## Phylogeny

* Human ABL1 is a non-receptor tyrosine kinase in the Abl subfamily defined by a conserved SH3–SH2–TK cassette (georgoulia2019thecatalyticactivity pages 10-10).
* A vertebrate paralog, ABL2 (ARG), emerged from an ancestral gene-duplication event (colicelli2010abltyrosinekinases pages 1-2).
* Experimentally annotated orthologs include Mus musculus Abl1, Danio rerio abl, Xenopus laevis abl, Drosophila melanogaster Abl, Strongylocentrotus purpuratus Abl and Monosiga brevicollis Abl (colicelli2010abltyrosinekinases pages 10-12).

## Reaction Catalyzed

* ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-O-phosphate (georgoulia2019thecatalyticactivity pages 10-10).

## Cofactor Requirements

* Catalytic activity requires Mg²⁺; Mn²⁺ can substitute with reduced efficiency (georgoulia2019thecatalyticactivity pages 10-10).

## Substrate Specificity

* Preferred consensus motif: Φ-x-Y-x-x-P with a hydrophobic residue at −1 and Pro at +3 (yaronbarir2024theintrinsicsubstrate pages 1-2).
* Acidic residues at +1/+2 further enhance phosphorylation efficiency (colicelli2010abltyrosinekinases pages 5-7).

## Structure

* Isoform 1b organization: N-Cap with Gly2 myristoylation, SH3, SH2, kinase domain, three NLS, one NES, DNA-binding region and C-terminal F-actin/microtubule binding modules (colicelli2010abltyrosinekinases pages 4-5).
* Autoinhibition is enforced by myristate insertion into a C-lobe pocket and an SH3–SH2 clamp over the kinase N-lobe (georgoulia2019thecatalyticactivity pages 10-10).
* Crystal structures (PDB 1OPK, 2FO0, 4WA9) define the SH2–kinase interface, activation-loop Tyr412, αC helix and hydrophobic spine that govern active/inactive states (tse2015moleculardeterminantsunderlying pages 35-36).
* The myristoyl pocket persists in BCR-ABL1 and is exploited by the allosteric inhibitor asciminib (manley2020thespecificityof pages 1-6).

## Regulation

* Autophosphorylation of Tyr412 (activation loop) and Tyr245 (SH2-kinase linker) stabilizes the active conformation (georgoulia2019thecatalyticactivity pages 10-10).
* Phosphorylation of Tyr89 within SH3 disrupts the SH3-linker interaction, promoting activation (colicelli2010abltyrosinekinases pages 4-5).
* Ser569 and Thr735 phosphorylation create 14-3-3 docking sites that bias cytoplasmic localization (colicelli2010abltyrosinekinases pages 4-5).
* N-terminal myristoylation at Gly2 maintains autoinhibition; loss or displacement activates the kinase (colicelli2010abltyrosinekinases pages 2-4).
* Active ABL1 is polyubiquitinated by CBL, targeting it for degradation (colicelli2010abltyrosinekinases pages 5-7).
* SRC-family kinases phosphorylate ABL1, establishing a positive feedback loop in cytoskeletal signaling (colicelli2010abltyrosinekinases pages 10-12).

## Function

* GTEx profiles show ubiquitous expression with highest levels in hematopoietic, neural and testicular tissues (georgoulia2019thecatalyticactivity pages 10-10).
* Cytoskeletal remodeling is driven by phosphorylation of WASF3, ANXA1, DBN1, DBNL, CTTN, RAPH1, ENAH, MAPT and PXN (colicelli2010abltyrosinekinases pages 10-12).
* Adhesion and motility are regulated via BCAR1, CRK, CRKL, DOK1, EFS and NEDD9 phosphorylation (colicelli2010abltyrosinekinases pages 10-12).
* Endocytosis of EGFR, ERBB2, MET and related regulators is promoted by ABL1 phosphorylation of CAV1, RIN1 and ITSN2 (colicelli2010abltyrosinekinases pages 10-12).
* Upon DNA damage ABL1 enters the nucleus and cooperates with ATM and RAD51 to enforce arrest or apoptosis (colicelli2010abltyrosinekinases pages 10-12).
* ABL1 integrates RAS-MAPK, PI3K-AKT and DNA-damage response pathways (georgoulia2019thecatalyticactivity pages 10-10, greuber2013roleofabl pages 14-15).

## Inhibitors

* Approved ATP-competitive inhibitors: imatinib, nilotinib, dasatinib, bosutinib and ponatinib (georgoulia2019thecatalyticactivity pages 10-10).
* Asciminib is an allosteric inhibitor that binds the myristoyl pocket and remains active against T315I; it can form ternary complexes with ATP-site inhibitors (manley2020thespecificityof pages 1-6).

## Other Comments

* Oncogenic fusions BCR-ABL1 (p210, p190) and NUP214-ABL1 remove the N-Cap, abolishing myristoyl autoinhibition and yielding constitutive kinase activity that drives leukemia (colicelli2010abltyrosinekinases pages 12-13).
* Resistance hotspots to ATP-site inhibitors include T315I, E255K and Y253H (georgoulia2019thecatalyticactivity pages 10-10).
* Germline variants K290N and Y245C are linked to congenital heart defects and perturb kinase function (georgoulia2019thecatalyticactivity pages 10-10).

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