

# Abl

## Key References

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## Overview

The Abl family of non-receptor linked tyrosine kinases relay signals from diverse stimuli to promote changes in cell morphology, migration, adhesion, proliferation and survival. Two Abl family kinases are found in vertebrates: Abl and the Abl-related gene (Arg, also known as Abl2) and homologs in metazoan organisms including *Drosophila*- (D-) Abl and ABL-1 in *C. elegans*. The N-terminus of mammalian Abl and Arg proteins is variable, encoded by alternative 5'-exons. The variable region is followed by Src homology 3 (SH3), SH2 and tyrosine kinase domains that are highly conserved through evolution. The Abl family kinases are distinguished from the Src-family kinases by their large C-terminal extensions that contain multiple functional domains to mediate interactions with the actin and microtubule cytoskeletons and other cellular components. The mammalian Abl protein contains three nuclear localization signals and one nuclear export signal. Abl has been shown to undergo nucleocytoplasmic shuttling in mammalian cells; its subcellular localization can be modulated by cell adhesion. The Arg and D-Abl proteins are primarily cytoplasmic, consistent with a role for these proteins in regulating cytoskeleton structure.

In the inactive state, the SH3 and SH2 domains of Abl family kinases form an inhibitory scaffold that holds the kinase domain in an inactive conformation. Several cellular proteins, including F-actin and retinoblastoma protein in the nucleus, have been reported to inhibit Abl kinase activity, possibly by stabilizing this inactive conformation. The kinases become activated by the disassembly of the SH3 and SH2 domains from their inhibitory lock on the kinase, possibly by association with higher affinity ligands on activated receptor complexes. Full

kinase activation also requires phosphorylation at two or more tyrosine residues in the short linker between the SH2 and kinase domains and in the kinase domain activation loop. Tyrosine phosphorylation of Abl can be catalyzed by autophosphorylation or by Src family kinases. Abl family kinases can be activated by growth factor stimulation, adhesion receptor engagement, DNA damage and under conditions of oxidative stress. Both Src family kinases and phospholipase C  $\gamma$ 1 have been shown to mediate Abl and Arg activation following growth factor stimulation, but it remains largely unclear how most stimuli activate Abl and Arg kinase activity.

Abl family kinases regulate cell morphology and motility by regulating cytoskeleton dynamics. Abl and Arg also act downstream of adhesion receptors to promote filopodial and lamellipodial dynamics and inhibit cell spreading and cell migration in cultured fibroblasts. Upon growth factor stimulation, Abl promotes membrane ruffling and attenuates chemotaxis. Abl family kinases can promote cytoskeletal rearrangements by phosphorylating the Crk and Dok1 adaptor proteins and the RhoA inhibitor p190RhoGAP. Arg can also promote cytoskeletal rearrangement independent of kinase activity by using its F-actin- and microtubule-binding domains to promote F-actin-rich protrusions at the cell periphery. Genetic studies in mice and flies have suggested that Abl family kinases are important regulators of neuronal and epithelial morphogenesis during development.

Although Abl and Arg can both function in the cytoplasm, the mammalian Abl performs a unique role in the nucleus. Nuclear Abl kinase is activated in response to DNA damage via pathways that depend on ATM and DNA-PK. Activation of nuclear

Abl kinase contributes to the growth arrest or apoptotic response to DNA damage, and Abl has been linked to the regulation of p53 and p73, which are related transcription factors with anti-proliferative and pro-apoptotic functions.

Mutational activation of Abl kinase activity causes greater than 95% of human chronic myelogenous leukemia (CML) and a small percentage of cases of acute lymphocytic leukemia, acute myeloid leukemia and chronic neutrophilic leukemia. Oncogenic activation results from translocation between chromosomes 9 and 22 that fuses exons of the Bcr gene to exons of Abl, resulting in a hybrid gene encoding a Bcr-Abl fusion oncoprotein. Bcr-Abl has hyperactive kinase activity and upregulates mitogenic and anti-apoptotic pathways. A selective Abl inhibitor, Imatinib (STI571;Gleevec), has proven effective in the treatment of chronic phase CML patients. CML patients in acute phase or blast crisis, however, develop resistance to imatinib at a high rate, thereby rendering the drug ineffective.

# Abl

<b>FAMILY MEMBERS</b>	Abl	Arg	Bcr-Abl	D-Abl	Abl-1
<b>OTHER NAMES</b>	c-Abl, Abl1, JTK7, P150, Abelson nonreceptor tyrosine kinase	Abl2, Ab11, Abelson murine leukemia viral oncogene 2, Abl-related gene	p210, Breakpoint cluster region, Abelson oncogene	Abl-1	Abl
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	123 kDa, 1130 aa	124 kDa, 1182 aa	210, 190, 230 kDa	171 kDa; 1620 aa	138 kDa, 1224 aa
<b>ISOFORMS</b>	Not known	Not known	Not known	Not known	Not known
<b>SPECIES</b>	Mouse, human, other vertebrates	Mouse, human, other vertebrates	Human, mouse, rat	<i>Drosophila melanogaster</i>	<i>Caenorhabditis elegans</i>
<b>DOMAIN ORGANIZATION</b>	1 SH2 domain, 1 SH3 domain	SH1 domain, SH2 domain, SH3 domain, proline-rich C-term	N-terminal serine/ threonine kinase domain, PH domain SH2 domain, SH3, domain	SH2 domain, SH3 domain	SH2 domain, SH3 domain
<b>PHOSPHORYLATION SITES</b>	Tyr <sup>185</sup> , Tyr <sup>253</sup> , Tyr <sup>257</sup> , Tyr <sup>264</sup> , Tyr <sup>393</sup> , Thr <sup>394</sup> , Tyr <sup>469</sup>	Tyr <sup>310</sup> , Tyr <sup>439</sup> , Thr <sup>440</sup> , Tyr <sup>515</sup>	Tyr <sup>177</sup> , Tyr <sup>328</sup> , Ser <sup>354</sup> , Tyr <sup>360</sup>	Tyr <sup>522</sup>	Not known
<b>TISSUE DISTRIBUTION</b>	Widely expressed	Widely expressed, but most abundant in brain and lymphocytes, thymus	Myeloid precursor cells, hematopoietic cells	CNS, epithelium	Not known
<b>SUBCELLULAR LOCALIZATION</b>	Nucleus and cytoplasm, focal membrane adhesions, actin cytoskeleton	Cytoplasm, lamellipodial protrusions	Cytoplasm, F-actin stress fibers	Cytoplasm	Not known
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	Ab1, crk-II, EVL, IK3-2 Cables, Sema6 D, MYR, p16, DOK1, ABL2, p17, Abi1, Mena	Not known	GAP, PLCγ1, Src, ARG, c-Abl, p210, Grb2, SOS1, Syp, p160 Bcr	Not known	Not known
<b>UPSTREAM ACTIVATORS</b>	PDGF receptor, T cell receptor, Src family kinases, integrin α5β1, PDGF or EGF stimulation, integrin- mediated adhesion, genotoxic stress, ionizing radiation, oxidative stress	PDGF receptor, T cell receptor, Src family kinases, integrin α5β1, PDGF or EGF stimulation, integrin- mediated adhesion, genotoxic stress, ionizing radiation	Chromosomal translocation creates oncogenic fusion protein which is constitutively active	Dlar, Robo, DE-cadherin, growth factors	Not known

## FOOTNOTES

## Abl

<b>DOWNSTREAM ACTIVATION</b>	Crk, Abi2, Actin, ATM, CD19, p73, Pag, Cables, ABL2	c-Crk, Siva-1, EphB2	PI3K, STAT1, STAT5, STAT6, Ras, PKC, IL-3 paxillin, vinculin, actin, Fak, c-Abl, Src, Bcl-2	Neural axon guidance receptors, Fra, Trio, Ena	Clk-2, hus-1, mrt-2, CCP-1
<b>IN VITRO SUBSTRATES</b>	Crk, RNA polymerase II C-terminal domain (CTD), various peptides, Shd, p190RhoGAP	Crk, various peptides, p190RhoGAP	Crk, various peptides	Not known	Not known
<b>IN VIVO SUBSTRATES</b>	Crk, paxillin, Dok1, Dok2	Crk, p190RhoGAP	Crk, CrkL, paxillin, Rin1, Jak2	Not known	Not known
<b>ACTIVATORS</b>	Not known	Not known	Not known	Not known	Not known
<b>INHIBITORS</b>	Imatinib (Gleevec®), PD180970, PD166325, PD173955	Imatinib (Gleevec®), PD180970, PD166325	Imatinib (Gleevec®), PD180970, PD173955, AG 568, AG 1112 ( <b>T6193</b> )		
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Regulates lymphocyte and osteoblast development, neuronal morphogenesis, neural tube formation	Regulates lymphocyte and osteoblast development, neuronal morphogenesis, tube formation, regulates cytoskeleton	Not known	Regulates neuronal and epithelial morphogenesis	Provides protection to ionizing radiation
<b>DISEASE RELEVANCE</b>	Chronic myeloid leukemia (CML)	Activated by chromosomal translocation in rare cases of acute myeloid leukemia, colon carcinoma, metastatic colon tumors	Causes chronic myelogenous and neutrophilic leukemia, acute lymphocytic leukemia, Philadelphia chromosome (Ph1)-positive acute lymphocytic leukemia	Not known	Not known

**Abbreviations**

**AG 568:** ( $\alpha$ Z)-5-Amino-4-cyano- $\alpha$ -[(3,4-dihydroxyphenyl)methylene]-1H-pyrazole-3-acetonitrile

**CNS:** Central nervous system

**Crk:** Cellular homolog of oncogene from CT10 avian sarcoma virus

**CrkL:** Crk-like protein

**dlar:** *Drosophila* leukocyte antigen-related protein

**Dok1:** Downstream of tyrosine kinases 1

**EGF:** Epithelial growth factor

**ena:** Enabled

**fax:** Failed axon connections

**PD173955:** 6-(2,6-Dichlorophenyl)-8-methyl-2-[[3-(methylthio)phenyl]amino]-Pyrido[2,3-d]pyrimidin-7(8H)-one

**PD180970:** 6-(2,6-Dichlorophenyl)-2-[(4-fluoro-3-methylphenyl)amino]-8-methyl-pyrido[2,3-d]pyrimidin-7(8H)-one

**PGDF:** Platelet-derived growth factor

**Robo:** Roundabout

**p190RhoGAP:** 190 kD GTPase activating protein for RhoA

**Rin1:** Ras-interactor 1

## FOOTNOTES