1. Phylogeny  
   Tyrosine‐protein kinase ABL2 (also known as ARG) belongs to the Abelson (ABL) family of non–receptor protein tyrosine kinases that also includes ABL1 (c‐Abl) and shares a conserved SRC homology (SH3–SH2–kinase) cassette in its N‐terminal region. This kinase family can be traced back to an ancestral Abl gene present in early metazoans, and the gene duplication that gave rise to ABL1 and ABL2 occurred early in vertebrate evolution, with ABL2 retaining a high degree of homology in its catalytic and regulatory domains compared to ABL1 while diverging considerably in its C‐terminal extension (hayes2013abelsonkinasebased pages 34-38, superti‐furga1995structure‐functionrelationshipsin pages 8-9). Orthologs of ABL2 have been identified in a wide range of vertebrate species, indicating its conserved role in essential cellular signaling and cytoskeletal regulation (mayro2022thecharacterizationof pages 17-24, kwon2019tracingtheevolution pages 65-69).
2. Reaction Catalyzed  
   ABL2 catalyzes the transfer of the γ‐phosphate from adenosine triphosphate (ATP) to specific tyrosine residues on target proteins. The reaction can be summarized as follows: ATP + [protein]–tyrosine → ADP + [protein]–phosphotyrosine + H⁺, thereby altering the phosphorylation state and function of its substrates (arrington2019identificationofthe pages 5-6, johnson2009proteinkinaseinhibitors pages 13-15).
3. Cofactor Requirements  
   The catalytic activity of ABL2 depends on the presence of divalent metal ions, particularly Mg²⁺, which is required for proper coordination of ATP in the active site during the phosphoryl transfer reaction (johnson2009proteinkinaseinhibitors pages 13-15).
4. Substrate Specificity  
   ABL2 displays substrate specificity that is determined in part by its structured SH2 and SH3 domains, which contribute to both substrate recognition and protein–protein interactions. In particular, studies indicate that ABL family kinases preferentially phosphorylate substrates exhibiting consensus motifs characterized by hydrophobic residues such as isoleucine, leucine, or valine at the –1 position relative to the targeted tyrosine, and a proline or aromatic residue at the +3 position (arrington2019identificationofthe pages 5-6). Experimentally derived substrate motifs for ABL kinases include sequences in which the tyrosine residue is embedded in a local context that favors phosphorylation and subsequent binding by SH2 domain–containing proteins, thereby facilitating signaling cascades associated with cytoskeletal reorganization and cell motility (arrington2019identificationofthe pages 6-7, mayro2022thecharacterizationof pages 29-34).
5. Structure  
   ABL2 features a modular architecture that is composed of an N‐terminal region that includes a CAP domain, followed by highly conserved SH3 and SH2 domains and a catalytic kinase (SH1) domain, and culminates in a long, more divergent C‐terminal tail. The N‐terminal region, which exhibits approximately 90% sequence similarity with ABL1, is essential for substrate recognition and regulatory inter‐domain interactions, whereas the C‐terminal region—characterized by additional F‐actin binding sites, an extra F‐actin binding motif, and a microtubule binding domain—confers specificity for cytoskeletal regulation (hayes2013abelsonkinasebased pages 34-38, mayro2022thecharacterizationof pages 17-24). Structural studies, including crystallographic analysis of Abl kinases and molecular dynamics simulations, have revealed key features such as the DFG motif in the activation loop, the positioning of the C‐helix, the hydrophobic spine, and the arrangement of the SH2 domain that all contribute to the enzyme’s active and inactive conformations. Unique to ABL2, in comparison to its paralogue ABL1 which shuttles between the nucleus and cytoplasm, ABL2 is predominantly localized in the cytoplasm where its actin‐binding capacity underlies its role in modulating the cellular cytoskeleton (panjarian2013structureanddynamic pages 2-3, hayes2013abelsonkinasebased pages 64-66).
6. Regulation  
   The activity of ABL2 is controlled by complex regulatory mechanisms that include intramolecular interactions, autophosphorylation events, and phosphorylation by upstream kinases such as Src. The autoinhibitory configuration is maintained via interactions between its SH3 domain and SH2–kinase linker, and these interactions can be disrupted by phosphorylation at key tyrosine residues such as those on the activation loop (e.g., analogous to Tyr412 in ABL1) and by phosphorylation events mediated by Src family kinases (hayes2013abelsonkinasebased pages 38-41, hantschel2012structureregulationsignaling pages 1-2). Post–translational modifications such as acetylation in the C-terminal region, ubiquitination leading to proteasomal degradation, and caspase cleavage further contribute to the regulation of ABL2 activity (hayes2013abelsonkinasebased pages 64-66, mayro2022thecharacterizationof pages 29-34). Additionally, ABL2 can undergo autophosphorylation, which not only enhances its catalytic activity but also serves as a mechanism for self-regulation through modification of its inhibitor-binding interfaces, as exemplified by its phosphorylation of ABI1, an established inhibitor (hayes2013abelsonkinasebased pages 38-41).
7. Function  
   Functionally, ABL2 plays a critical role in coordinating cytoskeletal remodeling in response to extracellular stimuli, thereby contributing to cell growth, adhesion, and motility. It phosphorylates a variety of substrates that regulate actin and microtubule dynamics including MYH10, cortactin (CTTN), and tubulin subunits such as TUBA1 and TUBB, which are crucial for the reorganization of the cytoskeleton (hayes2013abelsonkinasebased pages 38-41, hayes2013abelsonkinasebased pages 92-95). Through phosphorylation of key regulators like CRK, CRKL, DOK1, and ARHGAP35, ABL2 influences cell adhesion and migratory pathways by modulating the recruitment and localization of signaling molecules at the cell periphery (hayes2013abelsonkinasebased pages 38-41, hayes2013abelsonkinasebased pages 69-74). Moreover, ABL2 has been implicated in endocytosis regulation via substrates such as RIN1 and is also involved in the modulation of receptor tyrosine kinase signaling, exemplified by its phosphorylation of PDGFRB (mayro2022thecharacterizationof pages 29-34, arrington2019identificationofthe pages 7-8). In the nervous system, ABL2 may regulate neurotransmission by phosphorylating synaptic proteins, and it has been shown to positively regulate chemokine-mediated T-cell migration and polarization, indicating a role in immune cell homing and tissue infiltration (hayes2013abelsonkinasebased pages 64-66, hoj2020thecharacterizationof pages 161-164).
8. Other Comments  
   Several small molecule inhibitors developed for the ABL family, including imatinib, nilotinib, and dasatinib, target the ATP-binding pocket and have been used successfully in the context of chronic myelogenous leukemia (CML) driven by BCR–ABL fusion proteins. However, the efficacy of these inhibitors in solid tumors remains variable, likely reflecting the dual and context-dependent role of ABL2 in different cancer types, for instance its pro-invasive role in breast cancer versus its invasion-suppressive function in head and neck squamous cell carcinoma (hayes2013abelsonkinasebased pages 209-213, hayes2013abelsonkinasebased pages 69-74). Additionally, novel allosteric inhibitors that target the myristoylated pocket, such as those known as STAMPs (e.g., GNF-2 and GNF-5), have emerged as alternative therapeutic strategies based on structural insights from Abl kinases (johnson2009proteinkinaseinhibitors pages 11-13, panjarian2013structureanddynamic pages 5-6). ABL2 is also co-opted by pathogens to reorganize the actin cytoskeleton for intracellular movement and host cell exit, thereby highlighting its role in infection-associated signaling cascades (hayes2013abelsonkinasebased pages 38-41, siveen2018roleofnon pages 2-4).
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