1. Phylogeny  
   Tyrosine‐protein kinase ABL2 (also known as ARG) is a member of the Abelson (ABL) family, a subgroup of the non‐receptor tyrosine kinases. ABL2 shares high sequence conservation in its N‐terminal region (comprising SH3, SH2, and kinase domains) with ABL1, indicating a gene duplication event in vertebrates that generated two paralogs within the ABL family (khatri2018theroleof pages 16-21, mayro2022thecharacterizationofa pages 17-24). This kinase is evolutionarily conserved across metazoans, with orthologs present in organisms ranging from invertebrates to mammals, suggesting that the ABL family originated early in eukaryotic evolution (corwin2016decipheringhumancytoplasmica pages 13-16, siveen2018roleofnon pages 2-4). Phylogenetically, ABL2 belongs to a kinome group that is distinct from receptor tyrosine kinases and shares regulatory features with other non‐receptor kinases such as the Src family, although it lacks some of the regulatory C‐terminal residues present in Src proteins (khatri2018theroleof pages 135-138, laszlo2019structuralinsightsinto pages 1-2).
2. Reaction Catalyzed  
   ABL2 catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to the hydroxyl group of tyrosine residues on protein substrates. The generalized chemical reaction is:  
     ATP + [protein]-Tyr → ADP + [protein]-Tyr-phosphate + H⁺  
   This phosphorylation event induces a conformational or functional change in the substrate, thereby modulating protein–protein interactions and the activity of signaling pathways (azevedo2019nonreceptortyrosinekinases pages 1-3, siveen2018roleofnon pages 2-4). Although precise details regarding the catalytic mechanism of ABL2 have not been fully elaborated in the present texts, it is generally accepted that the ABL kinases utilize a similar bi–bi mechanism as other protein kinases, wherein nucleotide binding and catalytic base–assisted deprotonation of the tyrosine hydroxyl group are key steps (arrington2019identificationofthe pages 8-9).
3. Cofactor Requirements  
   Like most protein kinases, ABL2 requires divalent metal ions for its catalytic activity, with Mg²⁺ serving as the primary cofactor. Mg²⁺ ions coordinate to ATP, facilitating the correct positioning of the nucleotide for phosphate transfer (azevedo2019nonreceptortyrosinekinases pages 1-3). No alternative cofactors have been explicitly reported in the provided literature, but the dependence on Mg²⁺ is consistent with the canonical requirements of tyrosine kinases (siveen2018roleofnon pages 2-4).
4. Substrate Specificity  
   The substrate specificity of ABL2 is partially overlapping with that of ABL1; both kinases target proteins that influence cytoskeletal dynamics and receptor signaling. ABL2 phosphorylates a diverse range of substrates involved in actin remodeling and microtubule dynamics. Key physiological substrates include:  
    • MYH10 – a non–muscle myosin involved in cellular movement;  
    • CTTN (cortactin), which regulates actin dynamics and cellular signaling;  
    • TUBA1 and TUBB – subunits of microtubules required for appropriate cytoskeletal organization;  
    • Adaptor proteins CRK and CRKL, which serve as molecular linkers in multiple signal transduction pathways;  
    • DOK1 and ARHGAP35 – regulators of cell adhesion and motility – whose phosphorylation modulates their interaction with RASA1 leading to local inhibition of RHO GTPases (information section, khatri2018theroleof pages 135-138, hoj2020thecharacterizationofa pages 31-37).  
   Additionally, ABL2 phosphorylates receptor tyrosine kinases like PDGFRB and endocytosis regulators such as RIN1, extending its impact to receptor internalization processes (arrington2019identificationofthe pages 8-9, khatri2018theroleof pages 27-32). Although a precise consensus motif for ABL2 substrates is not specified in the provided context, the kinase is known to recognize target tyrosine residues that are embedded in specific local structural contexts which can include docking motifs recognized by its own SH2 domain (mayro2022thecharacterizationof pages 29-34, siveen2018roleofnon pages 2-4).
5. Structure  
   ABL2 exhibits a modular domain architecture common to the ABL family. The N-terminal portion comprises an SH3 domain—which mediates binding to proline-rich motifs—an SH2 domain that recognizes phosphotyrosine-containing sequences, and a catalytic (kinase) SH1 domain (khatri2018theroleof pages 16-21, mayro2022thecharacterizationofa pages 17-24). Uniquely, ABL2 possesses additional domains in its C-terminal region: an F-actin binding domain and a microtubule binding domain, which are absent in ABL1. These additional domains are believed to confer a predominant cytoplasmic localization and specialized functions in cytoskeletal remodeling (hoj2020thecharacterizationof pages 31-37, khatri2018theroleof pages 135-138). The regulatory mechanism involves an autoinhibited “clamp” wherein the SH3 domain interacts with a polyproline–rich linker connecting the SH2 and kinase domains; this intramolecular interaction maintains the kinase in an inactive conformation until relieved by activation signals (mayro2022thecharacterizationof pages 24-29, laszlo2019structuralinsightsinto pages 1-2). In addition, a myristoylated N-terminal glycine may participate in reinforcing the inactive state by binding a hydrophobic pocket in the kinase domain (hoj2020thecharacterizationofa pages 31-37, khatri2018theroleof pages 16-21). Structural studies using crystallography and small-angle X-ray scattering have provided insights into the conformation of the SH3 domain and how tyrosine phosphorylation can sterically block ligand interactions without causing large conformational shifts (laszlo2019structuralinsightsinto pages 1-2, vasUnknownyearbalázsmerő1lászló pages 1-2).
6. Regulation  
   The regulation of ABL2 is multifaceted, involving both autophosphorylation and phosphorylation by other kinases. Autocatalytic activity enables ABL2 to phosphorylate itself on key tyrosine residues, which can either stimulate its activity or modulate its interactions with regulatory proteins (mayro2022thecharacterizationofa pages 136-140, khatri2018theroleof pages 27-32). For example, phosphorylation of ABL2 can regulate the function of its SH3 domain by sterically hindering the binding of proline-rich ligands, thereby affecting downstream signaling cascades (laszlo2019structuralinsightsinto pages 1-2, vasUnknownyearbalázsmerő1lászló pages 1-2). Additionally, ABL2 can phosphorylate its own inhibitor ABI1, functioning in a feedback loop to regulate its own activity, and forms part of signaling complexes with adaptor proteins such as CRK and CRKL (information section, mayro2022thecharacterizationof pages 12-17, khatri2018theroleof pages 27-32). External regulatory cues, including growth factor signals and oxidative stress, further modulate ABL2 activity. In some contexts, phosphorylated substrates (such as ARHGAP35) are recruited to the cell periphery where they interact with other regulatory proteins (e.g., RASA1) to inhibit the RHO signaling pathway (information section, khatri2018theroleof pages 131-135). These layers of regulation ensure that ABL2 activity is tightly controlled, balancing its roles in promoting cell motility, adhesion, and receptor endocytosis (hoj2020thecharacterizationofa pages 49-55).
7. Function  
   ABL2 is a multifunctional kinase that plays a critical role in regulating cell growth, cytoskeletal dynamics, adhesion, and receptor trafficking. One of its primary functions is to mediate cytoskeletal remodeling by phosphorylating proteins that control actin and microtubule dynamics. For instance, its phosphorylation of MYH10 alters cell movement, while phosphorylation of CTTN (cortactin) modulates signaling events linked to actin rearrangements (information section). In addition, its ability to bind directly to F-actin and bundle filaments underscores its importance in maintaining and reorganizing the actin cytoskeleton (hoj2020thecharacterizationof pages 31-37, khatri2018theroleof pages 135-138).  
   Beyond its role in actin dynamics, ABL2 regulates cell adhesion and motility. It phosphorylates key regulators such as CRK, CRKL, DOK1, and ARHGAP35; the adhesion-dependent phosphorylation of ARHGAP35 promotes its association with RASA1 and the recruitment of ARHGAP35 to the cell periphery, culminating in the local inhibition of RHO GTPase activity. This regulatory pathway is essential for controlled cell spreading and migration (information section, khatri2018theroleof pages 131-135).  
   In receptor-mediated endocytosis, ABL2 phosphorylates receptor tyrosine kinases like PDGFRB and proteins involved in endocytic sorting such as RIN1, thereby influencing receptor internalization and signal attenuation (arrington2019identificationofthe pages 8-9, khatri2018theroleof pages 27-32).  
   In neural tissue, ABL2 is implicated in the modulation of neurotransmission at the synapse by phosphorylating synaptic proteins, which may affect synaptic plasticity and signal transmission in the brain (information section). Additionally, ABL2 is co-opted by pathogens during infection; certain microorganisms hijack ABL2 kinase signaling to reorganize the host actin cytoskeleton, facilitating processes like intracellular movement and egress from host cells (information section, moharram2021roleofflt3 pages 48-54).  
   Furthermore, ABL2 positively regulates chemokine-mediated T-cell migration, polarization, and homing to lymph nodes and immune-challenged tissues; this function is believed to occur via the activation of proteins such as NEDD9/HEF1 and RAP1, thereby influencing immune cell trafficking during inflammatory responses (information section).
8. Other Comments  
   Several kinase inhibitors developed to target the activity of ABL family kinases—originally in the context of leukemias driven by the BCR-ABL fusion protein—also have activity against ABL2. For example, ATP-competitive inhibitors such as imatinib, nilotinib, dasatinib, and especially ponatinib show high levels of inhibition against ABL2, which has broad implications for both hematologic and solid tumors in which ABL2 is activated (zeng2020ponatinibandother pages 3-4, moharram2021roleofflt3 pages 90-95).  
   In disease contexts, aberrant activation of ABL2 has been linked to various cancers, including chronic myelogenous leukemia (albeit more famously through BCR-ABL1 fusions), and numerous solid tumors such as breast, lung, colorectal, and pancreatic cancers, where its effects on actin remodeling, adhesion, and receptor endocytosis contribute to invasion and metastasis (hoj2020thecharacterizationofa pages 49-55, khatri2018theroleof pages 126-131).  
   Notably, pathogens are known to exploit ABL2-mediated pathways to induce cytoskeletal changes that favor their replication or spread. This emerging area of research underscores the significance of ABL2 not only in cancer biology but also in infectious diseases (information section, moharram2021roleofflt3 pages 48-54).  
   Current research is actively investigating the detailed regulatory networks involving ABL2, including its self-regulation via autophosphorylation and phosphorylation of inhibitor proteins such as ABI1, as well as its crosstalk with other signaling molecules like NEDD9 and RAP1 which govern immune cell behavior (information section, mayro2022thecharacterizationof pages 12-17).  
   Moreover, structural studies focusing on the phosphorylation of the SH3 domain in ABL2 provide key insights into the allosteric regulation of its interactions, with potential implications for the design of more selective inhibitors that target these regulatory interfaces (laszlo2019structuralinsightsinto pages 1-2, vasUnknownyearbalázsmerő1lászló pages 1-2).
9. References  
   arrington2019identificationofthe pages 8-9;  
   hoj2020thecharacterizationof pages 31-37;  
   hoj2020thecharacterizationofa pages 49-55;  
   khatri2018theroleof pages 16-21;  
   khatri2018theroleof pages 27-32;  
   khatri2018theroleof pages 131-135;  
   khatri2018theroleof pages 135-138;  
   mayro2022thecharacterizationof pages 17-24;  
   mayro2022thecharacterizationof pages 24-29;  
   mayro2022thecharacterizationof pages 29-34;  
   mayro2022thecharacterizationof pages 34-39;  
   mayro2022thecharacterizationofa pages 140-144;  
   mayro2022thecharacterizationofa pages 12-17;  
   mayro2022thecharacterizationofa pages 17-24;  
   mayro2022thecharacterizationofa pages 136-140;  
   siveen2018roleofnon pages 2-4;  
   azevedo2019nonreceptortyrosinekinases pages 1-3;  
   corwin2016decipheringhumancytoplasmic pages 13-16;  
   laszlo2019structuralinsightsinto pages 1-2;  
   laszlo2019structuralinsightsinto pages 11-12;  
   vasUnknownyearbalázsmerő1lászló pages 1-2;  
   zeng2020ponatinibandother pages 3-4;  
   moharram2021roleofflt3 pages 48-54;  
   moharram2021roleofflt3 pages 90-95.

References

1. (arrington2019identificationofthe pages 8-9): Justine Arrington, Liang Xue, Wen-Horng Wang, Robert L. Geahlen, and W. Andy Tao. Identification of the direct substrates of the abl kinase via kinase assay linked phosphoproteomics with multiple drug treatments. Journal of Proteome Research, 18:1679-1690, Mar 2019. URL: https://doi.org/10.1021/acs.jproteome.8b00942, doi:10.1021/acs.jproteome.8b00942. This article has 14 citations and is from a peer-reviewed journal.
2. (hoj2020thecharacterizationof pages 31-37): JP Hoj. The characterization of tyrosine kinase-dependent signaling networks required for lung cancer brain metastasis. Unknown journal, 2020.
3. (hoj2020thecharacterizationofa pages 31-37): JP Hoj. The characterization of tyrosine kinase-dependent signaling networks required for lung cancer brain metastasis. Unknown journal, 2020.
4. (hoj2020thecharacterizationofa pages 49-55): JP Hoj. The characterization of tyrosine kinase-dependent signaling networks required for lung cancer brain metastasis. Unknown journal, 2020.
5. (khatri2018theroleof pages 131-135): A Khatri. The role of abl kinases in lung injury and cancer. Unknown journal, 2018.
6. (khatri2018theroleof pages 135-138): A Khatri. The role of abl kinases in lung injury and cancer. Unknown journal, 2018.
7. (khatri2018theroleof pages 16-21): A Khatri. The role of abl kinases in lung injury and cancer. Unknown journal, 2018.
8. (mayro2022thecharacterizationof pages 17-24): BJ Mayro. The characterization of abl tyrosine kinase-regulated transcriptional networks. Unknown journal, 2022.
9. (mayro2022thecharacterizationofa pages 140-144): BJ Mayro. The characterization of abl tyrosine kinase-regulated transcriptional networks. Unknown journal, 2022.
10. (mayro2022thecharacterizationofa pages 17-24): BJ Mayro. The characterization of abl tyrosine kinase-regulated transcriptional networks. Unknown journal, 2022.
11. (siveen2018roleofnon pages 2-4): Kodappully S. Siveen, Kirti S. Prabhu, Iman W. Achkar, Shilpa Kuttikrishnan, Sunitha Shyam, Abdul Q. Khan, Maysaloun Merhi, Said Dermime, and Shahab Uddin. Role of non receptor tyrosine kinases in hematological malignances and its targeting by natural products. Molecular Cancer, Feb 2018. URL: https://doi.org/10.1186/s12943-018-0788-y, doi:10.1186/s12943-018-0788-y. This article has 159 citations and is from a highest quality peer-reviewed journal.
12. (corwin2016decipheringhumancytoplasmic pages 13-16): T Corwin. Deciphering human cytoplasmic protein tyrosine kinase phosphorylation specificity in yeast. Unknown journal, 2016.
13. (khatri2018theroleof pages 126-131): A Khatri. The role of abl kinases in lung injury and cancer. Unknown journal, 2018.
14. (khatri2018theroleof pages 27-32): A Khatri. The role of abl kinases in lung injury and cancer. Unknown journal, 2018.
15. (mayro2022thecharacterizationof pages 12-17): BJ Mayro. The characterization of abl tyrosine kinase-regulated transcriptional networks. Unknown journal, 2022.
16. (mayro2022thecharacterizationof pages 24-29): BJ Mayro. The characterization of abl tyrosine kinase-regulated transcriptional networks. Unknown journal, 2022.
17. (mayro2022thecharacterizationof pages 29-34): BJ Mayro. The characterization of abl tyrosine kinase-regulated transcriptional networks. Unknown journal, 2022.
18. (mayro2022thecharacterizationof pages 34-39): BJ Mayro. The characterization of abl tyrosine kinase-regulated transcriptional networks. Unknown journal, 2022.
19. (mayro2022thecharacterizationofa pages 12-17): BJ Mayro. The characterization of abl tyrosine kinase-regulated transcriptional networks. Unknown journal, 2022.
20. (mayro2022thecharacterizationofa pages 136-140): BJ Mayro. The characterization of abl tyrosine kinase-regulated transcriptional networks. Unknown journal, 2022.
21. (moharram2021roleofflt3 pages 48-54): S Moharram. Role of flt3 in acute myeloid leukemia: molecular mechanisms and therapeutic opportunities. Unknown journal, 2021.
22. (moharram2021roleofflt3 pages 90-95): S Moharram. Role of flt3 in acute myeloid leukemia: molecular mechanisms and therapeutic opportunities. Unknown journal, 2021.
23. (azevedo2019nonreceptortyrosinekinases pages 1-3): Ana Azevedo, Susana Silva, and José Rueff. Non-receptor tyrosine kinases role and significance in hematological malignancies. Tyrosine Kinases as Druggable Targets in Cancer, Sep 2019. URL: https://doi.org/10.5772/intechopen.84873, doi:10.5772/intechopen.84873. This article has 15 citations.
24. (corwin2016decipheringhumancytoplasmica pages 13-16): T Corwin. Deciphering human cytoplasmic protein tyrosine kinase phosphorylation specificity in yeast. Unknown journal, 2016.
25. (laszlo2019structuralinsightsinto pages 1-2): R László. Structural insights into the tyrosine phosphorylation-mediated inhibition of sh3 domain-ligand interactions. Unknown journal, 2019.
26. (laszlo2019structuralinsightsinto pages 11-12): R László. Structural insights into the tyrosine phosphorylation-mediated inhibition of sh3 domain-ligand interactions. Unknown journal, 2019.
27. (vasUnknownyearbalázsmerő1lászló pages 1-2): V Vas. Balázs merő1, lászló radnai1, gergő gógl2, orsolya tőke3, ibolya leveles1, 4, kitti koprivanacz1, bálint szeder1, metta dülk1, gyöngyi kudlik1, virág vas1 …. Unknown journal, Unknown year.
28. (zeng2020ponatinibandother pages 3-4): Peng Zeng and Alvin Schmaier. Ponatinib and other cml tyrosine kinase inhibitors in thrombosis. International Journal of Molecular Sciences, 21:6556, Sep 2020. URL: https://doi.org/10.3390/ijms21186556, doi:10.3390/ijms21186556. This article has 34 citations and is from a peer-reviewed journal.