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ABL Tyrosine Kinases: Evolution of Function, Regulation, and Specificity*

John Colicelli
Department of Biological Chemistry, Molecular Biology Institute and Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA. Phone 310-825-1251; fax 310-206-1929

John Colicelli: colicelli@mednet.ucla.edu

Abstract

ABL-family proteins comprise one of the best conserved branches of the tyrosine kinases. Each ABL protein contains an SH3-SH2-TK (Src homology 3–Src homology 2–tyrosine kinase) domain cassette, which confers autoregulated kinase activity and is common among nonreceptor tyrosine kinases. This cassette is coupled to an actin-binding and -bundling domain, which makes ABL proteins capable of connecting phosphoregulation with actin-filament reorganization. Two vertebrate paralogs, ABL1 and ABL2, have evolved to perform specialized functions. ABL1 includes nuclear localization signals and a DNA binding domain through which it mediates DNA damage-repair functions, whereas ABL2 has additional binding capacity for actin and for microtubules to enhance its cytoskeletal remodeling functions. Several types of posttranslational modifications control ABL catalytic activity, subcellular localization, and stability, with consequences for both cytoplasmic and nuclear ABL functions. Binding partners provide additional regulation of ABL catalytic activity, substrate specificity, and downstream signaling. Information on ABL regulatory mechanisms is being mined to provide new therapeutic strategies against hematopoietic malignancies caused by BCR-ABL1 and related leukemogenic proteins.

Introduction

ABL (1) genes were first encountered in the guise of a tumor gene in the Abelson murine lymphosarcoma virus (2). The product of the virally transduced oncogene, v-*abl*, showed tyrosine kinase activity (3,4) and was determined to be an altered form of cellular Abl1 (encoded by the c-*Abl* gene) (5). The human ortholog of Abl1 was later identified as part of a mutationally activated fusion oncoprotein, BCR-ABL1 (6), common in chronic myeloid leukemia (CML) patients. ABL2 [also known as Abl-related gene or Arg (7)] is a paralog of ABL1 identified by sequence similarity (8). Direct biochemical analyses, cell biology observations, animal experiments, and human leukemia studies have produced working models of ABL function in normal (9,10) and transformed cells (11).

Central to the biochemical and physiological functions of ABL proteins are their combination of a regulated SH3-SH2-TK (Src homology 3–Src homology 2–tyrosine kinase) domain cassette with cytoskeletal protein– and DNA-binding domains (Fig. 1), a combination that confers unique signaling capabilities. This review focuses on ABL protein evolution, function, and mechanisms of regulation.

The ABL Subfamily of Tyrosine Kinases

Evolution and domain structure

ABL genes are found in all metazoans, which suggests that their structure and function were fixed relatively early in tyrosine kinase evolution. Vertebrate genomes encode two closely related paralogs, ABL1 and ABL2, with conserved domain structure (Fig. 1) and intron-exon boundaries (www.ensembl.org), which suggests a gene duplication origin. Nonvertebrate metazoans (*Strongylocentrotus purpuratus*, *Caenorhabditis elegans*, and *Drosophila melanogaster*) have a single ABL gene, which shows strong conservation through the SH3-SH2-TK cassette and terminal actin-binding domain. The choanoflagellate *Monosiga brevicollis*, a unicellular protist and proximal progenitor of metazoans, encodes two nonreceptor tyrosine kinases that align throughout the ABL SH3-SH2-TK domain cassette but terminate soon thereafter (Fig. 1). This suggests an early origin for ABL kinases, with the addition of an extended carboxy terminus during the metazoan radiation.

The primary clade of human nonreceptor tyrosine kinases [see (12) for kinome dendrogram] has 22 members, all but three of which share an SH3-SH2-TK domain structure. The reiteration of this domain cassette implies strong selective pressure, which reflects multiple contributions to function and regulation (13–15). Alignments using the SH3-SH2-TK sequence from human and fly nonreceptor tyrosine kinases show that ABL1 and ABL2 are more closely related to each other, and to their fly ortholog, than any other nonreceptor tyrosine kinase is related to its closest paralog or ortholog (Fig. 2). Human ABL1 and ABL2 are more than 90% identical in this domain cassette (Fig. 3).

Downstream of the TK domain, vertebrate ABL proteins contain domains for binding cytoskeletal components (F-actin, G-actin, and microtubules) and DNA. Of these, only the carboxy-terminal F-actin–binding domain is identifiable in sea urchin (*S. purpuratus*) and fruit fly (*D. melanogaster*) Abl (Fig. 4). In addition, fruit fly Abl is overwhelmingly localized to the cytoplasm and plasma membrane (16–19), which suggests that it lacks the nuclear functions attributed to vertebrate Abl1. Considering proposed mechanisms of gene duplication and evolution [reviewed in (20)], it is tempting to speculate that the fixation of vertebrate Abl paralogs is attributable to the selective value of new functions, rather than to a simple partition of preexisting functions. During the “fate-determination phase” (20) following Abl gene duplication, nuclear-localization and DNA binding properties could have emerged in the nascent Abl1, whereas cytoskeletal remodeling capabilities were expanded and refined in Abl2. These changes might have been subsequently preserved by the complex demands of vertebrate development and differentiation, as well as the requirement for enhanced DNA damage repair capabilities in these longer-lived organisms.

Three PxxP (21) motif SH3-binding sites belonging to class 2 [αPxαPx(R or K), reviewed in (22)] are well conserved between ABL1 and ABL2 (Fig. 3). The first is conserved in sea urchin but not fruit fly, the third is apparent in fruit fly but not sea urchin, and the second is absent from both (Fig. 4). ABL1 proteins have an additional class 2 motif that is not found in ABL2 or in nonvertebrates (Fig. 4). Human ABL2 has a single class 1 motif [(R or K)xαPxαP] that is missing from all ABL orthologs except sea urchin Abl (Fig. 4). A PPxY motif implicated in WW domain binding (23) is present in the TK domain, and extended proline-rich sequences with potential for either SH3- or WW-domain interactions are found at variable positions near the carboxy termini of metazoan ABL proteins (Fig. 4). There does not appear to be a simple progressive development of these binding motifs, which suggests a complex evolutionary path.

Three K- and R-rich nuclear localization signal (NLS) motifs have been identified in ABL1 (24), consistent with its partial distribution in the nucleus. The equivalent positions in ABL2

have less K and R content (Fig. 3), consistent with its cytoplasmic localization. Alignments with sea urchin and fruit fly Abl proteins (Fig. 4) suggest that NLS function developed relatively late. An L-, V-, and I-rich nuclear export signal (NES), probably engaged by XPO1 (exportin 1) (25), is found in the ABL1 carboxy terminus and is likely responsible for the ability of ABL1 to shuttle between nucleus and cytoplasm (26). Sequence alignment (Fig. 4) suggests that this NES developed gradually and in concert with the nuclear functions of ABL1.

ABL gene expression

In mice, both *Abl* genes are expressed widely, but not uniformly [(27) and Biogps.gnf.org]. Relatively little is known, however, about the promoter elements and transcription factors that regulate the expression of *ABL* genes. *ABL1* mRNA translation is silenced by microRNA-203 (miR203) (28), and sequence analysis suggests additional posttranscriptional regulators for ABL1 (miR196) and ABL2 (miR26 and miR1297) (targetscan.org).

Each human *ABL* gene gives rise to two primary transcripts (a and b) using alternate exons. The first exons of *ABL1b* and *ABL2b* encode target sites for cotranslational myristoylation (glycine at position 2). The relative proportions and tissue distribution of each isoform have not been established.

Role in development

There is ample evidence for ABL functions during development. The single *Drosophila Abl* gene is essential for viability (29,30) and plays a key role in central nervous system development (29). Abl controls growth cone guidance and synaptogenesis, acting downstream of the Robo receptor (31,32) and antagonistically to tyrosine phosphatases (33,34). Abl is also required during dendritic morphogenesis (35). These developmental functions require reorganization of actin (34,35) and microtubule (36) structures and involve the Abl phosphorylation substrates Enabled (31,34,35,37), Abi (Abl interactor protein) (38), and Cables (32). Abl has a critical role in the developmental morphogenesis of epithelial tissues, including head involution and dorsal closure (39,40), ventral furrow formation (18), and wing construction (41). These epithelial cell functions reflect, at least in part, the contribution of Abl to actin dynamics (18,40). *C. elegans* Abl controls epithelial morphogenesis (42) but, in contrast to *Drosophila*, a null mutation in the *C. elegans Abl* gene confers only conditional phenotypes. These include sensitivity of germ cells to various types of stress (43,44), rescue of apoptotic cell engulfment defects (45), and altered *Shigella flexneri* pathogenesis (46).

Both vertebrate Abl1 and Abl2 are required for normal development. Mice with a disrupted *Abl1* gene show defective hematopoiesis and low viability (47,48), osteoporosis (49), decreased systolic blood pressure (50), and cardiac hyperplasia (51). Abl1 deficits also impair the development and responsiveness of B cells (52,53) and T cells (54). Ablation of the *Abl2* gene has distinct effects, leading only to relatively subtle neuronal defects (27,55). An $Abl1^{-/-}$ $Abl2^{-/-}$ double mutation, however, causes embryonic lethality with abnormalities in neuroepithelial cells and defects in neurulation (27). Hence, Abl paralogs make unique contributions to vertebrate development while retaining substantial functional overlap.

Biochemistry and Regulation of ABL Tyrosine Kinases

Tyrosine kinase activity

An essential property of ABL proteins is their tyrosine kinase activity. Tyrosine phosphorylation can modify substrate protein activity, localization, and partnering capacity. Consequently, knowledge of ABL catalytic regulation and substrate specificity is integral to understanding ABL function.

Structural data and biochemical studies have revealed multiple autoinhibitory mechanisms that constrain the enzymatic activity of the ABL-family kinases. A myristoyl group attached to the amino terminal glycine of ABL1 and ABL2 "b" isoform proteins can nestle into a surface pocket in the kinase domain, contributing to an autoinhibitory fold (56). A short amino-terminal "Cap" sequence stabilizes the inactive conformation of ABL1 through additional surface interactions (57). Downstream of the "Cap" peptide are SH3 and SH2 domains that cradle the kinase domain, imposing a "locked" inactive state (58,59). Tyrosine kinase activity of ABL1 is increased by disrupting these autoinhibitory interactions, as demonstrated with the Cap domain mutation in which lysine at position 7 is replaced by alanine (K7A) (56), the SH3 domain mutation W118A (60), the SH2 domain mutations E157A and Y158D (56) and the SH2-TK linker-region double mutation P242E, P249E (also known as "PP") (60). These key residues are identical (W118, E157, Y158, P242, and P249) or conserved (K7) in the ABL2 protein (Fig. 3).

Phosphatidylinositol 4,5-bisphosphate (PIP_2), a phospholipase C–generated second messenger, inhibits ABL1 and ABL2 tyrosine kinase activity (61). PIP_2 binds the ABL1 SH2 domain through residues normally required for phosphotyrosine binding (62), but the mechanism of inhibition has not been determined.

Phosphorylations in the amino-terminal half of ABL proteins, including phosphorylation within the kinase domain, can substantially alter catalytic activity (see below). These amino-terminal phosphorylation sites are conserved between ABL1 and ABL2, and phosphorylation at some sites can affect the activity of oncogenic ABL fusion proteins such as BCR-ABL1.

Covalent modification of ABL proteins

Tyrosine phosphorylation of members of the ABL family of kinases occurs in trans by ABL1 and ABL2 (63,64), a reaction often referred to as "autophosphorylation." ABL-family kinases are also phosphorylated by members of the SRC family of tyrosine kinases (63–65) and by PDGFR (61). Tyrosine phosphorylation of ABL1-Y^{245} (equivalent to ABL2-Y^{272}), which resides in the linker segment between the SH2 and kinase domains, and ABL1-Y^{412} (ABL2-Y^{439}), which lies in the activation loop of the kinase domain, correlate with increased kinase activity (63,64). Phosphorylation of ABL1-Y^{89} (conserved in ABL2) by members of the SRC family of kinases (66,67) disrupts SH3 domain–based autoinhibitory interactions and intermolecular associations, such as that with ABI1, and also enhances kinase activity (66). Phosphorylation of ABL2-Y^{261} (conserved in ABL1) promotes ABL function through protein stabilization (68). Tyrosine phosphorylation at these same sites within the oncogenic fusion protein BCR-ABL1 correlates with its ability to transform cells (67), which demonstrates that "constitutively active" ABL mutants still respond to positive regulation. Phosphorylation of ABL1-Y^{272} in the kinase domain P loop inhibits ABL1 kinase activity (69) and BCR-ABL1 transforming activity (70), whereas phosphorylation of the nearby ABL1-Y^{276} enhances transformation and appears to promote kinase activity (70). Phosphosite entries for ABL1 and ABL2 include other phosphorylated tyrosines (Fig. 3). Possible contributions of these modifications to ABL function are not clear, although ABL1-

Y^{158} and ABL1-Y^{331} contribute to intramolecular folding (56,71), which may be altered by phosphorylation,

Several ABL phosphotyrosines are predicted SH2 domain binding sites (lilab.uwo.ca/SMALI.htm). Phosphorylated ABL1-Y^{89} (ABL2-Y^{116}) and ABL1-Y^{276} (ABL2-Y^{303}) match well with the preferred pYDxV binding site for NCK-family SH2 domains (72) and may contribute to the interaction of ABL1 with NCK1 (73). ABL1-pY^{134} (ABL2-pY^{161}) and ABL1-pY^{147} (ABL2-pY^{174}) are predicted to associate with the RASA1 [Ras GTPase–activating protein 1] SH2 domain, consistent with RASA1 binding to BCR-ABL1 (74). ABL1-pY^{251} is predicted to bind the BLNK (B cell linker protein) SH2 domain, whereas ABL1-pY^{276} (ABL2-pY^{303}) is predicted to bind the HCK SH2 domain, but these interactions have not been experimentally validated.

ABL1 is phosphorylated on T^{754} (75), which resides at the position normally occupied by phosphoserine in type 1 consensus 14-3-3 binding sites: RSxpSxP (76). Phosphorylation of T^{754} leads to 14-3-3 binding, which favors the cytoplasmic localization of ABL1 (75). 14-3-3 proteins exist primarily as dimers, which allows them to cross-link multiple sites within a protein or to bridge two target proteins (76), but it is not yet know whether 14-3-3 dimerization contributes to ABL regulation. Phosphorylation of T^{754} can be carried out by the kinases CLK1, CLK4, MST1, MST2, and TTK in vitro (77) but has not been well studied in vivo. Although ABL2 has a conserved threonine at the same position as ABL1-T^{754} (Fig. 3), upstream elements of the 14-3-3–binding consensus sequence are absent, and there is no experimental evidence that ABL2 binds 14-3-3 proteins.

Phosphorylation of ABL1 residues S^{637} and S^{638} by PAK2 (p21-activated kinase 2) alters the surface charge environment immediately downstream of the third PxxP motif (PTPPKRSS^{638}) and reduces binding to the SH3 domain protein and ABL inhibitor ABI1 (78). This may explain in part the stimulatory effect of PAK2 on ABL kinase activity and the negative feedback resulting from ABL-mediated PAK2 phosphorylation (79). These residues are conserved in ABL2 (Fig. 3), which suggests a similar type of regulation. For reasons less well understood, phosphorylation of these same residues increases ABL1 binding to CRK (78). Additional phosphorylations on ABL1, including that on S^{588}, have been attributed to a CDC2-associated kinase and are coupled to cell division (80).

ABL1 is acetylated at K^{730} in the second NLS (81). This modification, performed by EP300 (E1A binding protein p300), promotes the cytoplasmic translocation of ABL1.

An amino-terminal myristoyl modification, likely carried out by a myristoyl-CoA:protein *N*-myristoyltransferase (NMT1 and NMT2 in humans), stabilizes the inactive ABL kinase conformational fold through an intramolecular interaction. Myristoylation of other proteins, including members of the SRC family of tyrosine kinases, has more typically been associated with lipid-membrane interactions that regulate protein localization (82). When the ABL1 myristoyl group is released from the kinase domain by treatment with GNF-2, an allosteric inhibitor compound that binds to the same pocket (83), ABL1 translocates to the endoplasmic reticulum (84). This result raises the possibility that physiological signals may also expose the myristoyl group on ABL proteins and trigger its subcellular relocalization.

Both ABL proteins are subject to polyubiquitination, which leads to their degradation (68,85). The ubiquitin ligase CBL, itself an ABL substrate (86,87), has been directly implicated in this modification (83). Some evidence suggests that ubiquitination of ABL2 may itself be regulated by phosphorylation of Y^{261} in response to oxidative stress (68). ABL1 is also targeted for caspase-mediated cleavage during some types of apoptosis (88).

Substrate specificity

Defining target site specificity is critical for understanding normal and leukemogenic ABL signal transduction pathways. ABL tyrosine phosphorylation can directly influence catalytic activity, SH2 domain binding, and subcellular localization of substrate proteins. Substantial progress has been made in defining ABL target phosphorylation sites, but the ability to accurately predict ABL substrates has remained elusive.

In vitro kinase reactions with peptide libraries suggest a preferred ABL target site: (L- or I- or V-) pY-x-x-P (89,90). Analysis of 119 separately validated ABL1, ABL2, and BCR-ABL1 substrates (Table 2) confirmed a strong preference for proline at position +3 and for aliphatic amino acids (L, I, or V) at position −1, as well as revealing an enrichment for acidic residues (D or E) at positions −4, −3, and +1 (Fig. 5). Global phosphopeptide analysis of cells expressing BCR-ABL1 is generally consistent with this result (91). These target site preferences presumably reflect structural requirements of the ABL catalytic site, a presumption confirmed, at least in part, by analyses of ABL active site mutations (92).

There are caveats to identification of phosphorylation targets on the basis of consensus-derived sequences. First, peptide substrates may not accurately mimic protein substrates. Second, protein substrates identified in cells may be indirect targets, in other words, they may be substrates for kinases activated downstream of ABL1, ABL2, or BCR-ABL1. Only a few direct ABL targets have been experimentally determined using mutations that render the kinase dependent on an ATP analog (93) (94).

The SH2 domain contributes to ABL catalytic activity (71) and target site specificity (15). When the ABL SH2 domain is replaced with the SH2 domain from another protein, there is a shift in substrate profile (95). Moreover, SH2 binding preference correlates with target site preference, and juxtaposition of an appropriate SH2 ligand site enhances phosphorylation of an ABL target site. This result suggests a processive phosphorylation mechanism, that is to say, successive phosphorylation of different tyrosines on the same substrate (96,97). Processivity would also explain why ABL-mediated phosphorylation shows accelerated, autocatalytic kinetics when substrate peptides are surface bound at high density (98). In this model, a newly phosphorylated tyrosine moves from the ABL catalytic site to the SH2 pocket, positioning another tyrosine residue for efficient phosphorylation.

Recent work in the field of histone modification has uncovered proteins such as Clr4 that contain both a catalytic site (histone modification “writer”) and a separate binding site (histone modification “reader”) that coordinate processive histone modification (99,100). By analogy, the combination of a tyrosine kinase domain (pY “writer”) with an SH2 domain (pY “reader”) in ABL and other nonreceptor tyrosine kinases may have evolved in part to increase phosphorylation efficiency of multitarget proteins or complexes. It may also facilitate the phosphorylation of “poor” target sites by docking them into the catalytic pocket. A corollary of the processivity model is that consensus ABL kinase targets based on a database of known phosphorylation sites, may over-represent amino acids that contribute little to substrate affinity (K_m) but facilitate SH2 binding.

Processive phosphorylation is probably integral to ABL function. Multiple target sites exist in many ABL substrates, including BCAR1 (96), CAT (101), CBL (86), DOK1 (102), GAB2 (103), CTTN (104), MDM2 (105), PIK3AP1 (106), PLCG1 (107), PTPN11 (108), PXN (109), POLR2A (RNA polymerase) (110), and RAD51 (111). Indeed, the ABL SH2 domain is essential for efficient phosphorylation of the 52 target sites in the repetitive carboxy-terminal domain of POLR2A (112). In addition, the list of known ABL substrates has many adaptor proteins (including CRK, CRKL, DOK1, GRB2, and NCK1) that,

subsequent to phosphorylation, might deliver their associated proteins to the ABL catalytic site after docking at the ABL-SH2 domain.

This simple processive phosphorylation model implies that the ABL catalytic site and SH2 pocket have coevolved to recognize the same sequences (in other words, the best kinase target sequences, once phosphorylated, would also be the best SH2-binding targets). However, some targets within a multitarget substrate appear to require the prior phosphorylation of another target site. RAD51, an established ABL substrate (113,114) has two ABL target sites: AY^{54}APK (poor consensus) and **I**Y^{315}**D**S**P** (good consensus). In transfected cells, a RAD51^{Y54F} mutant was efficiently phosphorylated on Y^{315}, but a RAD51^{Y315F} mutant had no detectable Y^{54} phosphorylation (115). This suggests that Y^{315} phosphorylation must occur first, followed by reorientation of the RAD51 substrate so that pY^{315} is bound to the ABL-SH2 domain and Y^{54} is positioned at the ABL catalytic site.

The processive phosphorylation data and RAD51 results suggest a “hierarchical processivity” model in which the substrate target site most compatible with ABL kinase domain preferences is phosphorylated with greatest efficiency. If this site is also compatible with the ABL SH2 domain specificity, it will then reposition and dock in the SH2 pocket. This mechanism could enable ABL kinases to phosphorylate otherwise poor targets on the same substrate if they are properly positioned (Fig. 6A). By extension, relatively poor substrate proteins might be recruited to ABL through a complex with strong substrates that can also dock with the SH2 pocket (Fig. 6B). A corollary to the hierarchical processivity model is that consensus ABL phosphorylation sites determined by statistical analysis may actually represent an average of “primary” sites, with high specificity for the catalytic pocket, and “secondary” sites that require the prior SH2 docking of an associated primary site to guide them into the catalytic site.

Target-site phosphorylation of some ABL substrates requires an escort for delivery to the ABL catalytic site, independent of processive phosphorylation. Enah (also known as Mena) phosphorylation at the target site AY^{296}ASA is enhanced by Abi1, which binds to both Enah and Abl1 (116). Similarly, CABLES enhances ABL-mediated tyrosine phosphorylation of CDK5 (117) and CTNNB1 (β-catenin) (32) by directly linking kinase and substrate. This use of adaptor proteins to recruit targets further extends the reach of ABL kinases beyond the restrictive preferences of its catalytic site and SH2 domain.

In summary, ABL substrate specificity is driven by both target sequence and domain-guided protein-protein interactions. The role of other determinants is suggested by quantitative shifts in substrate phosphorylation patterns among point mutation variants of BCR-ABL1 (70).

Regulation through tyrosine phosphatases

Given the importance of tyrosine phosphorylation in ABL activation and downstream signaling, the regulatory role of protein tyrosine phosphatases (PTPs) is perhaps not surprising. BCR-ABL1 transforming properties are blocked by PTPN1 (118) and by a variant form of PTPRO (119), which suggests that some PTPs function as negative regulators by reversing ABL-mediated tyrosine phosphorylation. In response to ionizing radiation treatment, ABL1 phosphorylates PTPN6 (also known as SHP-1), which binds to the SH3 domain of ABL1, on Tyr^{536} and Tyr^{564} (120). PTPN6 is also associated with BCR-ABL1, and PTPN6 overexpression diminishes some transformation-associated phenotypes of the CML-derived cell line K562 (121). PTPN11 (SHP-2) is an ABL1 substrate that facilitates growth factor–induced mitogenic responses (122). However, delivery of the PTPN11 phosphatase domain to BCR-ABL1 through an ABL-binding domain causes a transformation block (123), which indicates that this phosphatase can also inhibit ABL-

mediated tyrosine phosphorylation signaling. PTPN12 (PTP-PEST) and PTPN18 (PTP-HSCF) are recruited by the PSTPIP1 adaptor to dephosphorylated ABL and suppress its function (124).

Interaction Partners That Regulate ABL Activity and Function

ABL self-association

Any discussion of ABL protein partners must consider self-association. Wild-type ABL proteins in cultured cells can exist as oligomers, the formation of which requires their kinase activity and an intact amino-terminal domain (125). Chemically induced dimerization of ABL1 increases both its tyrosine kinase activity and transformation capacity (126), and homophilic interaction domains encoded by translocation partners markedly enhance the catalytic activity and leukemogenic potential of ABL fusion proteins such as BCR-ABL1 and ETV6-ABL1 (discussed below). These data suggest that close proximity of partners within a dimer or oligomer enhances transphosphorylation that directly activates ABL kinases. ABL1-ABL2 heterodimers can form in response to oxidative stress and mediate apoptosis (127), which suggests functional cooperativity between ABL-family members.

Cytoskeleton components

The capacity to directly bind cytoskeletal elements is a defining characteristic of ABL proteins (Fig. 1). A conserved calponin homology (CH)–type F-actin–binding domain is located at the C terminus of ABL proteins, and ABL1 also has G-actin binding properties (128). An (I or L)WEQ (talinlike) domain, found in ABL2 only, provides additional F-actin binding properties (129). These domains mediate the formation of F-actin bundles (128,129), which are critical for membrane protrusions. Binding to filamentous actin inhibits ABL kinase activity (130), which suggests regulatory feedback. The microtubule-binding domain of ABL2 (131) provides an additional capability for remodeling the cytoskeleton through cross-association with both thick and thin filaments.

A common signal transduction theme among ABL partners

Numerous ABL1 and ABL2 partners have been identified (Table 1). Many of these are ABL substrates, but their association with ABL is stable enough to be detected. The ABL SH2 domain may engage phosphotyrosines on a partner or, conversely, a partner SH2 domain may bind a phosphotyrosine on ABL. Similarly, the ABL SH3 domain engages PxxP motifs on partner proteins, whereas some partner SH3 domains bind to ABL PxxP motifs. Other binding motifs are also employed, and in some cases the mode of interaction is unknown.

The ABL interactor proteins ABI1 and ABI2 were initially identified as proteins that bind to PxxP motifs in the carboxy half of ABL1 through their own SH3 domain, while at the same time interacting with the SH3 domain of ABL1 through their own PxxP motifs (132,133). ABI proteins influence ABL function, although the mechanism for this is not well established. ABI1 can inhibit the transforming activity of v-*Abl* (133), and ABI1-derived phosphopeptides can inhibit ABL1 activity through an apparent allosteric effect (134). However, ABI1 also enhances the ABL-mediated phosphorylation of several substrates (116,135,136) and may facilitate the oligomerization of ABL proteins (125), normally an activating event. ABI1 and ABI2 participate in a WAVE protein complex that promotes actin remodeling at the leading edge of motile cells (137). A *Drosophila* ortholog, dAbi, plays an opposing role to Abl in axonogenesis and synaptogenesis (38), but appears to increase Abl kinase activity (138). A third mammalian ABI paralog, ABI3, is not well characterized.

The RAS effector protein RIN1 binds directly to ABL1 and ABL2, causing an increase in tyrosine kinase catalytic efficiency (139). The proposed activation mechanism invokes ABL-SH3–domain attachment to a PxxP motif in RIN1. Subsequent ABL kinase domain–mediated phosphorylation of RIN1-Y^{36} leads to ABL-SH2–domain binding at that site. By disengaging ABL autoinhibitory domains, RIN1 is thought to stabilize a catalytically active ABL conformation. Activation by RIN1 does not require prior phosphorylation of ABL by SRC-family kinases (139), which suggests that this is an independent activation pathway.

Several interacting proteins appear to function as negative regulators of ABL's catalytic activity. PRDX1 (PAG) binds to the ABL1-SH3 domain, inhibits ABL's kinase activity, and overcomes the cytostatic effects of overexpressed ABL1 (140). PSTPIP1 binds to the ABL1-P^{589}xxP and P^{779}xxP motifs and recruits PEST-type PTPs that inhibit ABL's kinase activity (124). ABL inhibition by TUSC2 (FUS1) involves a short (20 amino acid) peptide through an uncharacterized mechanism (141).

Many of the documented ABL-interacting proteins are adaptors that mediate signal transduction and cytoskeleton dynamics. The CRK and CRKL adaptor proteins bind to ABL1 (142–144), primarily through the interaction of two SH3 domains on CRK (and on CRKL) with the P^{545}xxP and P^{589}xxP motifs of ABL1 (145), and promote tyrosine kinase activity (146). These interactions serve to dock CRK proteins for subsequent tyrosine phosphorylation (145). Several other multi-SH3 domain adaptor proteins also form stable interactions with ABL1. These include NCK1 (145), SORBS1 (ponsin) (145), SORBS2 (ArgBP1) (145,147), and SORBS3 (vinexin) (148), all of which engage the P^{631}xxP motif of ABL1 (145). All three PxxP motifs mentioned above are well-conserved in ABL2 (Fig. 3), which suggests that it makes similar contacts with CRK, NCK, and SORBS proteins. Other SH3 domain–bearing adaptors implicated as ABL partners are the DOK- family (149,150), GRB- family (151), and SHC- family (152) proteins. Many of these are mediators of cytoskeleton remodeling.

Cortactin (CTTN), another SH3 domain protein involved in actin dynamics (153), binds to the P^{573}xxP of ABL2 (154). This sequence includes an unusual upstream iteration forming a PxαPxαPxαPxK motif, and mutation of all four prolines is needed to block cortactin binding. The additional upstream prolines are not observed in fish or frog ABL2, nor are they present in any ABL1 sequence (Fig. 4), which suggests that this extended motif evolved relatively late to mediate specialized functions. The fourth PxxP motif (P^{779}xxP) in ABL1 is not conserved in ABL2. Rather, ABL2 encodes a PxxP motif of type 2 (KxαP^{949}xαP) for which no specific binding partners have been identified.

The ABL-SH3 domain has a binding propensity distinct from the type 1 and type 2 categories discussed above, showing a preference for PPx(F,Y,W)xPPP(L,I,V,G,A)P peptides (155). Additional peptide-binding data and modeling were used to develop an ABL-SH3–binding site–motif matrix. WAS-family proteins (WASF1-4), actin reorganization proteins that activate ARP2/3 complexes, were among the strongest ABL-SH3–domain binders predicted with this matrix (156). These results are consistent with experimental evidence that ABL1 binds and signals through WASF proteins (157). Other ABL-SH3 domain–interacting proteins are listed in Table 2.

Both ABL1 and ABL2 have proline-rich sequences, distinct from their SH3-ligand motifs, that conform to established WW domain–ligand motifs of Group 1 (PPxY) and Group 2/3 (PPPPP) (158). The WW-domain protein APBB1 (Fe65) binds to ABL1 (159,160). From the structure of the APBB1 WW domain (161), it likely binds to PPPPP^{922}. The physiological relevance of this interaction, and potential interactions with APBB2 and APBB3, has not been fully explored.

Cellular Functions of ABL Proteins

Reviews focusing on ABL protein contributions to actin remodeling (162), cell adhesion and motility (9), DNA damage response (163,164), and microbial pathogen response (165) provide excellent and comprehensive coverage of these areas. Provided below is a brief overview of ABL functions, with an emphasis on ABL partners and substrates.

Actin binding, bundling, and remodeling

ABL-family tyrosine kinases act in the cytoplasm to coordinate actin remodeling in response to appropriate stimuli. This function is mediated by tyrosine phosphorylation of actin cytoskeleton-remodeling proteins and by the ABL carboxy-terminal filamentous actin (F-actin)–binding and –bundling domain (166). ABL-mediated actin remodeling has been studied primarily in the context of cell adhesion and motility (see below), axon guidance (34), and the formation of microspikes (167) and synapses (168–170).

The list of known ABL substrates (Table 1) and binders (Table 2) shows that cytoskeleton-remodeling proteins are highly represented. These include F-actin–binding proteins involved in branch formation (WASF and WASL); depolymerization and severing (CFL1); membrane anchoring (ANXA1 and ANXA2); movement (Myosin IIB); and signaling (DBN1, DBNL, CTTN, RAPH1, ENAH, VASP, and EVL). ABL also promotes the association of proteins within this group, as in the case of RAPH1 and ENAH during dorsal ruffling and axonal morphogenesis (171). Microtubule subunits (TUBA and TUBB) are ABL-kinase substrates, although the target sites and effects on polymerization are unknown. The microtubule-binding proteins MAPT (tau) and PXN (paxillin) are also ABL substrates.

Cell motility and adhesion

Mammalian cells mutated in both ABL genes (*Abl1*$^{-/-}$*Abl2*$^{-/-}$), or wild-type cells treated with an inhibitor of ABL's catalytic activity, show increased motility with altered adhesion and spreading (172–174). Conversely, increased ABL activity leads to reduced motility (172,173). Moreover, ABL proteins localize to sites of actin remodeling (102,131,154,175,176).

Among direct ABL partners and substrates, the CRK-family (CRK and CRKL) and CAS-family (BCAR1, NEDD9, and EFS) proteins are key regulators of cell attachment and motility (177). ABL-mediated phosphorylation of CRK disrupts its binding to CAS and leads to reduced cell migration (178). The CAS-associated proteins CASS4 and CD2AP are also ABL substrates. Of note is the phosphorylation of multiple YxxP sites on BCAR1, NEDD9, and CASS4 [12, 11, and 8 sites, respectively, in Phosphosite (www.phosphosite.org)].

Interaction of ABL1 with the integrin β_2–binding and –activating protein TLN2 (179) provides a direct means for ABL proteins to influence attachment to the extracellular matrix. The role of ABL1 in cell migration involves collaboration with SRC-family kinases (SFKs) (180), which likely involves the phosphoregulation of ABL proteins by SFKs (see *Covalent modification of ABL proteins*). In a *Drosophila* epithelial cell invasion model, Abl increased SFK activity through a positive-feedback loop (41), which demonstrates the integral relationship of ABL- and SRC-family kinases.

Receptor endocytosis and autophagy

Actin remodeling has been directly implicated in receptor endocytosis (181–183), and ABL proteins likely contribute to this process by coordinating cytoskeleton remodeling with phosphoregulation of receptors and endocytic factors. Multiple receptor tyrosine kinases

(EGFR, ERBB2, NTRK1, PDGFRB, ROS, MUSK, and EPHB2) interact with, and are in most cases phosphorylated by, ABL proteins (Tables 1 and 2). ABL interactions promote endocytosis of EGFR (184), facilitate the formation of neuromuscular synapses through MUSK (168), and inhibit PDGFRB-mediated chemotaxis (185). ABL-family tyrosine kinases also modulate the endocytosis of activated B cell receptor complexes (186).

ABL-family tyrosine kinases phosphorylate CAV1 [caveolin, a plasma membrane scaffolding protein that regulates receptor signaling (187)], as well as RIN1 [a RAS effector and RAB5 GEF in endocytosis (188,189)] and ITSN2 [CDC42 GEF required for caveolae endocytosis (190)]. In addition, ABL proteins functionally engage the CBL family of ubiquitin ligases that drive receptor down-regulation and actin remodeling (191), as well as the CBL-associated protein SORBS1. ABL phosphorylation of CBL leads to increased EGFR stability (184). The membrane invaginations associated with autophagy and the engulfment of apoptotic cells also depend on ABL proteins (45,192).

The role of ABL1 in DNA damage response and apoptosis

Three NLS motifs (24) and a NES motif (26), together with a regulated 14-3-3 interaction (75), facilitate ABL1 translocation between the cytoplasm and nucleus (193). Its DNA binding domain (194) allows ABL1 to associate directly with DNA in response to damage signals. Many ABL-binding partners and substrates are known mediators of DNA repair (Tables 1 and 2). These include ATM, ATR, DDB1, DDB2, ERCC3, ERCC6, RAD9A, RAD51, RAD52, and WRN. In addition, ABL proteins are found in complexes with MLH1 (195) and other functionally relevant DNA repair proteins. The DNA binding domain and NLS and NES motifs of ABL1 are weak or unrecognizable in fruit fly Abl, sea urchin Abl, and mammalian ABL2 proteins, which suggests that DNA damage-response functions evolved after ABL gene duplication.

ABL1 overexpression causes cell cycle arrest (196) and apoptosis (197) in cultured cells, which suggests that ABL facilitates a repair checkpoint following moderate DNA damage but cell death after severe damage. Several ABL targets (MDM2, MDM4, TP53, and TP73) are primary regulators for this type of damage-induced apoptosis.

Leukemogenic ABL Proteins

Several excellent reviews of ABL oncogenes in hematopoietic malignancies are available (11,198). This section provides a brief introduction to the topic and then focuses on the current understanding of ABL function in cell transformation and disease.

BCR-ABL1 and related fusion proteins

ABL genes are activated by chromosome translocations in various hematopoietic malignancies. Chronic myeloid leukemia (CML) is characterized in almost all cases by a t(9;22)(q34;q11) translocation (199) that fuses the *BCR* (breakpoint cluster region) and *ABL1* genes (6). Chromatin structural elements (200) and microhomologies and interspersed repeat sequences (201) may contribute to these translocations. The BCR-ABL1 fusion gene product (p210) has constitutive tyrosine kinase activity and is leukemogenic in model systems (11).

Three to 5% of childhood (202) and 20 to 30% of adult acute lymphoblastic leukemia (ALL) cases have a similar translocation (203). The resulting BCR-ABL1 (p190) fusion protein includes less BCR sequence than its CML counterpart. Additional *BCR-ABL1* fusion variants have been reported in some leukemias (204,205). Other leukemogenic ABL1 fusions include *NUP214-ABL1* (191) *EML1-ABL1* (206), and *ETV6-ABL1* (207). In

addition, *ABL2* is activated by a translocation in some acute myeloid leukemias (AMLs) (208).

Although ABL fusions vary in the amount and identity of upstream partners, and even in which ABL paralog is involved, the ABL breakpoint position consistently leads to removal of the amino-terminal Cap peptide but retention of the SH3 domain (Fig. 7). What remains unclear is why the autoinhibitory SH3 domain is preserved, given that deletion of this domain enhances the catalytic activity of human ABL1. Indeed, the murine *Gag-Abl1* (v-*Abl*) fusion disrupts the SH3 domain (Fig. 7) and is a potent oncogene (209). The presence of autoinhibitory SH3 sequences in human ABL fusion genes might be explained by a requirement for signaling through SH3-interaction partners (Table 2) during leukemia initiation or progression. Notably, murine v-*Abl*, with a disrupted SH3 domain, produces a phenotypically different disease from that caused by BCR-ABL1 in model systems (210).

There is a conspicuous absence of ABL-activating mutations in solid tumors, even though ABL fusion genes can transform human fibroblasts in culture (211) and enhanced ABL signaling may contribute to epithelial cell malignancies (212), as well as to the invasive growth of breast cancer cells (213). Furthermore, no other member of the SH3-SH2-TK type nonreceptor tyrosine kinase family is mutationally activated in spontaneous human cancers, even though SRC was first identified as the rodent oncogene in Rous sarcoma virus (214) and cultured human cells are transformed by mutationally activated SRC-family kinases (215) and TEK-family kinases (216). Overexpressed and overactive SRC-family kinases have been detected in many types of tumors [reviewed in (217)], however, and BCR-ABL1 may work in part through SRC activation (218–220).

Kinase activity of ABL fusion proteins

Elimination of the ABL myristoylation site and the amino-terminal Cap domain, both of which participate in stabilizing the inactive conformation of the kinase domain, partly explains the increased and constitutive kinase activity of oncogenic ABL fusion proteins. Homophilic interaction domains in BCR and ETV6 mediate fusion protein oligomerization (221,222), which promotes transphosphorylation and further increases ABL's catalytic activity. Reduced nuclear localization (223) may contribute further to transforming activity by ABL1 fusions by interfering with their DNA damage-response functions.

Consistent retention of the SH3 domain implies that the kinase activity of ABL fusion proteins, although constitutive, can be enhanced through derepression. Indeed, RIN1, which activates ABL1 and ABL2 by binding the SH3 and SH2 domains to relieve autoinhibition, increases the transforming ability of BCR in hematopoietic cell lines and primary bone marrow cells (224) and enhances the leukemogenic properties of BCR-ABL1 in a murine model system (224). Like ABL1 and ABL2, BCR-ABL1 proteins are subject to regulation by phosphatases, including PTPN1 (118) and PTPN6 (225). These observations show that constitutively active ABL oncoproteins remain responsive to positive and negative regulation.

ABL inhibitors in leukemia therapy

Transformation by ABL fusion proteins is inextricably tied to their tyrosine kinase activity, which suggests that targeted kinase inhibitors should be therapeutically useful. Imatinib mesylate (also known as STI571 or Gleevec) is an ATP-competitive inhibitor that stabilizes the inactive ABL kinase–domain conformation (226). Imatinib is an effective first-line treatment for CML (227), which validates the signal pathway blockade approach to cancer treatment, and other BCR-ABL1 inhibitors have been added to the CML pharmacopeia (228).

Some people with CML do not respond to imatinib (229), and even individuals with responsive disease, who must remain on the drug indefinitely, can relapse. Drug resistance is typically a consequence of mutations in the BCR-ABL1 kinase domain (230,231) but may also result from mutations in the SH3 and SH2 domains (232,233) or BCR-ABL1 amplification (230). BCR-ABL1–positive ALL is refractory to imatinib alone and shows high rates of resistance and relapse to chemotherapy combined with imatinib (234). Dasatinib, which is among the more effective second-generation ABL active-site inhibitors, also inhibits SRC-family kinases (235), and its efficacy in CML likely reflects the cooperation of SFKs with BCR-ABL1 in eliciting cell transformation. When different ABL inhibitors are used to treat disease sequentially, however, resistance can return through the accumulation of multiple kinase-domain mutations (236), which suggests that a combination approach might be more efficacious. One drug-resistant mutation in the kinase gatekeeper residue (237), BCR-ABL1^{T315I}, is refractory to all established inhibitors but may respond to new drugs (238).

The discovery of allosteric (noncompetitive with ATP) ABL inhibitors (83) represents a promising new direction for the treatment of BCR-ABL1–positive leukemias. These compounds (GNF-2 and GNF-5) target the ABL1 myristate-binding pocket (unoccupied in BCR-ABL1) to stabilize an inactive kinase-domain conformation (239). Combining GNF-5 with catalytic site inhibitors suppresses the emergence of resistance mutations. GNF compounds have limited potency against BCR-ABL1^{T315I} but worked additively with an ATP-competitive inhibitor to block this mutation in a bone marrow–transplantation leukemia model (239). Long-term effective therapy would likely benefit from pairing inhibitors of ABL's kinase activity with drugs that target ABL allosteric sites (239,240) or drugs that target direct activators of the ABL-family kinases (139). Other combination approaches to therapy of BCR-ABL1–driven leukemias include the pairing of inhibitors of ABL's catalytic activity with drugs that reduce BCR-ABL1 expression (241) or stability (242), or that disable collaborative pathways (243–246). Targeting functions required for leukemia cell survival might also provide a useful approach [reviewed in (247)].

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Glossary

GLOSS ABL, family proteins couple a highly regulated tyrosine kinase domain with an actin-binding and -bundling domain to carry out a set of unique and essential functions. The *ABL* genes are among the earliest identifiable genes encoding tyrosine kinases, and they show remarkable sequence conservation. Gene duplication produced two vertebrate ABL paralogs with specialized properties. ABL1 evolved nuclear localization signals and a DNA binding domain to mediate damage repair functions. ABL2 developed additional binding domains for actin and microtubules, extending its cytoskeletal remodeling functions. This review surveys the recent literature and available databases with a focus on ABL evolution and the mechanisms regulating ABL's catalytic activity and substrate specificity. A better understanding of these properties could facilitate the design of new treatments for malignancies driven by ABL fusion proteins

References and Notes

1. Upper case is used for human genes and proteins (ABL1 and ABL2) as well as for discussion of gene and protein families (ABL). First-letter-only upper case (Abl1 and Abl2) is used when referring to genes and proteins from all other species in this review. Human Genome Organization nomenclature (www.genenames.org) is used. More common gene names are provided in the text, with additional aliases given in Table 1 and Table 2.
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21. Single-letter abbreviations for the amino acid residues used in this review are as follows: A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine; x, any amino acid; α, hydrophobic amino acid.
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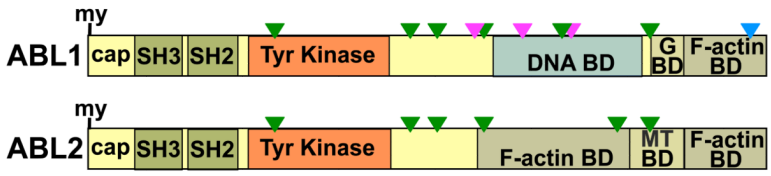


Fig. 1.

ABL domain structure and motif conservation. Linear depiction of human ABL1 and ABL2 (long, b isoforms), *D. melanogaster* Abl, and *M. brevicollis* Abl1 and Abl2. my, myristoylation site (*site present but modification not verified); G BD, G-actin–binding domain; and MT BD, microtubule-binding domain. Blue triangle, NES; magenta triangle, NLS; and green triangle, proline-rich motif with capacity to bind SH3 or WW domains.

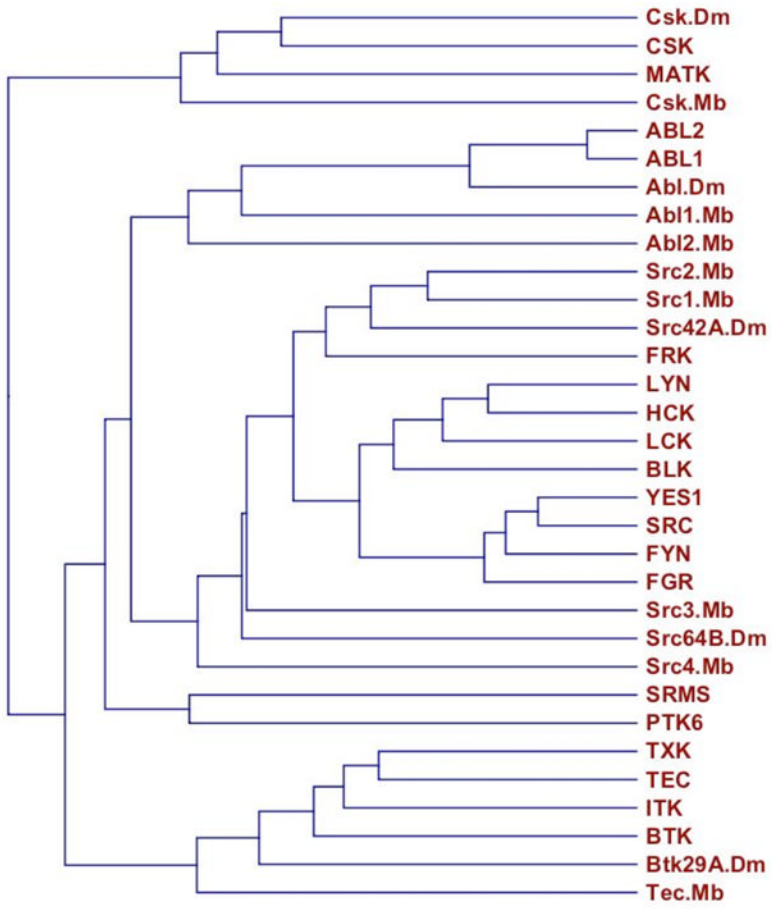


Fig. 2.

SH3-SH2-TK–family proteins. A dendrogram of the SH3-SH2-TK sequence cassettes from *H. sapiens*, *D. melanogaster* (*Dm*), and the protist *M. brevicollis* (*Mb*). The dendrogram was created using CLC Sequence Viewer (www.clcbio.com).

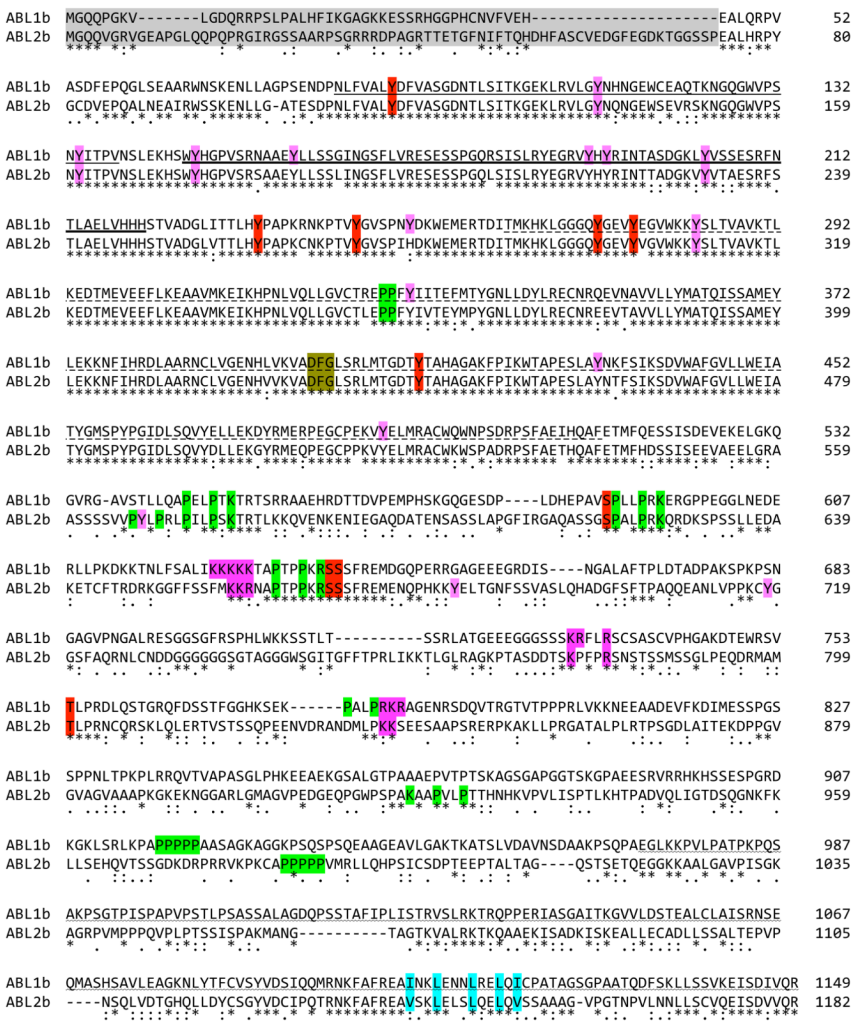
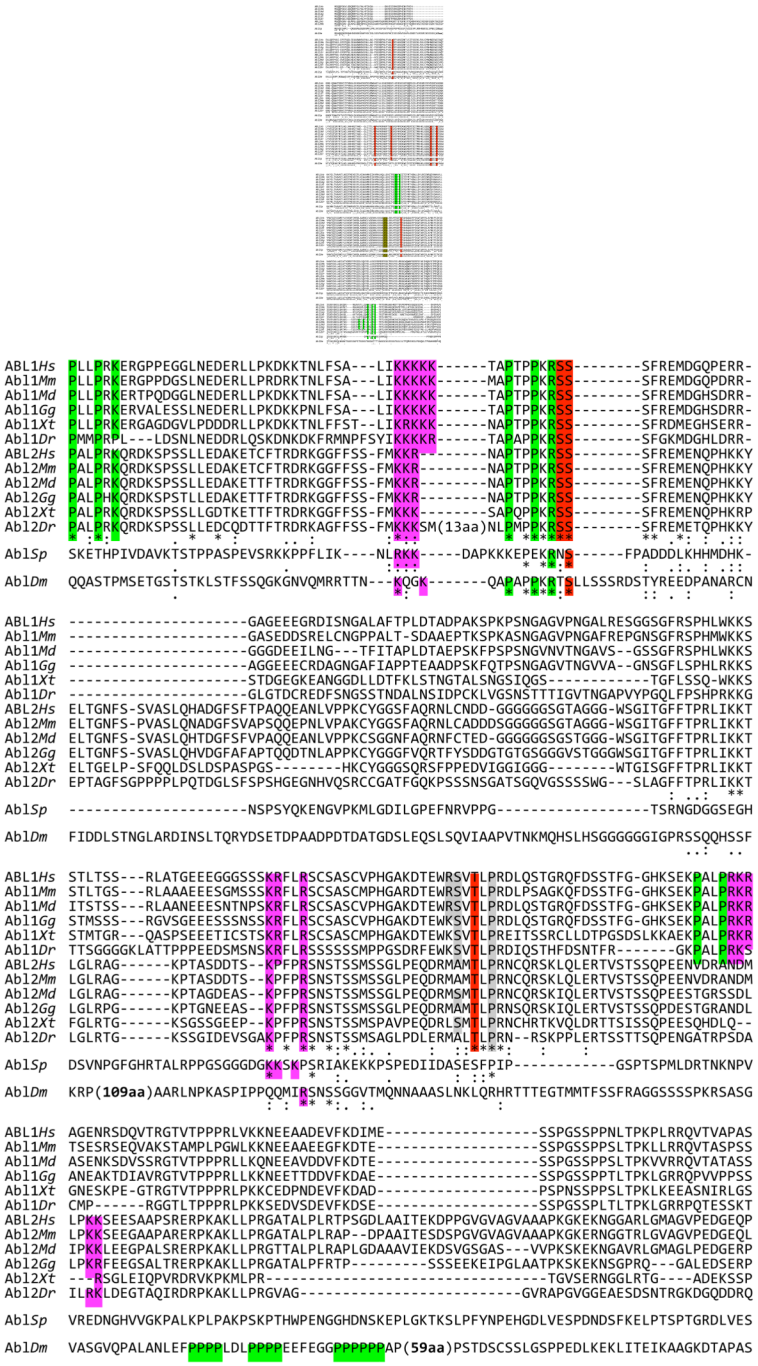


Fig. 3.

Sequence alignment of human ABL1b and ABL2b. Identity (*) and strong or weak sequence conservation [(:)colon for strong conservation; (.) period for weak conservation] are indicated. Domains are indicated with the following underlines: plain, SH3; heavy, SH2; dashed, TK; or wavy, terminal F-actin binding. Shading is used to highlight the following features: sequences deleted in human leukemogenic ABL fusions (gray), phosphorylation sites with known function (red), SH3 and WW domain proline-rich ligands (yellow), K- or R-rich NLS motifs (purple), and NES (blue). Additional reported phosphorylation sites are indicated with a red over-line. The DFG kinase signature is italicized. Alignment was performed using ClustalW (248).



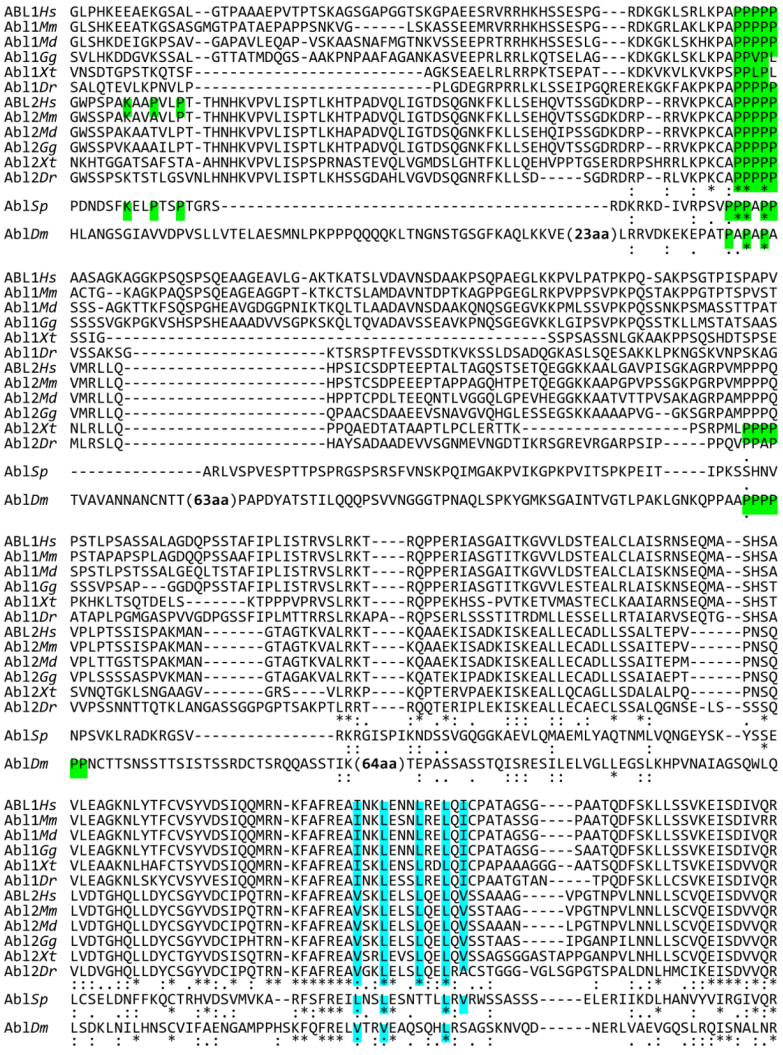
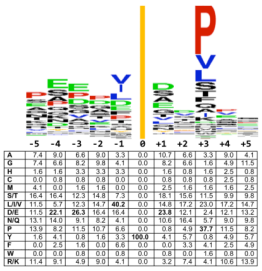


Fig. 4.

Sequence alignment of ABL proteins from representative organisms. Representative Chordates are: Primates (*Homo sapiens*, *Hs*); Rodentia (*Mus musculus*, *Mm*); Marsupialia (*Monodelphis domestica*, *Md*); Aves (*Gallus gallus*); Amphibia (*Xenopus tropicalis*, *Xt*); and Pisces (*Danio rerio*, *Dr*). Representative Echinoderm is sea urchin (*S. purpuratus*, *Sp*); representative Arthropod is fruit fly (*Drosophila melanogaster*, *Dm*). Sequence identity and similarity is denoted as in Fig. 3. Color shading corresponds to the description in Fig. 3. Note that the first line shows only those vertebrate ABL2 sequences for which a long (myristoylated) isoform was identified. A few large insertions (mostly in Abl*Dm*) relative to other sequences are indicated. Sequences were obtained from Ensemble and GenBank. Alignment was performed using ClustalW.



	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5
A	7.4	9.0	6.6	9.0	3.3	0.0	10.7	6.6	3.3	9.0	4.1
G	7.4	6.6	8.2	9.8	4.1	0.0	8.2	6.6	1.6	4.9	11.5
H	1.6	1.6	3.3	3.3	3.3	0.0	1.6	0.8	1.6	2.5	0.8
C	0.0	0.8	0.8	0.8	0.0	0.0	0.8	0.8	0.8	2.5	0.8
M	4.1	0.0	1.6	1.6	0.0	0.0	2.5	1.6	1.6	1.6	2.5
S/T	16.4	16.4	12.3	14.8	7.3	0.0	18.1	15.6	11.5	9.9	9.8
L/V	11.5	5.7	12.3	14.7	**40.2**	0.0	14.8	17.2	23.0	17.2	14.7
D/E	11.5	**22.1**	**26.3**	16.4	16.4	0.0	**23.8**	12.1	2.4	12.1	13.2
N/Q	13.1	14.0	9.1	8.2	4.1	0.0	10.6	16.4	5.7	9.0	9.8
P	13.9	8.2	11.5	10.7	6.6	0.0	0.8	4.9	**37.7**	11.5	8.2
Y	1.6	4.1	0.8	1.6	3.3	**100.0**	4.1	5.7	0.8	4.9	5.7
F	0.0	2.5	1.6	0.0	6.6	0.0	0.0	3.3	4.1	2.5	4.9
W	0.0	0.0	0.8	0.0	0.8	0.0	0.8	0.0	1.6	0.8	0.0
R/K	11.4	9.1	4.9	9.0	4.1	0.0	3.2	7.4	4.1	10.6	13.9

Fig. 5.

ABL target site consensus. (**Top**) Sequence logo was created from 119 phosphorylation sites in Table 2 using Weblogo (249) at weblogo.berkeley.edu. The line at position zero represents the phosphorylated tyrosine. (**Bottom**) Amino acid position weight matrix generated using Python. Positions contributing most heavily to the consensus target site, as described in the text, are shown in bold.

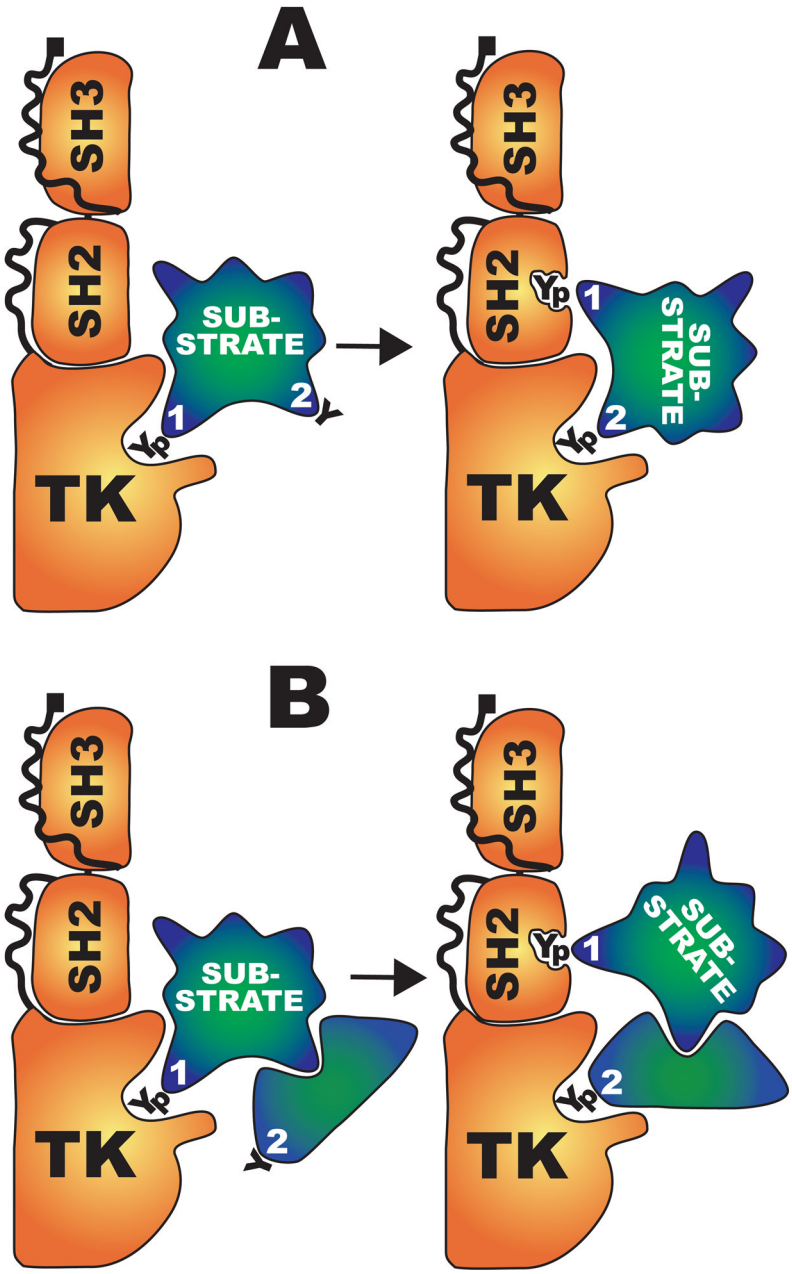


Fig. 6.

Hierarchical processivity model. (**A**) The catalytically active conformation of ABL1 is depicted with SH3, SH2, and TK domains labeled (carboxy-terminal domains not shown). A "primary," consensus, tyrosine target (1) is phosphorylated, then relocated to the SH2 domain. This guides a "secondary," nonconsensus, tyrosine (2) into the catalytic site. (**B**) Same steps as in (A) except that the secondary tyrosine is in a separate protein associated with the initial substrate.

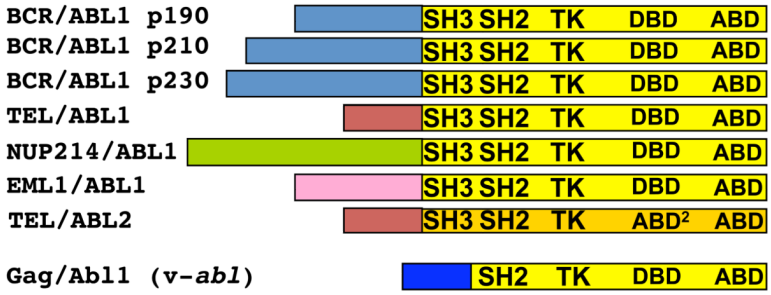


Fig. 7.

(**Top**) Seven translocation-derived ABL1 and ABL2 fusion oncoproteins. The following diseases are associated with each fusion: BCR-ABL1 p190 (also called p185) (ALL), p210 (CML), p230 (CNL), ETV6-ABL1 (CML and AML), NUP214-ABL1 (TALL), EML1-ABL1 (T-ALL), and ETV6-ABL2 (AML). (**Bottom**) The murine v-Abl oncoprotein results from a retroviral Gag gene fusion that deletes the Abl1 amino terminus and most of the SH3 domain. *v-Abl* causes B cell lymphomas.

Table 1

ABL-interacting proteins. Human protein names (www.genenames.org) are used throughout, although in some cases the murine gene and protein was reported.

PROTEIN	DOMAIN	REF	SUB	ALIASES	PARALOGS	FUNCTION COMMENTS
ABI1	SH3, PxxP	7590237	yes	NAP1BP	ABI2,3	cytoskeleton, ABL kinase reg
ABI2	SH3, PxxP	7590236		AblBP3	ABI1,3	cytoskeleton, ABL kinase reg
ACR	SH3	16446784		acrosin		protease
APBB1	PR	11279131	yes	Fe65	APBB2,3	transcription adaptor
ATM	SH3	9168117		TEL1, ATC	ATR	DNA repair, damage response
ATR	unknown	15050919		MEC1, SCKL	ATM	DNA repair, damage response
BCR	SH2	1383690			ABR	signaling, GAP for RAC
BIN1	C-term	9356459		AMPHL, ALP1		cytoskeleton, endocytosis
BRCA1	SH3	12024016		BRCC1		DNA repair, damage response
BTK	unknown	12445832	yes	AGMX1, XLA	BMX	tyrosine kinase
CABLES1	SH3+	10896159	yes	ik3-1	CABLES2	signal adaptor, cell cycle
CABLES2	unknown	11955625		ik3-2	CABLES1	signal adaptor, cell cycle
CASP9	SH3	15657060	yes		CASP2,8,10	protease, apoptosis
CAV1	unknown	16151024	yes	caveolin	CAV2,3	membrane protein, endocytosis
CBL	SH2, SH3	11494134	yes	CBL2	CBLB, C	ubiquitin ligase, endocytosis
CD19	unknown	11120811	yes			BCR co-receptor
CDON	SH3	19470755		CDO	BOC	Ig superfamily recpt, adhesion
CPSF6	SH3	8943360		AAP1, CFIM		cleavage & polyA factor
CREB1	SH2, TK	7565761		CREB	ATF1, CREM	transcription, cAMP response
CRK	PxxP	7926767	yes		CRKL	signal adaptor
CRKL	(PxxP)	8083188	yes		CRK	signal adaptor
CTNND1	SH3	11891774	yes	catenin δ	CTNND2, ARVCF	adhesion, signaling
DAB1	SH2	9009273		disabled	DAB2	signal adaptor
DDB1	TK	12107171	yes	XPE		DNA repair, complex w/DDB2
DOK1	pY	10567556	yes	p62Dok	DOK2,3-7	signal adaptor
DOK2	SH3	12777393	yes	p56Dok	DOK2,3-7	signal adaptor

PROTEIN	DOMAIN	REF	SUB	ALIASES	PARALOGS	FUNCTION COMMENTS
DOK3	pY	10567556	yes	DOKL	DOK1,2,4-7	signal adaptor
EGFR	SH2	7678409	yes	ERBB1	ERBB2-4	tyrosine kinase (receptor type)
ENAH	SH3	16446784	yes	MENA	VASP, EVL	cytoskeleton, actin polym
EPHB2	SH2+Cter	11494128	yes	Tyro5	EPHB1,3,4,6	tyrosine kinase (receptor type)
ERBB2	SH2	19275932		neu, HER2	EGFR, ERBB3,4	tyrosine kinase (receptor type)
ERCC6	SH3	17626041	yes	CSP, CKN2	ERCC6L	DNA repair
ESR1	SH3	20101225	yes	Era	ESR2	steroid recpt, transcript.
EVL	SH3	16446784		RNB6	ENAH, VASP	cytoskeleton, actin polym
GPX1	SH3	12893824	yes		GPX2-8	glutathione peroxidase
GRB2	PxxP	7926767	yes	NCKAP2	GRB7,10,14	signal adaptor
GRIN2D	SH3	10777567		NR2D	GRIN2A-C	NMDA recpt., ABL kinase inhib
HCLS1	SH2	18305217	yes	HS1	CTTN	cytoskeleton, actin regulator
HDAC4	SH3	16446784		HD4	HDAC5,7,9	deacetylase
INPPL1	SH3	10194451	yes	SHIP2	INPP5D	phosphoinositide phosphatase
JAK1	C-term	9774693		JTK3	JAK2,3, TYK2	tyrosine kinase
JAK2	C-term	11593427	yes	JTK10	JAK1,3, TYK2	tyrosine kinase
JUN	SH2	10637231	yes	AP-1	JUNB, JUND	transcription
LASP1	SH3	15138294	yes	MLN50	NEBL	cytoskeleton, cell migration
LRRN2	SH3	16446784		LRRN5, GAC1	LRRN1,3,4	leucine rich repeat, signaling
MAP3K1	SH3	10866655	yes	MEKK1	MAP3K2-15	MAPK (JNK) activation, signaling
MAP4K1	SH3	9003777		HPK1	MAP4K2-5	MAPK (JNK) activation, signaling
MAP4K5	unknown	9949177		KHS, GCKR	MAP4K1-4	MAPK (JNK) activation, signaling
MAPT	unknown	16014719	yes	tau		cytoskeleton, microtubule dynamics
MDM2	unknown	12110584	yes		MDM4	DNA damage/apoptosis/signaling
MDM4	unknown	19075013	yes	MDMX	MDM2	DNA damage/apoptosis/signaling
MSH5	SH3	16397227	yes	MutS hom5	MSH2-4,6	DNA repair
MUC1	SH2	16888623	yes	PUM, PEM		barrier function, signaling
MUSK	unknown	12796783	yes			tyrosine kinase (receptor type)
NCK1	PxxP	7926767	yes	NCKalpha	NCK2	signal adaptor

PROTEIN	DOMAIN	REF	SUB	ALIASES	PARALOGS	FUNCTION COMMENTS
NCK2	unknown	10887126	yes	GRB4, NCKβ	NCK1	signal adaptor
NEDD9	unknown	8668148	yes	HEF1, CAS-L	BCAR1, EFS	signal adaptor
NFKBIA	SH2+	12167702	yes	IKBA, NFKBI	NFKBIB, D, E,Z	signaling, NFKB inhibitor
NTRK1	unknown	10679771	yes	TrkA	NTRK2,3	neurotrophic RTK (also 10708759)
PAK2	unknown	11121037	yes	PAKgamma	PAK1,3	S/T kinase
PDE4D	SH3	10571082		DPDE3	PDE4A-C	cAMP phosphodiesterase
PDGFRB	SH2	19275932	yes	PDGFR	PDGFRA	tyrosine kinase (receptor type)
PIK3R1	pYXXM	8781408		p85	PIK3R2-5	phosphoinositide-3-kinase reg
PLCG1	SH2, SH3	12652307	yes	PLCgamma	PLCG2	phospholipase
PLSCR1	SH3	11390389	yes	MMTRA1B	PLSCR2-5	phospholipid scrablase
PLXNA1	unknown	18660502		plexin	PLXNA2-4	signaling, SEMA response
POLR2A	SH2	7533294	yes	RNA pol. 2	POLR2B-L	transcription, polymerase
PRDX1	SH3	9334312		PAG, MSP23	PRDX2-6	peroxiredoxin, ABL kinase inhib
PRKDC	SH3	9312071	yes	DNAPK		S/T kinase, DNA reapir
PSMA7	SH2, SH3	16678104	yes	C6, XAPC7	PSMA8	proteasome component
PSTPIP1	C-term	11163214	yes	PSTPIP	PSTPIP2	signal adaptor
PTK2B	SH2	14654952		FAK2, PYK2	PTK2	cytoskeleton, adhesion
PTPN6	SH3	8692915	yes	SHPTP1	PTPN11	tyrosine phosphatase
PXN	unknown	9603926	yes	paxillin		cytoskeleton, actin regulator
RAD9A	SH3	11971963	yes	RAD9	RAD9B	DNA repair
RAD51	SH3	9461559	yes	RECA		DNA repair
RAD52	unknown	12379650	yes			DNA repair
RAN	unknown	11420673	yes	TC4		GTPase, nuclear transport
RAPH1	SH2	20417104	yes	lamellipodin		cytoskeleton, actin reg
RB1	TK	8242749	yes	RB		cell cycle, inhibits ABL kinase
RFX1	SH3	9583676			RFX2-8	transcription factor
RIN1	SH2, SH3	9144171	yes		RIN2,3	RAS effector, RAB & ABL activator
ROBO	unknown	17618275			ROBO1-4	axon guidance receptor
SEM6A	SH3	16446784		semaphorin	SEMA6B-D	receptor-mediated signaling

PROTEIN	DOMAIN	REF	SUB	ALIASES	PARALOGS	FUNCTION COMMENTS
SEM6D	SH3	16446784		semaphorin	SEMA6A-C	receptor-mediated signaling
SH3BP1	SH3	1379745		3BP1	SH3BP2,4,5	Rac GAP
SH3BP2	SH3	1379745		3BP2	SH3BP1,4,5	TNFalpha regulator
SHC1	SH2	8617726	yes	SHC, p66	SHC2-4	signal adaptor
SHD	unknown	9315092	yes			signal adaptor
SHE	unknown	9315092		Shg		signal adaptor
SIVA1	SH2, SH3	11278261	yes	CD27BP		signaling, apoptosis
SLC9A2	SH3	10187839		NHE2	SLC9A1,3-11	Na+/H+ exchanger
SORBS1	PxxP	11374898	yes	ponsin, CAP	SORBS2,3	signal adaptor
SORBS2	PxxP	9211900	yes	ArgBP2	SORBS1,3	signal adaptor
SORBS3	PxxP	16831423	yes	vinexin	SORBS1,2	signal adaptor
SOS1	unknown	15039778	yes		SOS2	GEF for H/K/NRAS
ST5	SH3	9632734		HTS1	DENND2A, C, D	MAPK signal regulation
TERT	SH3	10837221	yes	TRT, TP2		telomerase reverse transcript.
TMEM131	SH3	16446784		RW1		transmembrane protein
TLN2	SH3	19234221		talin2	TLN1	cytoskeleton, integrin signaling
TOPBP1	DBD	15961388	yes	TOP2BP1		DNA repair
TP53	C-term	7651743	yes	p53	TP63, TP73	transcription; apoptosis
TP73	SH3	10391251	yes	p73	TP53, TP63	transcription; apoptosis
TREX1	SH3	16446784		AGS1, DRN3		DNA repair, exonuclease
TUB	SH2	10455176	yes	tubby	TULP1-4	transcription, signaling
VASP	unknown	12087107	yes		ENAH, EVL	cytoskeleton, actin regulator
VAV1	unknown	11790798	yes	VAV	VAV2,3	Rho GEF
WAS	TK	12899629		WASP	WASL	cytoskeleton, actin polym
WASF2	SH3	16899465	yes	WAVE2	WASF1,3,4	cytoskeleton, actin regulator
WASF4	SH3	16446784			WASF1-3	cytoskeleton, actin regulator
WRN	SH3	12944467	yes	RECQ3		DNA repair
YLPM1	SH3	16446784		ZAP3		assoc. w/PP1 phosphatase
YTHDC1	unknown	15175272		YT521	YTHDC2	splicing factor

PROTEIN	DOMAIN	REF	SUB	ALIASES	PARALOGS	FUNCTION COMMENTS
YWHA-	RSVpTLP	15696159		14-3-3	ABDEGHQZ	subcellular localization
ZAP70	SH2	7760813		SRK, STD	SYK, PTK2	tyrosine kinase
ZDHHC16	C-term	12021275	yes	APH2		signaling, apoptosis

"Domain" indicates site of interaction on ABL, if known. "Ref" provides literature citations as PMID numbers. "Sub" identifies proteins that are also known ABL substrates.

Table 2

Proteins reported as substrates of ABL1, ABL2, or BCR-ABL1 (nomenclature as in Table 1).

PROTEIN	SUBSTRATE	AA	REF	ALIASES	PARALOGS	FUNCTION
ABI1	PVKPPTVPNDYMTSPARLGSQ	213	18328268	Abi-1	ABI2,3	cytoskeleton, ABL reg
ABL1	ENDPNLFVALYDFVASGDNTL	89	18775435	c-Abl	ABL2	tyrosine kinase
ABL1	PAPKRNKPTVYGVSPNYDKWE	245	12748290	c-Abl	ABL2	tyrosine kinase
ABL1	GLSRLMTGDTYTAHAGAKFPI	412	12748290	c-Abl	ABL2	tyrosine kinase
ABL2	VADGLVTTLHYPAPKCNKPTV	261	15735735	Arg	ABL1	tyrosine kinase
ABL2	PAPKCNKPTVYGVSPIHDKWE	272	12748290	Arg	ABL1	tyrosine kinase
ABL2	GLSRLMTGDTYTAHAGAKFPI	439	12748290	Arg	ABL1	tyrosine kinase
ABL2	RAASSSSVVPYLPRLPILPSK	568	12748290	Arg	ABL1	tyrosine kinase
ABL2	REMENQPHKKYELTGNFSSVA	683	12748290	Arg	ABL1	tyrosine kinase
ANXA1	AWFIENEEQEYVQTVKSSKGG	21	2457390	lipocortin	ANXA2-12,13	signaling, endocytosis
APBB1	NELVQKFQVYYLGNVPVAKPV	547	15031292	Fe65	APBB2,3	transcription adaptor
APP	RHLSKMQQNGYENPTYKFFEQ	682	11279131	amyloid pp	AD1	unclear (signaling?)
BCAR1	HLLAPGPQDIYDVPPVRGLLP	267	7780740	p130CAS	NEDD9, EFS	signal adaptor
BCR	QPGADAEKPFYVNVEFHHERG	177	8112292	BCR1	ABR	GAP for RAC, signaling
BCR	PLEYQPYQSIYVGGMMEGEGK	283	8622703	BCR1	ABR	GAP for RAC, signaling
BCR	SSRVSPSPTTYRMFRDKSRSP	360	8622703	BCR1	ABR	GAP for RAC, signaling
BTK	TSELKKVVALYDYMPMNANDL	223	12445832	AGMX1, XLA	BMX	tyrosine kinase
CABLES1			10896159	ik3-1	CABLES2	signal adaptor, ccyc
CASP9	ESLRGNADLAYILSMEPCGHC	153	15657060		CASP2,8,10	protease, apoptosis
CAT	KLVNANGEAVYCKFHYKTDQG	231	12777400	catalase		catalase
CAT	NCPYRARVANYQRDGPMCMQD	386	12777400	catalase		catalase
CAV1	GKYVDSEGHLYTVPIREQGNI	14	12531427	caveolin, CAV	CAV2,3	microdomains, endocyt.
CBL	EQCEGEEDTEYMTPSSRPLRP	700	15556646	CBL2	CBLB, C	ubiquitin lig, endocyt.
CBL	PEESENEDDGYDVPKPPVPAV	774	8649859	CBL2	CBLB, C	ubiquitin lig, endocyt.
CD19			11120811			BCR co-receptor
CDK5	EKLEKIGEGTYGTVFKAKNRE	15	10896159	PSSALRE	CDK2,3, CDC2	S/T kinase, ccyc, cytosk
CDKN1B[#]	EVEKGSLPEFYYRPPRPPKGA	88	17254966	KIP1, p27	CDKN1A, C	kinase inhib, ccyc

PROTEIN	SUBSTRATE	AA	REF	ALIASES	PARALOGS	FUNCTION
CDV3*	WKEFEQREVDYSGLRVQAMQI	120	12606058	H41, TPP36		unknown
CHRNB1			15340048	nic Ach recpt	CHRND, E, G	ion channel, recpt
CRK	QPLGGPEPGPYAQPSVNTPLP	221	8194526	CRKII	CRKL	signal adaptor
CRKL	SYGIPEPAHAYAQPQTTTPLP	207	9710592		CRK	signal adaptor
CTNNB1	EMAQNAVRLHYGLPVVVKLLH	489	16099633	Catenin-beta	CTNNBL1	signaling, transcript.
CTNND1			11891774	Catenin-delta	CTNND2, ARVCF	signaling, adhesion
CTTN*	IEDRPPSSPIYEDAAPFKAEP	421	17306540	cortactin	HCLS1	signal adaptor, cytosk.
CTTN*	QGLTYTSEPVYETTEAPGHYQ	466	17306540	cortactin	HCLS1	signal adaptor, cytosk.
CTTN*	PGHYQAEDDTYDGYESDLGIT	482	17306540	cortactin	HCLS1	signal adaptor, cytosk.
DBN1			17892306	drebrin 1		cytosk. (postsynaptic)
DDB1			12107171	XPE		DNA repair, cplx w/DDB2
DDB2			12107171	UV-DDB2		DNA repair, cplx w/DDB1
DNM2			19833721	DYN2	DNM1,3	GTPase, endocyt.
DOK1#	QELLDSPPALYAEPLDSLRIA	296	16497976	p62Dok	DOK2-6	signal adaptor
DOK1#	IAPCPSQDSLYSDPLDSTSAQ	315	16497976	p62Dok	DOK2-6	signal adaptor
DOK1	KLTDPKEDPIYDEPEGLAPVP	362	15148308	p62Dok	DOK2-6	signal adaptor
DOK1#	WCQARVKEEGYELPYNPATDD	398	16497976	p62Dok	DOK2-6	signal adaptor
DOK1#	ELPYNPATDDYAVPPPRSTKP	409	16497976	p62Dok	DOK2-6	signal adaptor
DOK1#	SGIKSHNSALYSQVQKSGASG	449	16497976	p62Dok	DOK2-6	signal adaptor
DOK2#	APRPRGQEGEYAVPFDAVARS	299	16858728	p56dok-2	DOK1,3-6	signal adaptor
EGFR	FKGSTAENAEYLRVAPQSSEF	1173	16943190	ERBB1	ERBB2-4	tyrosine kinase (recpt)
ENAH	PPPPLPSGPAYASALPPPPGP	296	12672821	MENA	VASP, EVL	cytosk., actin pol.
ENO1	AVPSGASTGIYEALELRDNDK	44	6330085	Enolase	ENO2,3	metabolism
EPHB2			11494128	Tyro5	EPHB1,3,4,6	tyrosine kinase (recpt)
ERCC3			9874796	XPB, TFIIH		DNA repair
ERCC6	NLTGANRVVIYDPDWNPSTDT	932	17626041	CKN2, CSP	ERCC6L	DNA repair
ESR1	VYLDSSKPAVYNYPEGAAYEF	52	20101225	Era	ESR2	steroid recpt
ESR1	FKRSIQGHNDYMCPATNQCTI	219	20101225	Era	ESR2	steroid recpt

PROTEIN	SUBSTRATE	AA	REF	ALIASES	PARALOGS	FUNCTION
GNB2L1	MWKLTRDETNYGIPQRALRGH	52	19423701	RACK1, HLC-7	GNB2	signal scaffold
GPX1	KNEEILNSLKYVRPGGGFEPN	96	12893824		GPX2-8	enzyme, antioxidant
GRB2	HGQTGMFPRNYVTPVNRNV	299	11726515	NCKAP2	GRB7,10,14	signal adaptor
GRLF1*	VKPRN**EEE**N**IY**SV**P**H**D**STQGK	1105	15084284	p190RhoGAP	ARHGAP5	GAP for RHO, cytosk.
HCLS1			18305217	HS1	CTTN	signal adaptor, cytosk.
HSPA1A			17892306	HSP70	HSPA1B,1L	stress response
INPPL1	QMAKTLS**E**V**DY**A**P**AG**P**ARSAL	1135	16858728	SHIP2	INPP5D	PtdInsP phosphatase
IRS1			12560071	HIRS-1	IRS2,3L,4	signaling
JAK2	LTKVLPQ**D**K**EY**YKVK**E**PGESP	1007	11593427	JTK10	JAK1,3, TYK2	tyrosine kinase
JUN	SASLHS**E**PP**VY**ANLSNFNPGA	170	10637231	c-Jun	JUNB, JUND	transcription
LGALS3	AYPGAPAPG**VY**PG**P**PSGPGAY	79	20600357	GALIG, MAC-2	LGALS1-14	signaling lectin
LGALS3	ATGAYPATGP**Y**GA**P**AGPLIVP	107	20600357	GALIG, MAC-2	LGALS1-14	signaling lectin
LGALS3	GAPAGPLIVP**Y**NL**P**LPGGVVP	118	20600357	GALIG, MAC-2	LGALS1-14	signaling lectin
LASP1	PHHIPTSAP**VY**QQ**P**QQQPVAQ	171	15138294	MLN50	NEBL	cytoskeleton, migration
MAP3K1			10866655	MEKK1	MAP3K2-15	S/T kinase
MAPT	AKTDHGA**E**I**VY**KS**P**VVSGDTS	305	16014719	tau		cytosk., microtub.
MDM2	QELSD**EDDEVY**QVTVYQAGES	276	16702947	Hdm2	MDM4	DNA damage/apop/signal
MDM2	QASQSQ**ESEDY**SQ**P**STSSSII	394	12110584	Hdm2	MDM4	DNA damage/apop/signal
MDM4	EMFTVK**E**VMH**Y**LGQYIMVKQL	55	19075013	Mdmx	MDM2	DNA damage/apop/signal
MDM4	SFSVKNPSP**LYD**MLRKNLVTL	99	19075013	Mdmx	MDM2	DNA damage/apop/signal
MSH5			16397227	MutS hom 5	MSH2-4,6	DNA repair
MUC1	SAGNGGSSLS**Y**TN**P**AVAATSA	463	16888623	PUM, Y60		barrier funct., signal
MYOD1*	LCSFETA**DD**F**YDDP**CFDSPDL	30	12415271	MYF3, PUM		transcription
MYOD1*	RSNCS**D**GMM**DY**SG**PP**SGPRRQ	213	12415271	MYF3, PUM		transcription
MYH10			17892306	MyosinIIB	MYH9,11,14	motor prot., cytosk.
NCK1			11494134		NCK2	signal adaptor
NCOA3	MMQHPQAAS**IY**QSS**E**MKGWPS	1357	18765637	AIB1, SRC-3	NCOA1, 2	steroid recpt co-act.
NEDD9	TPVRTGHGY**VYE**Y**P**SRYQKDV	166	8668148	HEF1, Cas-L	BCAR1, EFS	signal adaptor
NFKBIA	FTEFT**ED**ELP**YDD**CVFGGQRL	305	12167702	IkBa	NFKBIB	signaling, NFKB inhib.

PROTEIN	SUBSTRATE	AA	REF	ALIASES	PARALOGS	FUNCTION
NFKBIB	PRRPR**E**AP**D**T**Y**LAQG**P**DRTPD	161	16286457	IkBb	NFKBIA	signaling, NFKB inhib.
OGDH			17892306	2oxoglut dhg	OGDHL, DHTKD1	metabolism
PAK2			11121037	PAKgamma	PAK1,3	S/T kinase
PDGFRB	PIYIITE**Y**CR**Y**G**D**LV**D**YLHRN	686	14993293	PDGFR	PDGFRA	tyrosine kinase (recpt)
PDGFRB	AQPAHAS**DE**I**YE**IMQKCWEEK	934	14993293	PDGFR	PDGFRA	tyrosine kinase (recpt)
PDGFRB	RLLGEGYKKK**Y**QQV**DE**EFLRS	970	14993293	PDGFR	PDGFRA	tyrosine kinase (recpt)
PIK3AP1	QCHLGQ**EEDVY**HTV**DD**DEAFS	513	15893754	BCAP		signal adaptor (BCR)
PIK3AP1	GAHQLP**DN**E**PY**IFKVFAEKSQ	553	15893754	BCAP		signal adaptor (BCR)
PIK3AP1	EKSQERPGNF**Y**VSS**ES**IRKGP	570	15893754	BCAP		signal adaptor (BCR)
PIK3AP1	PWRDRPQSS**IYDP**FAGMKTPG	594	15893754	BCAP		signal adaptor (BCR)
PIK3AP1	HLPAKV**E**FG**VYE**SG**P**RKSVIP	694	15893754	BCAP		signal adaptor (BCR)
PLCG1	LEKIGTA**EPDY**GALY**E**GRNPG	771	12652307	PLCg-1	PLCG2	phospholipase
PLCG1	NKAKGKKFLQ**Y**NRLQLSRIYP	1003	12652307	PLCg-1	PLCG2	phospholipase
PLSCR1	AGFPVPNQ**PVYN**Q**P**VYNQPVG	69	11390389	MMTRA1B	PLSCR2-5	phospholipid scrablase
PLSCR1	PNQPVYNQP**VYN**QP**V**GAAGVP	74	11390389	MMTRA1B	PLSCR2-5	phospholipid scrablase
POLR2A	SPS**YSP**T repeat	CTD	7504297	POLR2	POLR2B-L	RNA polym., transcript.
PRKCD	KLDTT**E**SVG**IY**QGFEKKPEVS	311	17126298	PKC-δ	PRKCE, H, Q	S/T kinase
PRKD1	LFQNETGSR**YYKE**I**P**LSEILR	463	12637538	PKD, PKCμ	PRKD2,3	S/T kinase
PRKDC			9109492	DNA-PK		S/T kinase, DNA reapir
PSMA7	RLYQT**D**PSGT**Y**HAWKANAIGR	153	16678104	C6, XAPC7	PSMA8	proteasome component
PSTPIP1	TPTPERN**E**G**VY**TAIAVQEIQG	345	11163214	H-PIP, PAPAS	PSTPIP2	signal adaptor
PTPN6	LQSQKGQ**ES**E**Y**GNITYPPAMK	536	8692915	SHPTP1	PTPN11	tyrosine phosphatase
PTPN6	RTSSKHK**EDVYE**NLHTKNKRE	564	8692915	SHPTP1	PTPN11	tyrosine phosphatase
PTPN11	THIKIQNTG**DY**Y**D**LYGGEKFA	62	8195176	SHPTP2	PTPN6	tyrosine phosphatase
PTPN11	AEMRE**D**SAR**VYE**NVGLMQQQK	580	18827006	SHPTP2	PTPN6	tyrosine phosphatase
PXN	RPVFLS**EE**TP**YS**Y**P**TGNHTYQ	31	11695992	paxillin		cytoskeleton, actin reg
PXN	CSRVG**EEEHVY**SFP**N**KQKSAE	118	11695992	paxillin		cytoskeleton, actin reg
RAD9A	HSLSRIG**DEL**Y**LE**P**L**EDGLSL	28	11971963	RAD9	RAD9B	DNA repair
RAD51	AGFHTVEAVA**Y**A**P**KK**E**LINIK	54	9461559	RECA		DNA repair

PROTEIN	SUBSTRATE	AA	REF	ALIASES	PARALOGS	FUNCTION
RAD51	GRGETRICK**IY**D**SP**CLPEAEA	315	11684015	RECA		DNA repair
RAD52	DFVDLNNGKF**Y**VGVCAFVRVQ	104	12379650			DNA repair
RAN	VFHRKKNLQY**YD**ISAKSYNNF	147	11420673	TC4		GTPase, nucl. transport
RAPGEF1	QSTAPIPSVP**Y**APFAAILPFQ	504	20581864	C3G	RAPGEF2-6	signaling, GEF for RAP
RAPH1	RYFLLRASG**IY**YV**P**KGKAKVS	426	20417104	lamellipodin		cytoskeleton, actin reg
RAPH1	DHVNVYYGQD**Y**RNKYKAPTDY	456	20417104	lamellipodin		cytoskeleton, actin reg
RAPH1	AGYGGSHISG**Y**ATLRRGPPPA	1226	20417104	lamellipodin		cytoskeleton, actin reg
RB1	SPLRIPGGN**IY**IS**P**LKSPYKI	805	16158058	RB		transcript., ccyc
RIN1	AREKPAQ**DP**L**YD**V**P**NASGGQA	36	15886098		RIN2,3	RAS eff, RAB & ABL activ
ROBO1	TNLMLP**E**ST**VY**G**D**V**D**LSNKIN	1038	17618275		ROBO2-4	axon guidance recpt
ROBO1	FVNPSGQPTP**Y**ATTQLIQSNL	1073	17618275		ROBO2-4	axon guidance recpt
ROBO1	QQKQEVAPVQ**Y**NIV**E**QNKLNK	1114	17618275		ROBO2-4	axon guidance recpt
SHC1	EEEEPPDHQY**Y**N**DF**P**P**GKEPPL	350	1623525	SHC, p66	SHC2-4	signal adaptor
SHD			9315092			signal adaptor
SHE			9315092	Shg		signal adaptor
SIVA1	ELSRGVCA**E**R**Y**SQ**E**VFEKTKR	34	11278261	CD27BP		signaling, apop.
SORBS1*	RKYRA**E**PKS**IY**E**Y**Q**P**GKSSVL	326	19891780	CAP, ponsin	SORBS2,3	signal adaptor
SORBS1*	DITSEPPGY**IY**SSNFHAVKRE	360	19891780	CAP, ponsin	SORBS2,3	signal adaptor
SORBS1*	SLDLCSYQA**LY**SYV**P**QNDDEL	632	19891780	CAP, ponsin	SORBS2,3	signal adaptor
SORBS2			9211900	ArgBP2	SORBS1,3	signal adaptor
SORBS3*	DGSLNP**D**PAW**Y**QTW**P**GPGSRP	127	16831423	vinexin	SORBS1,2	signal adaptor
SOS1			15039778		SOS2	GEF for H/K/NRAS
STAT1			8940193	STAT91	STAT2-4	signaling, transcript.
STAT3	PEADPGSAAP**Y**LKTKFICVTP	705	8940193	APRF	STAT1,2,4	signaling, transcript.
STAT5A	TPVLAKAV**D**G**Y**VK**P**QIKQVVP	694	8940193	MGF	STAT5B,6	signaling, transcript.
STAT5B	GFLLKIKLGH**Y**ATQLQNTYDR	90	8940193		STAT5A,6	signaling, transcript.
STAT6			8940193	IL-4-STAT	STAT5A,B	signaling, transcript.
STXBP1			17892306	MUNC18-1	STXBP2,3	trafficking, exocytosis

PROTEIN	SUBSTRATE	AA	REF	ALIASES	PARALOGS	FUNCTION
SYNJ2			15659545	synaptojanin2	SYNJ1	PtdInsP phosph, endocyt
TERT			10837221	TRT, TP2		telomerase RTase
TOP1	TFFAKML**D**H**EY**TTK**E**IFRKNF	268	15448168		TOP1MT	topoisom, DNA repl/rep
TP73	HAASVPTHSP**Y**AQ**P**SSTFDTM	99	10391251	p73	TP63, TP53	transcription; apop.
TRIP10			19631450	CIP4	FNBP1,FNBP1L	signal adaptor, endocyt
TUB			10455176	tubby	TULP1-4	transcript., signaling
TUBA1			17892306	alpha-tubulin	TUBA1A-C	cytoskeleton, microtub.
TUBB			17892306	beta-tubulin	TUBB1	cytoskeleton, microtub.
WASF2	RDDGK**E**ALKF**Y**T**DP**SYFFDLW	150	15657136	WAVE2	WASF1,3,4	cytoskeleton, actin reg
WASF3	RDDKK**D**GLKF**Y**T**DP**SYFFDLW	151	17623672	WAVE3	WASF1,2,4	cytoskeleton, actin reg
WASF3	TRSHAS**D**VT**DY**SY**P**ATPNHSL	248	17623672	WAVE3	WASF1,2,4	cytoskeleton, actin reg
WASF3	YGMLPAQII**EY**YN**P**SGPPPPP	337	17623672	WAVE3	WASF1,2,4	cytoskeleton, actin reg
WASF3	TILSRRIAV**EY**S**D**S**DD**DSEFD	486	17623672	WAVE3	WASF1,2,4	cytoskeleton, actin reg
WASL	KNPEITTNRF**Y**G**P**QVNNISHT	175	16199863	N-WASP	WAS	cytoskeleton, actin reg
WASL	LKDRETSKV**IYD**FI**E**KTGGVE	256	16199863	N-WASP	WAS	cytoskeleton, actin reg
WRN			12944467	RECQ3		DNA repair
YAP1	STDSGLSMSS**Y**SV**P**RTPDDFL	357	18280240	YES-AP1		transcript., apop.
YTHDC1			15175272	YT521	YTHDC2	splicing factor
ZDHHC16			12021275	APH2		signaling, apoptosis

"Substrate" shows phosphorylated tyrosine (bold black) and 10 residues flanking each side. Also highlighted: P (+1 to +5, red); D and E (−5 to +5, green) and I, L, and V (−1, blue). No sequence appears if a target has not been mapped. "AA" gives the position of target Y;

#indicates targets shown for BCR-ABL1 only;

*indicates sites reported for mouse or rat ortholog, but conserved in human.

"Ref" provides literature citations as PMID numbers.