## Phylogeny

Tyrosine-protein kinase ABL2 (ARG) is one of two members of the Abelson (ABL) family of non-receptor tyrosine kinases. The family originated from a single ancestral Abl gene in early metazoans; gene duplication in early vertebrates produced the paralogues ABL1 and ABL2. The two paralogues retain very high homology in their N-terminal SH3–SH2–kinase cassette, whereas ABL2 has diverged markedly in its long C-terminal extension (Hayes, 2013, pp. 34–38; Superti-Furga & Courtneidge, 1995, pp. 8-9). Orthologues of ABL2 are present throughout vertebrates, underscoring its conserved role in cytoskeletal signalling (Mayro, 2022, pp. 17–24; Kwon, 2019, pp. 65–69).

## Reaction Catalyzed

ATP + [protein]-tyrosine ⇌ ADP + [protein]-phosphotyrosine + H⁺ (Arrington et al., 2019, pp. 5-6; Johnson, 2009, pp. 13-15).

## Cofactor Requirements

Requires divalent Mg²⁺ for ATP coordination during catalysis (Johnson, 2009, pp. 13-15).

## Substrate Specificity

Substrate recognition is guided by the SH2 and SH3 domains. ABL2 preferentially phosphorylates motifs containing a hydrophobic residue (Ile, Leu or Val) at the –1 position relative to the target Tyr and a Pro or aromatic residue at +3 (Arrington et al., 2019, pp. 5-7). These sequence preferences facilitate binding of downstream SH2-containing proteins that drive cytoskeletal remodelling (Mayro, 2022, pp. 29-34).

## Structure

ABL2 is modular: N-terminal CAP, SH3, SH2 and catalytic (SH1) domains are followed by an extended C-terminal tail that harbours multiple F-actin-binding elements and a microtubule-binding region (Hayes, 2013, pp. 34-38; Mayro, 2022, pp. 17-24). Canonical kinase features include the DFG motif, C-helix positioning and hydrophobic spine that toggle between active and autoinhibited states; SH3–SH2–linker contacts stabilise the inactive conformation (Panjarian et al., 2013, pp. 2-3). Unlike ABL1, ABL2 is predominantly cytoplasmic, consistent with its actin-binding C-terminus (Panjarian et al., 2013, pp. 2-3; Hayes, 2013, pp. 64-66).

## Regulation

Activity is autoinhibited by intramolecular SH3/SH2–linker interactions. Relief of inhibition occurs via autophosphorylation of activation-loop tyrosines and phosphorylation by Src-family kinases (Hayes, 2013, pp. 38-41; Hantschel, 2012, pp. 1-2). Additional layers include C-terminal acetylation, ubiquitin-mediated degradation and caspase cleavage (Hayes, 2013, pp. 64-66). ABL2 also phosphorylates its own inhibitor ABI1, providing feedback regulation (Hayes, 2013, pp. 38-41).

## Function

ABL2 coordinates cytoskeletal dynamics in response to extracellular cues, influencing cell growth, adhesion and motility. Documented substrates include MYH10, cortactin, tubulin (TUBA1/TUBB), CRK, CRKL, DOK1, ARHGAP35 and RIN1 (Hayes, 2013, pp. 38-41, 69-74, 92-95; Mayro, 2022, pp. 29-34). Phosphorylation of these targets modulates actin and microtubule rearrangements, endocytosis, and receptor tyrosine-kinase signalling (Arrington et al., 2019, pp. 7-8). ABL2 also supports chemokine-driven T-cell migration and may regulate synaptic transmission (Hayes, 2013, pp. 64-66; Hoj, 2020, pp. 161-164).

## Inhibitors

Clinically approved ATP-competitive inhibitors of the ABL family (imatinib, nilotinib, dasatinib) bind the ABL2 active site; their efficacy in solid tumours is context-dependent (Hayes, 2013, pp. 209-213, 69-74). Allosteric inhibitors that occupy the myristoyl pocket (e.g., GNF-2, GNF-5) have been developed from structural studies (Johnson, 2009, pp. 11-13; Panjarian et al., 2013, pp. 5-6).

## Other Comments

ABL2 can be hijacked by bacterial and viral pathogens to reorganise host actin for intracellular motility and egress (Hayes, 2013, pp. 38-41; Siveen et al., 2018, pp. 2-4). In cancer, ABL2 displays dual roles: it promotes invasion in breast cancer yet suppresses invasion in head and neck squamous cell carcinoma (Hayes, 2013, pp. 69-74).

## 9. References

Arrington, J., Xue, L., Wang, W.-H., Geahlen, R. L., & Tao, W. A. (2019). 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. https://doi.org/10.1021/acs.jproteome.8b00942

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

Hayes, K. E. (2013). Abelson kinase based regulation of tumor cell invasion in HNSCC (Doctoral dissertation, West Virginia University). https://doi.org/10.33915/etd.472

Hoj, J. P. (2020). The characterization of tyrosine kinase-dependent signaling networks required for lung cancer brain metastasis. [Institutional repository].

Johnson, L. N. (2009). Protein kinase inhibitors: Contributions from structure to clinical compounds. Quarterly Reviews of Biophysics, 42, 1–40. https://doi.org/10.1017/S0033583508004745

Kwon, H. A. (2019). Tracing the evolution of the tyrosine kinome from sequence to function. [Institutional repository].

Mayro, B. J. (2022). The characterization of ABL tyrosine kinase-regulated transcriptional networks. [Institutional repository].

Panjarian, S., Iacob, R. E., Chen, S., Engen, J. R., & Smithgall, T. E. (2013). Structure and dynamic regulation of ABL kinases. Journal of Biological Chemistry, 288, 5443–5450. https://doi.org/10.1074/jbc.R112.438382

Siveen, K. S., Prabhu, K. S., Achkar, I. W., Kuttikrishnan, S., Shyam, S., Khan, A. Q., Merhi, M., Dermime, S., & Uddin, S. (2018). Role of non-receptor tyrosine kinases in hematological malignancies and its targeting by natural products. Molecular Cancer, 17, Article 57. https://doi.org/10.1186/s12943-018-0788-y

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