1. Phylogeny – ABL2 (also known as ARG) belongs to the Abl family of non‐receptor tyrosine kinases that are a distinct subgroup within the tyrosine kinome. ABL2 shares a close evolutionary relationship with ABL1 and is classified within the Src module (SrcM) subgroup in which members display a conserved SH3–SH2–kinase domain organization. Orthologs of ABL2 can be identified across mammalian species and other vertebrates, and its evolutionary origin dates back to the common ancestor of metazoans, similar to its paralog ABL1 (fabbro2015tenthingsyou pages 4-5, kwon2019tracingtheevolution pages 41-45).
2. Reaction Catalyzed – ABL2 catalyzes the transfer of the γ-phosphate group from ATP to a tyrosine residue on protein substrates. In biochemical terms, its catalytic reaction is as follows: ATP + [protein]-tyrosine → ADP + [protein]-phosphotyrosine + H⁺ (fabbro2015tenthingsyou pages 22-23, tse2015moleculardeterminantsunderlying pages 1-2).
3. Cofactor Requirements – The kinase activity of ABL2 requires the presence of divalent metal ions as cofactors, with Mg²⁺ being essential for coordinating ATP binding and facilitating the phosphoryl transfer reaction (lund2013biotechapplicationsof pages 23-27).
4. Substrate Specificity – ABL2 is a tyrosine kinase that phosphorylates target proteins on tyrosine residues. Its substrate specificity is defined by its recognition of motifs present on substrates involved in cytoskeletal regulation and receptor signaling. Identified substrates include proteins that control actin dynamics such as MYH10, cortactin (CTTN), and components of microtubules including TUBA1 and TUBB, as well as signaling adaptors such as CRK and CRKL (fabbro2015tenthingsyou pages 4-5, zh… identificationofksr1 pages 71-75). Although a detailed consensus sequence for ABL2 has not been explicitly established in the current context, its substrate recognition patterns are inferred to be similar to those found for other cytoplasmic tyrosine kinases that preferentially phosphorylate tyrosine residues within specific biochemical contexts (tse2015moleculardeterminantsunderlying pages 1-2, bhanumathy2021proteintyrosinekinases pages 2-4).
5. Structure – ABL2 exhibits a modular domain structure characteristic of Abl family kinases. It contains an N-terminal region that includes Src homology 3 (SH3) and Src homology 2 (SH2) domains, followed by a well-conserved catalytic (kinase) domain. The kinase domain adopts the typical bilobed structure of eukaryotic protein kinases with an N-terminal lobe comprising a glycine-rich loop and a C-helix, and a larger C-terminal lobe containing the activation loop, catalytic loop, and motifs required for substrate binding and phosphoryl transfer. In addition, ABL2 possesses regions that mediate F-actin binding and bundling, which contribute to its role in cytoskeletal remodeling; these regions may be located within its C-terminal portion and can include intrinsically disordered segments that are critical for protein stability and regulation (hantschel2012structureregulationsignaling pages 1-2, rogers2021abelsonkinase’sintrinsically pages 26-26). Unique structural features include the presence of autoinhibitory interactions mediated by its SH3 and SH2 domains with the kinase domain and its direct binding to filamentous actin, which distinguishes it functionally from other tyrosine kinases (fabbro2015tenthingsyou pages 4-5, kwon2019tracingtheevolution pages 41-45).
6. Regulation – ABL2 is subject to multiple layers of regulation that control its kinase activity and stability. Autophosphorylation in its activation loop leads to a conformational change that increases its catalytic activity. In its inactive state, intramolecular interactions involving its SH3 and SH2 domains help maintain an autoinhibited conformation, a mechanism that is conserved among Abl family kinases (hantschel2012structureregulationsignaling pages 1-2, kwon2019tracingtheevolution pages 32-37). Additionally, ABL2 regulates its own activity through autocatalytic phosphorylation as well as through phosphorylation of its inhibitory protein ABI1. Post-translational modifications, such as phosphorylation at key regulatory residues, modulate its interaction with cytoskeletal regulators and adaptor proteins. Furthermore, the kinase is regulated by its binding to F-actin, which not only localizes it to specific subcellular compartments but also modulates its activity in response to extracellular stimuli. Pathogens can hijack ABL2 signaling to reorganize the host actin cytoskeleton, indicating that regulatory pathways converging on ABL2 are critical for proper cellular function (fabbro2015tenthingsyou pages 22-23, hantschel2012structureregulationsignaling pages 2-3, rogers2021abelsonkinase’sintrinsically pages 1-2).
7. Function – ABL2 functions primarily as a non-receptor tyrosine kinase with overlapping roles to ABL1 in controlling cell growth and survival. It plays a central role in cytoskeletal remodeling by phosphorylating proteins that regulate the actin and microtubule networks, such as MYH10, CTTN, TUBA1, and TUBB. Through these modifications, ABL2 regulates events including cell motility, adhesion, and receptor endocytosis. Moreover, ABL2 phosphorylates adaptor proteins such as CRK, CRKL, and DOK1, and modulates the activity of Rho regulatory proteins like ARHGAP35, influencing cell adhesion dynamics by controlling the localization of RASA1 and the inhibition of RHO signaling. In neuronal tissue, ABL2 may regulate neurotransmission at synapses. It is also implicated in pathological signaling cascades during infections, wherein pathogens exploit ABL2 signaling to reorganize the host cytoskeleton for intracellular movement and cell exit. Additionally, ABL2 positively regulates chemokine-mediated T-cell migration, polarization, and homing to lymph nodes and inflamed tissues, likely through activation of effectors such as NEDD9/HEF1 and RAP1 (fabbro2015tenthingsyou pages 4-5, hantschel2012structureregulationsignaling pages 3-4, bhanumathy2021proteintyrosinekinases pages 1-2).
8. Other Comments – Several small-molecule tyrosine kinase inhibitors that target Abl family kinases have been developed, including imatinib, ponatinib, dasatinib, and bosutinib. These inhibitors are used predominantly in the treatment of chronic myelogenous leukemia and other cancers driven by dysregulated ABL kinase activity; although many studies focus on ABL1, similar pharmacological agents are being evaluated for broader activity against related kinases such as ABL2 (wong2004thebcrablstory pages 14-17, kim2017proteintyrosinesignaling pages 25-27). ABL2 is also a target of pathogen-mediated signaling, and its modulation may have implications for infectious disease as well as immune regulation. Notable disease associations for ABL2 include its involvement in oncogenic transformation and chemokine signaling processes that mediate T-cell migration. Functional mutations in Abl family kinases have been linked with drug resistance in cancer therapy, and although most well-characterized mutations are in ABL1, studies of resistance mechanisms often inform understanding of ABL2 function (hantschel2012structureregulationsignaling pages 5-6, tse2015moleculardeterminantsunderlying pages 2-3).
9. References  
   fabbro2015tenthingsyou pages 4-5, fabbro2015tenthingsyou pages 22-23, hantschel2012structureregulationsignaling pages 1-2, hantschel2012structureregulationsignaling pages 2-3, hantschel2012structureregulationsignaling pages 3-4, hantschel2012structureregulationsignaling pages 5-6, kwon2019tracingtheevolution pages 41-45, lund2013biotechapplicationsof pages 23-27, tse2015moleculardeterminantsunderlying pages 1-2, bhanumathy2021proteintyrosinekinases pages 1-2, bhanumathy2021proteintyrosinekinases pages 2-4, rogers2021abelsonkinase’sintrinsically pages 26-26, kwon2019tracingtheevolution pages 32-37, kim2017proteintyrosinesignaling pages 25-27.

References

1. (fabbro2015tenthingsyou pages 4-5): Doriano Fabbro, Sandra W Cowan‐Jacob, and Henrik Moebitz. Ten things you should know about protein kinases: iuphar review 14. British Journal of Pharmacology, Jun 2015. URL: https://doi.org/10.1111/bph.13096, doi:10.1111/bph.13096. This article has 459 citations and is from a highest quality peer-reviewed journal.
2. (hantschel2012structureregulationsignaling pages 1-2): O. Hantschel. Structure, regulation, signaling, and targeting of abl kinases in cancer. Genes & Cancer, 3:436-446, May 2012. URL: https://doi.org/10.1177/1947601912458584, doi:10.1177/1947601912458584. This article has 192 citations.
3. (hantschel2012structureregulationsignaling pages 2-3): O. Hantschel. Structure, regulation, signaling, and targeting of abl kinases in cancer. Genes & Cancer, 3:436-446, May 2012. URL: https://doi.org/10.1177/1947601912458584, doi:10.1177/1947601912458584. This article has 192 citations.
4. (hantschel2012structureregulationsignaling pages 3-4): O. Hantschel. Structure, regulation, signaling, and targeting of abl kinases in cancer. Genes & Cancer, 3:436-446, May 2012. URL: https://doi.org/10.1177/1947601912458584, doi:10.1177/1947601912458584. This article has 192 citations.
5. (hantschel2012structureregulationsignaling pages 5-6): O. Hantschel. Structure, regulation, signaling, and targeting of abl kinases in cancer. Genes & Cancer, 3:436-446, May 2012. URL: https://doi.org/10.1177/1947601912458584, doi:10.1177/1947601912458584. This article has 192 citations.
6. (kwon2019tracingtheevolution pages 41-45): HA Kwon. Tracing the evolution of the tyrosine kinome from sequence to function. Unknown journal, 2019.
7. (lund2013biotechapplicationsof pages 23-27): BA Lund. Biotech applications of protein kinase affinity interactions. Unknown journal, 2013.
8. (tse2015moleculardeterminantsunderlying pages 1-2): Amanda Tse and Gennady M. Verkhivker. Molecular determinants underlying binding specificities of the abl kinase inhibitors: combining alanine scanning of binding hot spots with network analysis of residue interactions and coevolution. PLOS ONE, 10:e0130203, Jun 2015. URL: https://doi.org/10.1371/journal.pone.0130203, doi:10.1371/journal.pone.0130203. This article has 38 citations and is from a peer-reviewed journal.
9. (tse2015moleculardeterminantsunderlying pages 2-3): Amanda Tse and Gennady M. Verkhivker. Molecular determinants underlying binding specificities of the abl kinase inhibitors: combining alanine scanning of binding hot spots with network analysis of residue interactions and coevolution. PLOS ONE, 10:e0130203, Jun 2015. URL: https://doi.org/10.1371/journal.pone.0130203, doi:10.1371/journal.pone.0130203. This article has 38 citations and is from a peer-reviewed journal.
10. (fabbro2015tenthingsyou pages 22-23): Doriano Fabbro, Sandra W Cowan‐Jacob, and Henrik Moebitz. Ten things you should know about protein kinases: iuphar review 14. British Journal of Pharmacology, Jun 2015. URL: https://doi.org/10.1111/bph.13096, doi:10.1111/bph.13096. This article has 459 citations and is from a highest quality peer-reviewed journal.
11. (kwon2019tracingtheevolution pages 32-37): HA Kwon. Tracing the evolution of the tyrosine kinome from sequence to function. Unknown journal, 2019.
12. (rogers2021abelsonkinase’sintrinsically pages 26-26): Edward M. Rogers, S. Colby Allred, and Mark Peifer. Abelson kinase’s intrinsically disordered region plays essential roles in protein function and protein stability. Cell Communication and Signaling, Feb 2021. URL: https://doi.org/10.1186/s12964-020-00703-w, doi:10.1186/s12964-020-00703-w. This article has 18 citations and is from a peer-reviewed journal.
13. (wong2004thebcrablstory pages 14-17): Stephane Wong and Owen N. Witte. The bcr-abl story: bench to bedside and back. Annual Review of Immunology, 22:247-306, Apr 2004. URL: https://doi.org/10.1146/annurev.immunol.22.012703.104753, doi:10.1146/annurev.immunol.22.012703.104753. This article has 508 citations and is from a highest quality peer-reviewed journal.
14. (bhanumathy2021proteintyrosinekinases pages 1-2): Kalpana K. Bhanumathy, Amrutha Balagopal, Frederick S. Vizeacoumar, Franco J. Vizeacoumar, Andrew Freywald, and Vincenzo Giambra. Protein tyrosine kinases: their roles and their targeting in leukemia. Cancers, 13:184, Jan 2021. URL: https://doi.org/10.3390/cancers13020184, doi:10.3390/cancers13020184. This article has 73 citations and is from a peer-reviewed journal.
15. (bhanumathy2021proteintyrosinekinases pages 2-4): Kalpana K. Bhanumathy, Amrutha Balagopal, Frederick S. Vizeacoumar, Franco J. Vizeacoumar, Andrew Freywald, and Vincenzo Giambra. Protein tyrosine kinases: their roles and their targeting in leukemia. Cancers, 13:184, Jan 2021. URL: https://doi.org/10.3390/cancers13020184, doi:10.3390/cancers13020184. This article has 73 citations and is from a peer-reviewed journal.
16. (kim2017proteintyrosinesignaling pages 25-27): Mihwa Kim, Minwoo Baek, and Dae Joon Kim. Protein tyrosine signaling and its potential therapeutic implications in carcinogenesis. Current Pharmaceutical Design, Nov 2017. URL: https://doi.org/10.2174/1381612823666170616082125, doi:10.2174/1381612823666170616082125. This article has 78 citations and is from a peer-reviewed journal.
17. (rogers2021abelsonkinase’sintrinsically pages 1-2): Edward M. Rogers, S. Colby Allred, and Mark Peifer. Abelson kinase’s intrinsically disordered region plays essential roles in protein function and protein stability. Cell Communication and Signaling, Feb 2021. URL: https://doi.org/10.1186/s12964-020-00703-w, doi:10.1186/s12964-020-00703-w. This article has 18 citations and is from a peer-reviewed journal.