1. Phylogeny  
   ABL1 (also known as c‑Abl or p150) is a member of the Abl family of non‐receptor tyrosine kinases, which includes the paralog ABL2 (commonly referred to as Arg). Orthologs of ABL1 are conserved throughout metazoans, with homologous proteins identified in both vertebrates and invertebrates. The Abl kinases belong to the tyrosine kinase group of the human kinome and share structural and evolutionary characteristics with other non‐receptor tyrosine kinases, albeit with a distinctive regulatory mechanism that includes a myristoylated N‑terminus and an “SH3–SH2 clamp.” This evolutionary conservation implies that ABL1 has an ancient origin and an essential role in coordinating signaling networks from yeast through to man (colicelli2010abltyrosinekinases pages 1-2, greuber2013roleofabl pages 1-2, koleske2006mechanismsofactivation pages 1-3).
2. Reaction Catalyzed  
   ABL1 catalyzes the transfer of a phosphate group from ATP to the hydroxyl group of a tyrosine residue on substrate proteins. The reaction can be summarized as follows:  
   ATP + [protein]‑(L‑tyrosine) → ADP + [protein]‑phospho‑tyrosine + H⁺  
   This phosphorylation reaction modulates the function of substrate proteins by altering their activity, interactions, or subcellular localization (colicelli2010abltyrosinekinases pages 2-4).
3. Cofactor Requirements  
   The catalytic activity of ABL1 depends on the presence of divalent metal ions, most notably Mg²⁺. Mg²⁺ is essential for the proper coordination of ATP within the active site and for facilitating the phosphoryl transfer reaction (irgit2025structureanddynamics pages 1-3, hantschel2012structureregulationsignaling pages 1-2).
4. Substrate Specificity  
   ABL1 displays substrate specificity that is determined both by intrinsic features of its kinase domain and by docking interactions mediated by its SH2 and SH3 domains. Biochemical studies, particularly in ancestral Abl kinases, have indicated a preference for peptide motifs such as “IYAAP” and related sequences. More generally, ABL1 appears to favor substrate sequences containing specific hydrophobic and proline residues that are critical for effective binding and phosphorylation. In addition to sequence preferences, substrate specificity is also dictated by the ability of substrates to engage the regulatory docking sites provided by the SH2 and SH3 domains (aleem2015constitutiveactivityin pages 10-11, colicelli2010abltyrosinekinases pages 7-8, greuber2013roleofabl pages 5-7).
5. Structure  
   ABL1 exhibits a multi‐domain architecture that is central to its catalytic and regulatory functions. At the N‑terminus, the protein contains a region that in some isoforms undergoes co‑translational myristoylation; this lipid modification plays an important role in maintaining the enzyme’s autoinhibited state by facilitating binding of the myristoyl group within a deep hydrophobic pocket of the kinase domain. Adjacent to this is an N‑terminal “Cap” region that also contributes to autoinhibition. Following the N‑terminal regulatory elements, ABL1 contains a tandem arrangement of the SH3 and SH2 domains. The SH3 domain, which typically binds polyproline type II helices, in this context participates in intramolecular interactions with a linker region between the SH2 and kinase domains, while the SH2 domain binds to a phosphotyrosine motif within the kinase domain’s C‑lobe. These interactions collectively form an “SH3–SH2 clamp” that keeps the kinase in a low‑activity conformation.  
   The central catalytic (kinase) domain exhibits a bilobal structure: a smaller N‑terminal lobe containing a glycine‑rich P‑loop responsible for ATP binding and positioning, and a larger C‑terminal lobe that provides the substrate binding site. Critical to its activation is the conformation of the activation loop, which contains conserved tyrosine residues (for example, Tyr412 in mammalian ABL1) that must become phosphorylated to permit full catalytic activity. Additionally, features such as the C‑helix and hydrophobic spines help stabilize either the inactive or active conformations. The C‑terminal region of ABL1 harbors domains involved in binding actin and DNA, thereby influencing cytoskeletal dynamics and nuclear functions, respectively. This structural organization is supported by crystallographic studies and computational models (colicelli2010abltyrosinekinases pages 1-2, hantschel2012structureregulationsignaling pages 1-2, irgit2025structureanddynamics pages 1-3, koleske2006mechanismsofactivation pages 1-3).
6. Regulation  
   ABL1 is subject to elaborate regulatory mechanisms that ensure its kinase activity is tightly controlled. Autoinhibition is a hallmark of ABL1 regulation: the SH3 domain binds a proline‐rich linker between the SH2 and kinase domains, and the SH2 domain simultaneously interacts with the C‑lobe of the kinase domain, collectively stabilizing an inactive conformation. Myristoylation of the N‑terminal region further reinforces autoinhibition by docking into a hydrophobic pocket within the kinase domain. Activation of ABL1 is associated with specific phosphorylation events, most notably at tyrosines such as Tyr245 and Tyr412; these phosphorylation events relieve the autoinhibitory interactions, leading to a conformational reorganization that permits substrate access. In addition to autophosphorylation, binding of regulatory adaptor proteins—for example, RIN1—can enhance ABL1 catalytic efficiency by promoting structural rearrangements that favor the active state. Other post‑translational modifications, including ubiquitination and acetylation, impact ABL1 stability and subcellular localization. Lipid interactions, such as those with PIP₂, can also modulate kinase activity by influencing membrane association and conformational transitions (colicelli2010abltyrosinekinases pages 4-5, hantschel2012structureregulationsignaling pages 2-3, aleem2015constitutiveactivityin pages 4-6).
7. Function  
   ABL1 is a multifunctional kinase with roles in a wide range of cellular processes essential for cell growth, survival, and homeostasis. In the cytoplasm, ABL1 regulates cytoskeletal remodeling by phosphorylating several proteins that control actin dynamics, such as WASF3 (which is critical for lamellipodia formation and cell migration), ANXA1, DBN1, DBNL, CTTN, RAPH1, and ENAH. Phosphorylation of these substrates facilitates changes in cell shape, motility, and adhesion. ABL1 modulates microtubule dynamics by targeting proteins such as MAPT and PXN, thereby contributing to the regulation of cell polarity and intracellular transport.  
   In addition, ABL1 phosphorylates receptor tyrosine kinases (e.g., EGFR) and other membrane-associated proteins, such as CAV1 and RIN1, functioning in receptor endocytosis and down-regulation. Through its regulation of the CBL family of ubiquitin ligases, ABL1 indirectly contributes to the modulation of receptor stability and turnover. ABL1 also plays a key role in autophagy, particularly in the late stages where it supports trafficking and function of lysosomal components.  
   Within the nucleus, ABL1 is capable of DNA binding and is a significant mediator of the DNA damage response. It phosphorylates components of the DNA repair machinery—including DDB1, DDB2, ERCC3, ERCC6, RAD9A, RAD51, RAD52, and WRN—thereby facilitating repair processes or, in cases of excessive damage, activating proapoptotic pathways by phosphorylating factors such as TP73 and CASP9. Furthermore, ABL1 phosphorylates other substrates involved in cell cycle regulation (for example, PSMA7) which contribute to cell cycle arrest under stress conditions. Beyond these roles, ABL1 is involved in regulating T-cell differentiation and migration through phosphorylation of TBX21 and modulation of NEDD9/HEF1 and RAP1 signaling (greuber2013roleofabl pages 19-22, wang2014thecapableabl pages 1-2, sato2012functionalmechanismsand pages 2-4).
8. Other Comments  
   ABL1 is a high-profile target in therapeutic oncology. Its aberrant activation is most famously represented by the BCR‑ABL1 fusion protein, which arises from the Philadelphia chromosome translocation in chronic myeloid leukemia (CML) and certain acute lymphoblastic leukemias. This fusion protein loses portions of the N‑terminal autoinhibitory regions, including the myristoylation site and Cap domain, resulting in constitutive kinase activity. ABL1 inhibitors such as imatinib, nilotinib, dasatinib, and ponatinib are used clinically to target BCR‑ABL1, while newer allosteric inhibitors (e.g., GNF‑2 and GNF‑5) that bind the myristoyl pocket offer promising strategies for overcoming resistance due to mutations. In addition to its oncogenic roles in hematological malignancies, abnormal ABL1 signaling has been implicated in various solid tumors through its regulation of cell motility, invasion, and apoptosis. Moreover, ABL1 is hijacked by microbial proteins during infection—for example, by Vaccinia virus A36R and H. pylori CagA—to manipulate the host actin cytoskeleton. Mutations that disrupt normal regulatory interactions, particularly those affecting the SH3/SH2 module or the myristoylation-dependent autoinhibition, have been associated with enhanced kinase activity and cellular transformation (aleem2015constitutiveactivityin pages 10-11, keersmaecker2008intrinsicdifferencesbetween pages 8-9, koleske2006mechanismsofactivation pages 9-10). This multifaceted regulatory complexity underpins both the physiological roles of ABL1 and its pathological contributions when misregulated.
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