1. Phylogeny  
   Tyrosine‐protein kinase ABL1 is a deeply conserved non‐receptor tyrosine kinase that belongs to the Abl family, which includes ABL1 (often called c‑Abl) and its paralog ABL2 (also known as Arg). Evolutionary studies have placed these kinases as part of the cytoplasmic tyrosine kinase group that shares considerable sequence and domain conservation with the Src family; however, the Abl family is distinct in its regulatory mechanisms (eshaq2024nonreceptortyrosinekinases pages 28-29, luttman2021roleofthe pages 1-2). ABL1 can be traced back to early metazoan ancestors and is present in all vertebrates. The duplication event that gave rise to the ABL1/ABL2 pair occurred early in vertebrate evolution, and orthologs of ABL1 are found from mammals to lower vertebrates, where its conserved modular structure—including the SH3, SH2, and kinase domains—is maintained (wang2015theemergingrole pages 4-5, mayro2022thecharacterizationof pages 17-24). Moreover, phylogenetic analysis groups ABL kinases within a broad evolutionary core set of signaling enzymes that emerged early on, together with other key regulators such as Src family kinases, receptor tyrosine kinases, and the components of the DNA damage response systems (eshaq2024nonreceptortyrosinekinases pages 28-29, luttman2021roleofthe pages 1-2).
2. Reaction Catalyzed  
   ABL1 catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to specific tyrosine residues on protein substrates. The chemical reaction can be summarized as:  
   ATP + protein‑L‑tyrosine → ADP + protein‑L‑phosphotyrosine + H⁺.  
   This phosphorylation reaction modulates the activity, localization, and interaction capabilities of substrate proteins, thereby altering their cellular functions. ABL1 phosphorylates a broad range of substrates involved in cytoskeletal organization, receptor endocytosis, signal transduction, DNA repair, and apoptosis (liu2022allostericregulationof pages 1-2, arrington2019identificationofthe pages 7-8).
3. Cofactor Requirements  
   The enzymatic activity of ABL1 is strictly dependent on ATP as the phosphate donor, and its proper catalytic function requires divalent metal ions, usually magnesium (Mg²⁺), that coordinate ATP binding within the active site. While no unusual cofactors are reported beyond these essentials, the kinase’s regulation and catalytic efficiency are further modulated by non-catalytic features such as myristoylation of the N-terminal glycine in one of its splice isoforms (ABL1 1b), which influences intramolecular interactions and autoinhibition (eshaq2024nonreceptortyrosinekinases pages 12-14, wu2024clinicalinsightsinto pages 2-4).
4. Substrate Specificity  
   ABL1 displays a broad substrate specificity that reflects its role in coordinating diverse cellular processes. Its substrates include key regulators of the cytoskeleton and adhesive structures, such as WASF3—which is critical for lamellipodia formation and cell migration—as well as proteins involved in receptor endocytosis such as caveolin (CAV1) and RIN1 (eshaq2024nonreceptortyrosinekinases pages 12-14). In addition, ABL1 phosphorylates adaptor molecules such as CRK and CRKL, which contribute to cytoskeletal remodeling and signaling cascades linked to cell motility and adhesion (eshaq2024nonreceptortyrosinekinases pages 28-29). Although a strict consensus motif has not been uniformly defined across all cases, the presence of docking sites for the SH2 and SH3 domains on ABL1 appears to facilitate processive phosphorylation events, thereby enhancing substrate recognition and selectivity. This processive mechanism is supported by the coupling of substrate binding to subsequent phosphorylation in a manner that may rely on target sequence features—particularly regions containing tyrosine residues embedded in flexible or disordered segments that allow for repeated encounters with the catalytic cleft (mayro2022thecharacterizationof pages 24-29, luttman2021roleofthe pages 8-9).
5. Structure  
   ABL1’s structure is characterized by a modular domain organization that defines its catalytic and regulatory functions. The core of the protein is organized into a well-conserved N-terminal segment that includes the Src homology 3 (SH3) and Src homology 2 (SH2) domains, followed by the kinase (SH1) domain. The SH3 domain binds poly-proline sequences, whereas the SH2 domain recognizes phosphotyrosine-containing motifs; these domains participate in intramolecular autoinhibitory interactions that normally keep the kinase in a downregulated state (grover2015understandingactiveabl pages 25-31, eshaq2024nonreceptortyrosinekinases pages 12-14).  
   In many mammalian isoforms such as ABL1 1b, an N-terminal myristoylation sequence is present. After removal of the initiating methionine, the exposed glycine becomes covalently linked to a myristoyl group that engages a hydrophobic pocket located in the C-lobe of the kinase domain. This binding is central to maintaining an autoinhibited “closed” conformation (liu2022allostericregulationof pages 1-2, shah2017identificationandcharacterization pages 11-15).  
   Further structural features include nuclear localization signals (NLSs) within the unique C-terminal extensions of ABL1, distinguishing it from its paralog ABL2, which lacks these signals and instead has domains favoring interaction with the actin cytoskeleton. Three-dimensional structural studies – derived from crystallography and supported by NMR spectroscopy – have elucidated the active (DFG-in) and inactive (DFG-out and Src-like) conformations of the kinase domain, demonstrating conformational plasticity that is critical for both catalysis and regulation. Key regulatory residues include tyrosine 412 on the activation loop (whose phosphorylation is essential for full kinase activity) and tyrosine 245 in the SH2-kinase linker, which modulates autoinhibitory interactions (grover2015understandingactiveabl pages 39-44, shah2017identificationandcharacterization pages 15-19).
6. Regulation  
   The activity of ABL1 is tightly regulated by multiple, interconnected mechanisms. Autoinhibition is achieved through intramolecular interactions between the SH3, SH2, and kinase domains. In its inactive state, the SH3 domain engages the SH2-kinase linker region, while myristoylation of the N-terminal glycine (particularly in the ABL1 1b isoform) further stabilizes the autoinhibited conformation by binding to a specific hydrophobic pocket in the kinase domain (eshaq2024nonreceptortyrosinekinases pages 12-14, grover2015understandingactiveabl pages 25-31).  
   Activation of ABL1 occurs through several processes. Phosphorylation of tyrosine residues within the activation loop (notably Y412) and the SH2-kinase linker (e.g., Y245) disrupts the autoinhibitory clamp, thereby shifting the equilibrium toward an open, active conformation. This phosphorylation can be a result of autophosphorylation, as well as contributed by other kinases such as Src family members (liu2022allostericregulationof pages 1-2, luttman2021roleofthe pages 10-11).  
   In addition, allosteric regulation plays a prominent role. Novel inhibitors that target the myristoyl-binding pocket exploit the natural autoinhibitory mechanism to stabilize the inactive conformation, as exemplified by asciminib. This mode of regulation not only prevents ATP binding but also reduces potential off‐target effects by selectively locking ABL1 in an inactive state (jones2020allostericinhibitionof pages 5-8, shah2017identificationandcharacterization pages 11-15).  
   Other regulatory mechanisms involve protein–protein interactions mediated by the SH2 and SH3 domains with adaptor proteins such as CRK/CRKL; these interactions modulate both substrate recognition and the spatial distribution of kinase activity within the cell (luttman2021roleofthe pages 8-9). Additionally, post-translational modifications such as ubiquitination and acetylation have been reported to influence ABL1’s subcellular localization and stability, thereby indirectly affecting its kinase activity (esaq2024nonreceptortyrosinekinases pages 28-29).
7. Function  
   ABL1 fulfills multifaceted roles in normal cellular physiology and in pathological conditions. It orchestrates key biological processes through its phosphorylation of a wide array of substrates. In the cytoplasm, ABL1 regulates actin cytoskeleton dynamics by phosphorylating proteins involved in lamellipodia formation and focal adhesion (for example, WASF3 and regulators like CRK and CRKL), thereby promoting cell motility, adhesion, and receptor endocytosis (eshaq2024nonreceptortyrosinekinases pages 28-29, jones2020allostericinhibitionof pages 5-8).  
   In endocytosis, ABL1 phosphorylates receptor tyrosine kinases such as EGFR; this activity facilitates receptor internalization and influences receptor recycling and degradation. ABL1 also phosphorylates proteins such as caveolin (CAV1) and RIN1 that are involved in membrane trafficking (eshaq2024nonreceptortyrosinekinases pages 28-29).  
   When translocated to the nucleus, ABL1 exercises DNA-binding activity and contributes to the DNA damage response. It phosphorylates several substrates involved in DNA repair—like RAD51, RAD52, and WRN—and activates proapoptotic pathways through phosphorylation of TP73 and caspase CASP9 when the severity of DNA damage exceeds repair capacity. In this way, ABL1 is an important mediator of stress-induced apoptotic signals (eshaq2024nonreceptortyrosinekinases pages 28-29, wu2024clinicalinsightsinto pages 1-2).  
   Moreover, ABL1 plays a role in autophagy by positively regulating the trafficking and function of lysosomal components, affecting degradation pathways that control protein homeostasis. Under conditions of oxidative stress, ABL1 can target mitochondria and phosphorylate key proteins such as PRKD2, thereby mediating mitochondrial dysfunction and ultimately influencing cell death (eshaq2024nonreceptortyrosinekinases pages 28-29).  
   Beyond its central roles in growth, survival, and stress responses, ABL1 is implicated in modulating immune cell functions. It contributes to T-cell differentiation and migration by phosphorylating regulators like TBX21 and NEDD9, which are important for immune surveillance and homing (luttman2021roleofthe pages 8-9). Finally, the oncogenic activity of ABL1 is most dramatically illustrated in its fusion with BCR to form the BCR‑ABL1 oncoprotein, which drives chronic myeloid leukemia (CML) and certain acute lymphoblastic leukemias (ALL) by abrogating normal autoinhibition and causing constitutive kinase activity (jones2020allostericinhibitionof pages 1-5, shah2017identificationandcharacterization pages 15-19).
8. Other Comments  
   ABL1 has been a major focus of therapeutic intervention due to its role in cancer. ATP-competitive inhibitors such as imatinib, nilotinib, dasatinib, and ponatinib have been developed to target the kinase domain of both native ABL1 and its oncogenic fusion forms. However, resistance often arises because of point mutations in the kinase domain—for example, the gatekeeper mutation T315I—and through mechanisms that disrupt autoinhibitory interactions (manley2020thespecificityof pages 1-6, shah2017identificationandcharacterization pages 19-24).  
   To address these hurdles, a new generation of allosteric inhibitors has been developed. These agents, including asciminib and GNF-2-like compounds, bind to the myristoyl-binding pocket rather than the ATP site, thereby stabilizing the inactive conformation of ABL1. This mode of inhibition offers enhanced specificity and, in many cases, reduced off-target toxicity (jones2020allostericinhibitionof pages 5-8, manley2020thespecificityof pages 22-26).  
   Mutational analyses have revealed that activating point mutations can occur in both the native ABL1 gene and in the BCR‑ABL1 fusion, which emphasizes the importance of comprehensive mutation screening to tailor therapeutic strategies (shah2017identificationandcharacterization pages 30-39).  
   Given its involvement in cytoskeletal remodeling, receptor endocytosis, autophagy, and the DNA damage response, ABL1 remains a critical node in a variety of signaling cascades. This multifunctional role extends its impact beyond hematological malignancies into solid tumors, where gene amplification or dysregulated activation of ABL1 has also been implicated (wang2015theemergingrole pages 5-8, wu2024clinicalinsightsinto pages 1-2).  
   Research is ongoing to better understand the complex cross-talk between ABL1 and other signaling pathways and to design combination therapies that mitigate resistance, such as coupling ATP-competitive inhibitors with allosteric agents. In addition, studies are addressing the roles of ABL1 in cellular processes during infection, where pathogens hijack its signaling to modulate the host cell cytoskeleton (eshaq2024nonreceptortyrosinekinases pages 28-29).
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