cap, contiguous SH3 and SH2 domains, the bilobed kinase (SH1) domain, and an intrinsically disordered, proline-rich C-terminal tail (Hantschel, 2012; Rogers et al., 2021). Autoinhibition is achieved when the myristoyl group docks into a hydrophobic pocket of the kinase C-lobe and the SH3 domain binds the SH2-kinase linker, locking the enzyme in an inactive conformation (Hantschel, 2012). The activation loop within the kinase domain contains Tyr412, whose autophosphorylation switches the enzyme to an active state. The C-terminal disordered region mediates additional protein-protein interactions and influences stability and localization (Rogers et al., 2020; Kornev & Taylor, 2015).

## Regulation

1. Autoinhibition via myristoyl/SH3-linker interactions maintains the inactive state (Hantschel, 2012).
2. Activating autophosphorylation on Tyr412 (activation loop) and Tyr245 (SH2-kinase linker) disrupts inhibitory contacts and promotes activity (Hantschel, 2012; Roskoski, 2003).
3. Ubiquitination by CBL family ligases targets ABL1 for degradation under stress (Rogers et al., 2021).
4. Allosteric and ATP-competitive inhibitors bias the conformational equilibrium (Roskoski, 2003; Tse & Verkhivker, 2015).
5. Nuclear localization and export signals mediate shuttling; nuclear ABL1 participates in DNA repair and apoptosis, whereas cytoplasmic ABL1 regulates cytoskeletal remodeling and endocytosis (Hantschel, 2012).

## Function

ABL1 acts as a versatile signaling hub:  
• Cytoskeleton – phosphorylates WASF3, CRK/CRKL and other regulators to drive lamellipodia formation and cell migration (Hantschel, 2012).  
• Receptor endocytosis – modulates EGFR internalization via phosphorylation of CBL and RIN1 (Lund, 2013; Hantschel, 2012).  
• DNA damage response – interacts with DDB1/2, RAD51 and TP73, balancing repair and apoptosis in the nucleus (Hantschel, 2012).  
• Autophagy – influences lysosomal trafficking during late autophagy (information in Nomenclature).  
• Oxidative stress – translocates to mitochondria to phosphorylate PRKD2, promoting cell death (Rogers et al., 2021).  
• Host–pathogen interactions – phosphorylates viral and bacterial proteins (e.g., Vaccinia A36R, H. pylori CagA) to remodel host actin (information in Nomenclature).  
ABL1 is ubiquitously expressed in mammalian tissues (Hantschel, 2012).

## Inhibitors

Clinically used ATP-competitive inhibitors include imatinib (binds inactive DFG-out conformation), dasatinib, nilotinib and ponatinib; they are central to chronic myelogenous leukemia therapy and to overcoming resistance mutations such as T315I (Roskoski, 2003; Hantschel, 2012; Wong & Witte, 2004). Allosteric inhibitors targeting the myristate pocket illustrate alternative therapeutic strategies (Tse & Verkhivker, 2015).

## Other Comments

Oncogenic BCR-ABL fusions delete autoinhibitory regions, yielding constitutive kinase activity that drives leukemogenesis. Kinase-domain mutations can confer drug resistance. Insights from ABL1 structure and regulation underpin modern kinase-inhibitor design paradigms (Wong & Witte, 2004; Roskoski, 2003).

## 9. References

Hantschel, O. (2012). Structure, regulation, signaling, and targeting of Abl kinases in cancer. Genes & Cancer, 3, 436–446. https://doi.org/10.1177/1947601912458584

Kornev, A. P., & Taylor, S. S. (2015). Dynamics-driven allostery in protein kinases. Trends in Biochemical Sciences, 40, 628–647. https://doi.org/10.1016/j.tibs.2015.09.002

Lund, B. A. (2013). Biotech applications of protein kinase affinity interactions. [Journal unidentified].

Rogers, E. M., Allred, S. C., & Peifer, M. (2020). Abelson kinase’s intrinsically disordered linker plays important roles in protein function and protein stability. bioRxiv. https://doi.org/10.1101/2020.05.20.106708

Rogers, E. M., Allred, S. C., & Peifer, M. (2021). Abelson kinase’s intrinsically disordered region plays essential roles in protein function and protein stability. Cell Communication and Signaling, 19, 1–29. https://doi.org/10.1186/s12964-020-00703-w

Roskoski, R. (2003). STI-571: An anticancer protein-tyrosine kinase inhibitor. Biochemical and Biophysical Research Communications, 309, 709–717. https://doi.org/10.1016/j.bbrc.2003.08.055

Superti-Furga, G., & Courtneidge, S. A. (1995). Structure-function relationships in Src family and related protein tyrosine kinases. BioEssays, 17, 321–330. https://doi.org/10.1002/bies.950170408

Tse, A., & Verkhivker, G. M. (2015). Molecular determinants underlying binding specificities of the Abl kinase inhibitors. PLOS ONE, 10, e0130203. https://doi.org/10.1371/journal.pone.0130203

Wong, S., & Witte, O. N. (2004). The BCR-ABL story: Bench to bedside and back. Annual Review of Immunology, 22, 247–306. https://doi.org/10.1146/annurev.immunol.22.012703.104753