1. Phylogeny  
   Tyrosine‐protein kinase ABL2, also known as Abelson murine leukemia viral oncogene homolog 2, Abelson tyrosine‐protein kinase 2, ARG, is a member of the Abl family of non‐receptor tyrosine kinases. Evolutionarily, ABL2 and its closely related paralog ABL1 emerged via gene duplication from a single ancestral Abl gene that is conserved in invertebrates; in vertebrates, two distinct Abl isoforms now exist. As part of the human kinome, the Abl kinases are classified within the tyrosine kinase (TK) group, and orthologs of ABL2 have been identified across a broad range of metazoans including mammals, birds, reptiles, amphibians, and fish. This high degree of conservation underscores the critical roles that Abl kinases play in cellular signaling, particularly in pathways that regulate cytoskeletal organization, cell proliferation, motility, and survival (arrington2019identificationofthe pages 3-3, azevedo2019nonreceptortyrosinekinases pages 3-6, baryyan2022newkinasebasedmolecular pages 21-26).
2. Reaction Catalyzed  
   ABL2 catalyzes the classical phosphorylation reaction characteristic of tyrosine kinases. In this reaction, the enzyme transfers the gamma‐phosphate group from ATP to a tyrosine residue on a substrate protein. The chemical reaction can be represented as:  
     ATP + [protein]–L‑tyrosine → ADP + [protein]–L‑tyrosine‑phosphate + H⁺  
   This ATP‐dependent phosphotransfer reaction is essential for modulating the function, localization, and interactions of target proteins through reversible phosphorylation (arrington2019identificationofthe pages 3-3).
3. Cofactor Requirements  
   The catalytic efficiency of ABL2, as with most protein kinases, is contingent upon the availability of divalent metal ion cofactors. In particular, Mg²⁺ ions are required to coordinate the binding of ATP within the kinase’s active site and to facilitate the proper transfer of the phosphate group to tyrosine residues on substrate proteins. This cofactor dependency is a hallmark of tyrosine kinase enzymology and is critical for achieving optimal catalytic activity (arrington2019identificationofthe pages 10-11, baryyan2022newkinasebasedmolecular pages 21-26).
4. Substrate Specificity  
   Systematic profiling of the substrate specificity within the human tyrosine kinome has revealed that ABL2 exhibits intrinsic phosphorylation preferences that are largely overlapping with those of other members of the Abl family. Detailed phosphopeptide assays have determined that ABL2 displays a preferential affinity for substrate sequences in which the central tyrosine residue is flanked by hydrophobic amino acids such as leucine, isoleucine, or valine. In some experimental systems, flanking acidic residues appear to be disfavored, resulting in a distinct consensus motif. More specifically, recent studies have indicated an upstream preference for sequences that may conform to an [E/D]x[V/L/I] motif in proximity to the phosphoacceptor tyrosine. Although the inherent substrate specificity of ABL2 substantially resembles that of ABL1, subtle differences in peptide recognition exist that likely impact the regulation of downstream signaling pathways. The elucidation of these motifs has been aided by high‐throughput kinase assays that print a detailed “atlas” of substrate preferences for the tyrosine kinase family (yaronbarir2024theintrinsicsubstrate pages 10-11, yaronbarir2024theintrinsicsubstrate pages 7-8, yaronbarir2024theintrinsicsubstrate pages 8-8).
5. Structure  
   The three‐dimensional structure of ABL2 is organized into several modular domains that are characteristic of the Abl family of non‐receptor tyrosine kinases. At the N-terminus, ABL2 contains an SH3 (Src homology 3) domain that mediates binding to proline‐rich motifs present in interacting proteins. Adjacent to the SH3 domain is an SH2 (Src homology 2) domain, which specifically recognizes phosphotyrosine-containing sequences; this domain plays a crucial role in substrate recruitment as well as in intramolecular autoinhibitory interactions. Central to the protein is the catalytic kinase domain (often termed the SH1 domain), which adopts a bilobed structure comprising an N-terminal lobe (dominated by beta-sheets) and a C-terminal lobe (predominantly alpha-helical). Within the kinase domain, several key structural elements play pivotal roles in catalysis: the activation loop, whose phosphorylation status modulates the transition from an inactive to an active conformation; the C-helix, which is essential for the proper orientation of ATP and catalytic residues; and the hydrophobic spine, which serves to stabilize the active conformation of the kinase. In addition to these core domains, ABL2 possesses a unique C-terminal region that contains an F-actin binding domain. This domain is responsible for the direct association with filamentous actin and the bundling of actin filaments, thus providing a mechanistic link between kinase activity and the regulation of the cytoskeleton. Structural insights derived from experimental crystallography on homologous Abl kinases, coupled with predictive models from AlphaFold, support a model in which intramolecular interactions among the SH3, SH2, and kinase domains maintain the enzyme in an autoinhibited state that is released upon binding to upstream activators or as a result of post-translational modifications (arrington2019identificationofthe pages 8-9, baryyan2022newkinasebasedmolecular pages 21-26, loris2007exploringstructureand pages 143-146).
6. Regulation  
   The enzymatic activity of ABL2 is subject to precise regulation by several interdependent mechanisms. One primary mode of regulation is autophosphorylation: phosphorylation events within the activation loop relieve autoinhibitory constraints and promote the transition to an active conformation. In parallel, ABL2 is known to phosphorylate its own inhibitor, ABI1, thereby establishing a negative feedback loop that modulates its catalytic output. Furthermore, phosphorylation of specific tyrosine residues located in the SH2-kinase linker region by upstream kinases—such as members of the Src family—can destabilize the autoinhibited conformation, thereby enhancing kinase activity. Additionally, intramolecular interactions contribute to regulation; the SH3 domain interacts with a polyproline region within the SH2–kinase linker, while the presence of a myristoylated N-terminus facilitates binding into a hydrophobic pocket in the kinase C-lobe. Such interactions are critical for maintaining the inactive state under basal conditions. Alterations in subcellular localization, particularly those mediated by dynamic binding to F-actin, also influence ABL2 activity by modulating access to substrates and regulatory proteins (arrington2019identificationofthe pages 12-12, daraiseh2017tyrosinephosphorylationof pages 39-44, mayro2022thecharacterizationof pages 17-24).
7. Function  
   ABL2 plays a multifaceted role in the orchestration of cellular signaling networks. Central to its function is the regulation of cytoskeletal dynamics. By phosphorylating key cytoskeletal regulatory proteins such as MYH10 (a non‐muscle myosin essential for movement), cortactin (CTTN, which participates in actin assembly and signaling), and the microtubule subunits TUBA1 and TUBB, ABL2 directly modulates the organization and dynamics of both the actin and microtubule networks. In addition to its direct effects on the cytoskeleton, ABL2 phosphorylates adaptor proteins involved in cell adhesion and motility—including CRK, CRKL, and DOK1—which further fine-tune cellular responses to extracellular cues. Notably, phosphorylation of the Rho GTPase regulator ARHGAP35 promotes its association with RASA1, thereby recruiting ARHGAP35 to the cell periphery where it exerts inhibitory control over RHO activity and thus remodels cell shape and motility. Beyond cytoskeletal regulation, ABL2 also phosphorylates receptor tyrosine kinases, such as PDGFRB, and proteins implicated in receptor endocytosis like RIN1, which positions ABL2 as a key modulator of receptor internalization and turnover. In the nervous system, ABL2 may contribute to the regulation of neurotransmission by phosphorylating synaptic proteins, while in the immune system, it plays a role in chemokine-mediated T-cell migration, polarization, and homing. These diverse functions are further underscored by the observation that certain pathogens hijack ABL2 signaling to reorganize the host actin cytoskeleton, thereby facilitating intracellular movement and cellular egress (arrington2019identificationofthe pages 8-9, azevedo2019nonreceptortyrosinekinases pages 3-6, creeden2020kinomearrayprofiling pages 32-34, yaronbarir2024theintrinsicsubstrate pages 8-8).
8. Other Comments  
   ABL2 has attracted considerable attention for its clinical relevance, particularly because of its overlapping inhibitor sensitivity with ABL1. Several tyrosine kinase inhibitors (TKIs) that target the Abl family, including imatinib, dasatinib, nilotinib, bosutinib, and ponatinib, have been approved for the treatment of chronic myeloid leukemia in which aberrant kinase activity drives disease progression. Although specific mutations or rearrangements in ABL2 have not been as prominently characterized as those in ABL1, dysregulation of ABL2 activity is implicated in a variety of pathological states, including oncogenic transformation and infection-mediated cytoskeletal remodeling. Recent kinome profiling studies have also identified dysregulated ABL2 activity in contexts such as pancreatic ductal adenocarcinoma and fibrotic processes, suggesting that altered ABL2 signaling may contribute to the pathogenesis of these conditions. Inhibitor development remains an active area of research, with ongoing efforts to identify compounds that can selectively target ABL2 over ABL1 despite the high degree of conserved domain structure. These disease associations and pharmacological challenges underscore the importance of further dissecting the regulatory mechanisms that govern ABL2 activity and its role in cellular signaling (arrington2019identificationofthe pages 10-11, malnassy2022abl2promotesalcoholassociated pages 36-39, creeden2022pancreaticcancerkinome pages 25-27, tan2015discoveryoftype pages 12-16, creeden2020kinomearrayprofiling pages 16-18).
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