1. Phylogeny  
   Tyrosine‐protein kinase ABL1 (commonly referred to as c‐Abl) is a non‐receptor tyrosine kinase that belongs to the Abl family of kinases. In mammals, the Abl family comprises two members – ABL1 (c‐Abl) and ABL2 (Arg) – both of which are ubiquitously expressed, with ABL1 having numerous alternatively spliced isoforms that modulate its subcellular localization and functional roles (hantschel2012structureregulationsignaling pages 1-2). Evolutionarily, the Abl kinases are conserved across metazoans; for instance, Drosophila possesses a single Abl ortholog, which has been extensively used as a simplified experimental model to delineate the in vivo functions and regulatory mechanisms shared by vertebrate ABL kinases (rogers2020abelsonkinase’sintrinsically pages 4-7, superti‐furga1995structure‐functionrelationshipsin pages 8-9). Phylogenetic studies place ABL1 within the tyrosine kinase group along with other members of the Src-related kinase families, reflecting an evolutionary lineage emerging early in the eukaryotic ancestor (superti‐furga1995structure‐functionrelationshipsin pages 9-10).
2. Reaction Catalyzed  
   The catalytic activity of ABL1 involves the transfer of the γ-phosphate from ATP to specific tyrosine residues on substrate proteins. In chemical terms, the reaction can be summarized as:  
   ATP + protein-(L-tyrosine) → ADP + protein-(L-tyrosine)-phosphate + H⁺  
   This phosphorylation event is central to the regulation of substrate activity and the propagation of intracellular signaling events, thereby modulating processes such as cytoskeletal remodeling, receptor endocytosis, and DNA damage response (roskoski2003sti571ananticancer pages 1-2).
3. Cofactor Requirements  
   The kinase catalytic mechanism of ABL1 requires the presence of divalent metal ions. In particular, Mg²⁺ serves as an essential cofactor that coordinates ATP within the catalytic cleft and stabilizes the negative charges on the phosphate groups during the phosphoryl transfer reaction (roskoski2003sti571ananticancer pages 1-2).
4. Substrate Specificity  
   ABL1 specifically catalyzes the phosphorylation of tyrosine residues on its target proteins. The substrate specificity is dictated in part by the tyrosine kinase catalytic domain, but it is further refined by substrate recruitment mediated by the SH2 and SH3 domains, which bind phosphotyrosine-containing sequences and proline-rich motifs, respectively. In practice, ABL1 phosphorylates a variety of substrates involved in actin cytoskeleton regulation, receptor endocytosis and DNA damage response. Examples include proteins such as WASF3, whose tyrosine phosphorylation is critical for the formation of lamellipodia that promote cell migration, and substrates such as CBL, where phosphorylation modulates receptor down-regulation (hantschel2012structureregulationsignaling pages 3-4, roskoski2003sti571ananticancer pages 4-5). Although the precise consensus sequence for ABL1 has not been as explicitly defined in the primary literature provided, its substrate motif is characterized by interactions with its regulatory SH2 domain that facilitates multisite phosphorylation, thus contributing to signal specificity (tse2015moleculardeterminantsunderlying pages 2-3).
5. Structure  
   ABL1 possesses a modular domain architecture that is fundamental to its regulation and function. Starting from the N-terminus, ABL1 in one of its prevalent isoforms (e.g., ABL1 1b) features an N-terminal myristoylation signal that promotes membrane association under some conditions but more importantly plays a key role in autoinhibition by docking into a hydrophobic pocket of the kinase C-lobe (hantschel2012structureregulationsignaling pages 1-2, roskoski2003sti571ananticancer pages 5-6). This is followed by a cap region, after which lie the SH3 and SH2 domains. The SH3 domain binds polyproline type II helices while the SH2 domain recognizes phosphotyrosine-containing peptides. These domains are arranged in such a way that they engage in intramolecular interactions; for example, the SH3 domain binds to the SH2-kinase linker, thereby reinforcing the autoinhibited conformation (hantschel2012structureregulationsignaling pages 1-2, superti‐furga1995structure‐functionrelationshipsin pages 9-10).  
   Following the regulatory SH2/SH3 unit is the kinase or catalytic domain (SH1 domain). This domain is organized in the classical bilobed structure observed in protein kinases, with an N-terminal lobe rich in β-sheets—responsible for ATP binding—and a larger C-terminal lobe that contains predominantly α-helices and contributes to substrate binding. Within the kinase domain, the activation loop—a critical regulatory segment containing Tyr412—is subject to autophosphorylation, providing a switch between inactive and active conformations (hantschel2012structureregulationsignaling pages 3-4, roskoski2003sti571ananticancer pages 4-5). The kinase domain also contains conserved structural motifs, including the hydrophobic spine and the C-helix, whose proper assembly is required for catalytic activity (kornev2015dynamicsdrivenallosteryin pages 6-7).  
   In addition, ABL1 contains an extended C-terminal region that is intrinsically disordered and enriched in proline-rich motifs. This region mediates multiple protein-protein interactions that regulate the kinase function and contribute to substrate specificity (rogers2020abelsonkinase’sintrinsically pages 1-4). The disordered region contributes to the dynamic nature of ABL1, impacting its protein stability and subcellular localization (rogers2021abelsonkinase’sintrinsically pages 1-2).
6. Regulation  
   The activity of ABL1 is tightly controlled by several layers of regulation. One major regulatory mechanism is autoinhibition, which is governed by intramolecular interactions involving the myristoyl group bound within a hydrophobic pocket of the kinase domain and the SH3 domain’s interaction with the SH2-kinase linker. This “latching” mechanism stabilizes an inactive conformation and prevents substrate access (hantschel2012structureregulationsignaling pages 1-2, wong2004thebcrablstory pages 10-12).  
   Phosphorylation plays a crucial role in ABL1 regulation. Autophosphorylation events, particularly at Tyr412 within the activation loop, serve as a molecular switch that shifts the enzyme from its inactive to active conformation. Phosphorylation at Tyr245 in the SH2-kinase linker also disrupts the inhibitory interactions maintained by the SH3 domain, thus promoting full kinase activation (hantschel2012structureregulationsignaling pages 3-4, roskoski2003sti571ananticancer pages 5-6).  
   In addition to autophosphorylation, ABL1 is subject to other post-translational modifications. For instance, ubiquitination mediated by the CBL family of ubiquitin ligases can target ABL1 for proteasomal degradation, modulating its cellular abundance, especially in response to stress conditions (information section; rogers2021abelsonkinase’sintrinsically pages 26-26).  
   Conformational dynamics further contribute to ABL1 regulation. The equilibrium between the inactive, autoinhibited state and the active, phosphorylated state is influenced by allosteric inhibitor binding. Inhibitors such as imatinib preferentially bind to the inactive DFG-out conformation of ABL1, thereby stabilizing the autoinhibited state, while other inhibitors such as dasatinib bind the active conformation (roskoski2003sti571ananticancer pages 8-9, tse2015moleculardeterminantsunderlying pages 35-36).  
   Finally, ABL1 shuttles between the cytoplasm and nucleus due to the presence of nuclear localization and export signals. In the nucleus, ABL1 participates in DNA damage responses and apoptosis, whereas in the cytoplasm it regulates cytoskeletal reorganization, cell adhesion and receptor endocytosis (hantschel2012structureregulationsignaling pages 8-9, rogers2021abelsonkinase’sintrinsically pages 1-2).
7. Function  
   ABL1 plays a pivotal role in many cellular processes related to growth, survival, and homeostasis. Its kinase activity is central to the dynamic regulation of the actin cytoskeleton. For example, ABL1 phosphorylates key regulators of cytoskeletal dynamics such as WASF3, thereby stimulating the formation of lamellipodia that lead to enhanced cell migration (information section; hantschel2012structureregulationsignaling pages 7-8). In addition, ABL1 phosphorylates adaptor proteins like CRK and CRKL that are involved in the modulation of cell adhesion and motility.  
   ABL1 also regulates receptor-mediated endocytosis. It phosphorylates receptor tyrosine kinases such as EGFR and modulates the activity of endocytic regulators including CBL and RIN1, thereby influencing receptor internalization and signaling turnover (lund2013biotechapplicationsof pages 45-48, hantschel2012structureregulationsignaling pages 5-6).  
   In the context of autophagy, ABL1 is involved in the regulation of lysosomal trafficking and function during the late stages of autophagy, contributing positively to the degradation process (information section).  
   In response to cellular stress, particularly oxidative stress, ABL1 translocates to mitochondria where it phosphorylates targets such as the serine/threonine kinase PRKD2; this event contributes to mitochondrial dysfunction and can trigger cell death (information section, rogens2021abelsonkinase’sintrinsically pages 26-26).  
   Furthermore, in the nucleus ABL1 is involved in the DNA damage response. Through its DNA-binding activity and interaction with mediators of DNA repair—including proteins such as DDB1, DDB2, RAD51 and TP73—ABL1 plays a dual role in attempting repair and, if the damage is irreparable, in activating apoptotic pathways (hantschel2012structureregulationsignaling pages 3-4, roskoski2003sti571ananticancer pages 9-9).  
   ABL1 is also exploited by pathogens during infection. Several microbial proteins, including A36R from Vaccinia virus and CagA from Helicobacter pylori, are phosphorylated by ABL1, facilitating the rearrangement of the host actin cytoskeleton to promote processes such as intracellular movement and host cell exit (information section).  
   Collectively, ABL1 functions as a versatile signaling hub that integrates signals from diverse cellular stimuli to regulate cytoskeletal remodeling, receptor dynamics, autophagy, DNA repair and apoptotic decisions while also impacting T-cell differentiation and chemokine-mediated migration through phosphorylation of transcription factors and adaptor proteins (information section; rogers2020abelsonkinase’sintrinsically pages 1-4).
8. Other Comments  
   Numerous small-molecule inhibitors have been developed against ABL1 due to its prominent role in oncogenic transformation, particularly in the context of the BCR-ABL fusion protein observed in chronic myelogenous leukemia (CML). Imatinib mesylate, a pioneering ATP-competitive inhibitor, binds specifically to the inactive conformation of ABL1 and has significantly improved clinical outcomes for CML patients (roskoski2003sti571ananticancer pages 1-2, wong2004thebcrablstory pages 10-12). Second-generation inhibitors such as dasatinib, nilotinib, and ponatinib possess different binding profiles and are used in cases where resistance mutations (for example, the T315I mutation) have rendered imatinib less effective (hantschel2012structureregulationsignaling pages 7-8, roskoski2003sti571ananticancer pages 8-9).  
   ABL1 is implicated in various pathological signaling cascades beyond leukemia. Dysregulated ABL1 activity has been documented in neural development disorders, immune dysfunction, and may contribute to processes exploited by infectious agents to modulate host cell architecture (information section; wong2004thebcrablstory pages 47-49).  
   Notable mutations, particularly those generating the BCR-ABL fusion, alter the regulatory domains such that the autoinhibitory mechanisms are lost, resulting in constitutive kinase activity that underpins leukemogenesis. Additionally, mutations in the kinase domain may affect drug binding, leading to therapeutic resistance (roskoski2003sti571ananticancer pages 8-9, wong2004thebcrablstory pages 38-41).  
   The extensive study of ABL1 regulation and structure has helped establish paradigms for kinase inhibitor design, including the concept of allosteric inhibition targeting the myristate binding pocket. These efforts continue to yield new agents that overcome resistance and offer increased specificity (tse2015moleculardeterminantsunderlying pages 35-36).
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