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EnABLing Tumor Growth and Progression: Recent progress in unraveling the functions of ABL kinases in solid tumor cells

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Abstract

Purpose of Review—The goal of this review is to summarize our current knowledge regarding how ABL family kinases are activated in solid tumors and impact on solid tumor development/ progression, with a focus on recent advances in the field.

Recent Findings—Although ABL kinases are known drivers of human leukemia, emerging data also implicates the kinases in a large number of solid tumor types where they promote diverse processes such as proliferation, survival, cytoskeletal reorganization, cellular polarity, EMT (epithelial-mesenchymal-transition), metabolic reprogramming, migration, invasion and metastasis via unique signaling pathways. ABL1 and ABL2 appear to have overlapping but also unique roles in driving these processes. In some tumor types, the kinases may act to integrate pro- and anti-proliferative and -invasive signals, and also may serve as a switch during EMT/MET (mesenchymal-epithelial) transitions.

Conclusions—Most data indicate that targeting ABL kinases may be effective for reducing tumor growth and preventing metastasis; however, ABL kinases also may have a tumor suppressive role in some tumor types and in some cellular contexts. Understanding the functions of ABL kinases in solid tumors is critical for developing successful clinical trials aimed at targeting ABL kinases for the treatment of solid tumors.

Keywords

ABL1; ABL2; tyrosine kinase; solid tumor; EMT; metastasis

Introduction to ABL Kinases

The ABL (ABL1) non-receptor tyrosine kinase (encoded by the *ABL1* gene) was first identified as the oncogene from the Abelson leukemia virus, and later characterized as a critical driver of leukemia due its activation as a result of chromosomal translocation (see below). These studies were followed by a series of manuscripts that uncovered normal

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cellular functions of ABL1 and its homolog, ABL2 (also known as ABL-related gene, Arg; encoded by the *ABL2* gene), demonstrating that the kinases are activated by growth factor signals and adhesion, and regulate growth, actin cytoskeletal rearrangement, and motility [1–4]. Subsequently, studies over the past 10–12 years have uncovered a role for ABL kinases in solid tumors, in addition to leukemia. This review will focus on recent data which add to our understanding regarding how ABL kinases are activated in solid tumors, as well as the unique mechanisms that they utilize to drive tumor progression.

Structure and Regulation.

ABL1 and ABL2 are highly homologous, particularly in their N-termini, which contain a myristoylated residue that target the proteins to the plasma membrane (1b isoforms), as well as SH3, SH2 and kinase domains [reviewed in [5–8]]. The 1a isoforms, which contain an alternatively spliced first exon, do not contain the myristoylated residue. The C-termini are more divergent. Both proteins contain PxxP motifs that bind SH3-containing proteins, as well as conserved F-actin-binding domains [reviewed in [5–8]]. ABL1 has a DNA binding domain, nuclear localization and export signals and a G-actin binding domain that are not present in ABL2, and ABL2 contains a microtubule binding domain [9]. As a result, ABL1 localizes to the plasma membrane, cytoplasm, and nucleus, whereas ABL2 resides in the cytoplasm and at F-actin-rich sites, (e.g. plasma membrane, focal adhesions) [reviewed in [5–8]]. The catalytic activities of ABL kinases are tightly controlled to prevent oncogenic activity. The kinases are negatively regulated via autoinhibitory interactions: a) the N-myristoylated residue binds the C-lobe of the kinase domain; b) the SH3 domain binds PxxP motifs in the C-terminus; and c) the SH2-domain binds internal phosphotyrosines [see the following reviews for detailed structural diagrams [5–8,10]. ABL1/ABL2 also are negatively regulated by F-actin [11], lipids [1, 12, 13], negative regulatory proteins [14–18, 11] and phosphatases [19, 20]. Their activities are stimulated by mutations or binding of proteins that disrupt the autoinhibitory interactions, loss of expression of cellular inhibitors, and auto- and transphosphorylation (mediated by Src Family Kinases-SFKs) of kinase domain and interlinker (between the kinase and SH2 domains) residues [5–8, 2, 21, 18].

ABL Kinases as Leukemia Drivers.

ABL1 and ABL2 are best known for their role in driving leukemia development. The t(9;22) Philadelphia (Ph^+) chromosome, which is present in >95% of patients with chronic myelogenous leukemia (CML), occurs as a result of a translocation between chromosomes 9 and 22, which results in a *BCR-ABL1* chimeric fusion protein. This protein, which has constitutively active ABL1 kinase activity, induces leukemia by increasing myeloid cell proliferation and survival [reviewed in [5–8]]. In addition to BCR, *ABL1* (and more rarely, *ABL2*) also is translocated next to other genes and the resulting chimeric proteins are involved in the genesis of other leukemias [reviewed in [5–8]].

Subcellular localization.

Unlike ABL2, which is exclusively cytoplasmic/membrane associated, ABL1 localizes to both the nucleus and cytoplasm, and has distinct roles in the two compartments. Constitutively active forms of ABL1 (e.g. BCR-ABL, v-ABL, and Abl-P242/P249E) are cytoplasmic, and agents/mutations that inhibit nuclear export result in pro-apoptotic rather

than oncogenic proteins [22–24]. Moreover, signaling molecules that activate endogenous cytoplasmic ABL1 (growth factors/RTKs, cytokines/cytokine receptors) are distinct from those that activate nuclear ABL1 (DNA damaging agents), and downstream pathways/proteins activated by cytoplasmic ABL1 (e.g. cytoskeletal proteins) are distinct from those activated by nuclear ABL1 (e.g. DNA Damage Response-DDR proteins) [18]. Thus, activation of cytoplasmic ABL1 induces proliferation and migration, whereas activation of nuclear ABL1 induces apoptosis [5–8, 11, 25].

ABL Inhibitors.

The 1st generation, ATP-competitive ABL1/ABL2 tyrosine kinase inhibitor (TKI), imatinib, has been utilized for decades to treat BCR-ABL$^+$ CML [26]. However, despite high response rates, primary and secondary resistance is common and results in shorter progression-free survival [26]. Secondary/acquired resistance develops via a variety of mechanisms including point mutations that prevent drug binding [26, 27]. Nilotinib (2nd generation TKI), dasatinib, and bosutinib inhibit most point mutations that drive resistance; however, they are not effective for the T315I gatekeeper mutation [26, 27]. Ponatinib (3rd generation TKI) and a newer drug, GNF-7, are effective for T315I [26–29], as are allosteric inhibitors (see below). Other drugs that target ABL kinases such as danusertib and rebastinib (Aurora kinase, and TIE2 inhibitors, respectively) also are effective against T315I; however, Phase I trials using these compounds have been suspended due to lack of efficacy [27]. The advantage of ATP-competitive inhibitors is their high potency; however, they are not selective and have additional drug targets. Imatinib and nilotinib also target CSF1R, DDR1/2, KIT, and PDGFRA/B; dasatinib targets more than 50 kinases, including SFKs; and ponatinib inhibits SFKs, FGFR, VEGFR, TRK, and TEK, in addition to ABL1 and ABL2 [5]. Highly specific allosteric inhibitors that bind the N-myristoyl binding pocket of the C-lobe of the kinase domain have recently been developed (GNF-2, GNF-5); however, these are less potent than TKIs [30–33]. A newer analog with increased potency (ABL001; a.k.a. asciminib) is currently in clinical development [34]. ABL001 is well-tolerated, and has significant activity in previously treated CML patients who have TKI-resistant mutations [34, 27]. Unfortunately, mutations develop in the myristoyl binding pocket which confer resistance to ABL001 [35]. Clinical trials are now focused on the use of ABL001 in combination with nilotinib, imatinib or dasatinib as animal data indicate that nilotinib/ABL001 resistance profiles do not overlap [34].

Mechanism of ABL1/ABL2 Activation in Solid Tumors

Emerging evidence over the past decade indicates that ABL1 and ABL2 also play important roles in solid tumors. ABL kinases are phosphorylated and/or activated in melanoma, gastric, liver, prostate, colon, breast, ovary, pancreatic, and cervical cancers, as well as in glioblastoma (GBM) [reviewed in [5–8]; recent papers are discussed below]. Generally, the mechanisms by which ABL1 and ABL2 are activated in solid tumors are distinct from the translocation events that activate the kinases in leukemia.

mRNA/protein upregulation.

Early reports showed that ABL1 and more consistently ABL2 mRNA and/or protein was highly expressed in a variety of solid tumors from patients; however, the reports lacked mechanistic data showing that ABL1 or ABL2 overexpression contributes to the disease state [reviewed in [5, 6]]. Examination of the cBioPortal website for Cancer Genomics reveals that ABL1 and ABL2 are amplified or their mRNAs are increased in a subset (5–15%) of a variety of solid tumors (e.g. breast, stomach, ovary, head and neck, lung, pancreas). Moreover, *ABL1* genomic gains of >25% are observed in prostate cancer [36], and *ABL1* mRNA is part of a 5-gene urine screen for bladder cancer [37, 38]. Since ABL1 and ABL2 are tightly regulated, low level overexpression is insufficient to activate the kinases and other events also are required for activation (e.g. loss of negative regulation, activation of upstream activators)[39]. However, increased expression may constitute an important step in activation. Indeed, ABL1 and ABL2 mRNA/protein levels are increased in a majority of melanoma lines (25 were queried), which suggests that increased expression is likely critical for the disease process [40]. However, the kinases are only activated in 40–60% of the lines indicating that other alterations (e.g. differences in the genetic make-up of the lines) also contribute to activation [40]. Importantly, *ABL1* and/or *ABL2* mRNAs are associated with disease progression in melanoma, breast cancer, and hepatocellular carcinoma [41, 40, 42, 43], confirming that mRNA upregulation is indeed an important step in ABL kinase activation. Consistent with these data, downregulation of microRNAs (miRNAs; miRs) that inhibit ABL1/2 expression, also drives disease development. ABL1 is a direct target of miR-3127–5p, which is downregulated in non-small cell lung cancer (NSCLC) patients and is associated with a poor prognosis [44]; miR-3127–5p and ABL1 expression is inversely correlated in patient samples; and loss of miR-3127–5p correlates with dasatinib sensitivity in NSCLC lines lacking KRAS mutations [44]. Likewise, miR-125a-5p, which is downregulated in cervical cancer cell lines and primary tumors, directly targets ABL2, and ABL2 knockdown parallels the effects of miR-212a-5p overexpression on proliferation/migration [45]. Finally, miR-4723, whose loss is associated with decreased prostate cancer survival, represses *ABL1* and *ABL2* mRNAs; silencing ABL1 phenocopies re-expression of miR-4723; and miR-4723 and ABL1 are inversely correlated in prostate cancer specimens [46].

Tyrosine Kinase-Mediated Phosphorylation.

Since receptor tyrosine kinases (RTKs) and SFKs activate ABL kinases in fibroblasts [2, 12, 25, 21], early studies tested whether these kinases are involved in ABL1/2 activation in solid tumors. Indeed, activated RTKs (EGFR, ErbB2/Her-2, IGF1R, Ron, MET), cytokine receptors (CXCR4) and SFKs contribute to ABL1/2 activation in breast cancer; PDGFR and EGFR activate the kinases in GBM; SFKs and IGF1R contribute to increased ABL1/2 activity in melanoma; and MET, PDGFR, and RET RTKs activate ABL1/ABL2 in liver, colon, and thyroid cancer, respectively [47–49, 5–8, 50–54]. Moreover, EML4-ALK, a constitutively active form of the RTK, ALK, an oncogenic driver for non-small cell lung cancer (NSCLC), also induces ABL1/2 activation [50]. Interestingly, visfatin, a secreted adipocytokine that promotes breast cancer growth and metastasis, induces ABL tyrosine phosphorylation and downstream signaling potentially via an RTK [55]. RTKs may indirectly activate ABL1/2 via activation of non-receptor tyrosine kinases (e.g. SFKs) that

directly phosphorylate and activate ABL kinases [21, 2]. Indeed, another non-receptor tyrosine kinase, PYK2/FAK, also activates ABL kinases in breast cancer cells [56]. Alternatively, RTKs might directly phosphorylate ABL1/ABL2 [12]. Interestingly, although silencing/inhibiting SFKs and RTKs reduces ABL1/2 activity, in most cases, their activities are not reduced to levels observed in non-transformed cells [51, 48, 49]; thus, additional alterations likely also contribute to ABL1/2 activation in solid tumor cells.

Stimulation of Autocatalytic Activity.

Disabled-1 (DAB1), a positive regulator of ABL, acts downstream of the Notch signaling pathway. In human colon cancer cells, DAB1 binds ABL1, and stimulates its autophosphorylation and activation, which drives invasion/metastasis [57].

Serine/Threonine Phosphorylation.

In addition to tyrosine phosphorylation, which directly activates ABL1/2, serine/threonine phosphorylation also can alter ABL1 function. In HeLa cells, ABL1 is phosphorylated on T735 by the TTK kinase, 14–3-3 proteins bind T735, which masks ABL nuclear localization signals, thereby inducing ABL1 cytoplasmic retention and subsequent transforming activity [58]. Likewise, in melanoma cells, $BRAF^{V600E}$/ERK induce ABL1/ABL2 phosphorylation, which causes ABL1 cytoplasmic retention and facilitates phosphorylation of ABL1 and ABL2 by SFKs [51].

Loss of Inhibitory Interactions.

Loss of expression of negative regulatory proteins, which stabilize the inactive conformation of the kinases, also can activate ABL1 in solid tumors. The stearic-acid modified form of the FUS1 (TUSC2) tumor suppressor, whose expression is downregulated in a majority of NSCLC primary tumors, is an ABL1 inhibitor, and FUS1 loss induces ABL1 expression, activity and oncogenic behavior [16]. Binding of proteins to the ABL1/2 SH3 domains or PxxP motifs also induces loss of autoinhibition, and thus, contributes to their activation in solid tumors. Birge and colleagues demonstrate that binding of the negative regulator, Abi1, to ABL1 polyproline motifs in GBM cells, competitively inhibits binding and subsequent phosphorylation of the ABL1 substrate, CRK, which binds the same motifs [52]. Moreover, phosphorylation of CRK induces a feedforward mechanism to further activate ABL1 [52]. Thus, differential binding of Abi1 and CRK controls the invasive behavior of GBM cells, and GBMs harboring low levels of Abi1 and high levels of pCrk-Y251 may serve as a biomarker for GBMs that are more likely to respond to imatinib [52].

In summary, increased expression, phosphorylation by kinases, loss of expression of negative regulators, and binding of substrates contribute to ABL kinase activation in solid tumors. Future research is needed to determine whether this entire sequence of events is required for full activation.

Mutational Activation.

The era of NextGeneration sequencing has revolutionized our ability to identify low frequency mutations. In addition to being activated by upstream signals, a query of cBioportal and Cosmic primary tumor databases indicates that ABL1 and ABL2 mutations

exist in a small percentage of a variety of solid tumor types (5–10%). The Cancer Cell Line Encyclopedia website also reveals ABL1 and ABL2 mutations in cell lines from a variety of different cancers. Mutations identified in cell lines/primary tumors are not concentrated in particular hot spots, which suggests that they could be passenger mutations rather than oncogenic drivers. However, many mutations occur within conserved residues in domains that are critical for ABL1/ABL2 function, indicating they may be clinically relevant. Recently, Brognard and colleagues characterized mutations from lung cancer cell lines and solid tumors [59]. They identified two ABL1 kinase domain mutations (R351W, G340L) which result in proteins that are primarily cytoplasmic and drive NSCLC viability [59]. Interestingly, ABL1 mutations observed in primary lung, breast, and skin tumors (R166K, A137S, I242M, R712S, and P806L) had elevated tyrosine kinase activity, even though the mutations resided in regions outside the kinase domain (interlinker, SH2 domain, C-terminus) [59]. Thus, some ABL mutations identified in cell lines/primary tumors indeed have functional consequences. Further experimentation is needed to characterize additional mutations as identification of small tumor subsets driven by ABL mutations could define groups of patients that are exquisitely sensitive to ABL inhibitors, akin to ALK mutations in NSCLC [60].

DNA Damage-Mediated Activation of Nuclear ABL1.

Ultraviolet light, ionizing radiation, and genotoxic stress induced by cytotoxic chemotherapeutic agents, which induce high levels of reactive oxygen species (ROS), activate the nuclear pool of ABL1 [11, 5, 18]. Once activated nuclear ABL1 induces cell cycle arrest and apoptosis as part of the DNA Damage Response (DDR) [11, 5, 18]. This topic has been reviewed elsewhere and will not be covered here [11, 61].

ABL Kinases Regulate Tumor Growth

Growth and Survival.

Since cytoplasmic ABL kinases are activated by growth factors and cytokines, they promote cell cycle progression in cancer cells that have upregulated growth factor/receptor pathways. In breast cancer cells, ABL kinases promote anchorage-independent growth, survival in response to nutrient deprivation, and proliferation induced by IGF-1R, EGFR, RON and estrogen receptor (ER)-αvia various pathways including Rac/ERK5, BRAF/ERK [49, 62, 53, 63, 51]. Interestingly, in some breast cancer cell lines, proliferation is mediated by ABL2 and not ABL1 (BT-549)[49], whereas in other lines (MDA-MB-231), ABL2 has an anti-proliferative role [64]. In MDA-MB-231 and MDA-MB-468 breast cancer cells, EGFR and ABL kinase inhibitors synergize to prevent *in vitro* and *in vivo* growth by inhibiting nuclear translocation of β-catenin and subsequent repression of the long non-coding RNA (lcRNA), *HOTAIR,* a known tumor promoter [65]. In HeLa cervical cancer cells, ABL1 promotes proliferation, mitotic entry, and xenograft growth by phosphorylating and stabilizing the serine-threonine kinase, polo-like-kinase-1 (PLK1), an essential mitotic regulator [66]. Stable silencing of ABL1 also dramatically blocks proliferation and xenograft growth of glioblastoma cells [67], and in gastric and hepatocellular carcinoma cells, ABL1 is required for proliferation and anchorage-independent growth downstream of MET [68]. In melanoma, ABL1 and ABL2 are both required for proliferation; they potentiate

$BRAF^{V600E}$-mediated proliferation; and induce *in vivo* growth of melanomas harboring $BRAF^{V600E}$ and PTEN mutations [69, 51].

In most cases, the pro-proliferative role of ABL1 is linked to activation of cytoplasmic signaling pathways (e.g. Rac/ERK5, BRAF/ERK), implicating the cytoplasmic pool of ABL1. However, some data suggest that nuclear ABL1, in some contexts, might also have oncogenic roles. Geminin is a nuclear protein involved in maintaining chromatin integrity. In basal-like breast cancer cells with high geminin expression, ABL1 is primarily nuclear; it phosphorylates geminin in G2/M cells; and silencing/inhibiting ABL1, converts geminin from an oncogene to a pro-apoptotic protein, thereby inhibiting xenograft growth and recruitment of mesenchymal stem cells [70, 71]. Likewise, following activation by the RON RTK, ABL1 phosphorylates proliferating cell nuclear antigen (PCNA), inducing its association with chromatin and subsequent proliferation of breast cancer cells [53]. Although these reports suggest an oncogenic function for nuclear ABL1, they do not rule out the possibility that cytoplasmic ABL1 phosphorylates these proteins prior to their nuclear localization.

Metabolism.

In contrast to normal cells, which rely primarily on mitochondrial oxidative phosphorylation to generate energy for growth/survival, cancer cells utilize aerobic glycolysis even in the presence of functional mitochondria (Warburg effect), which results in low-level, increased steady-state ROS that promotes proliferation [72]. Fumarate hydratase, an essential tricarboxylic acid cycle (TCA) gene, is mutated in hereditary kidney cancer, and its expression also is reduced in other cancers. Loss of fumarate hydratase function results in fumarate accumulation that drives aerobic glycolysis [73]. ABL1 is indirectly activated by fumarate, promotes aerobic glycolysis via activation of the mTOR-HIF1α pathway, and induces NRF2 transcription/activity, which protects cells from ROS-induced injury [73]. Moreover, ABL1 has been postulated to mediate gastric cancer development following activation by depression-induced oxidative stress [74]. Consistent with the above reports, multiple metabolic pathway genes that regulate energy metabolism are altered in MCF-7 cells expressing ABL1/ABL2-targeted siRNA [75]. Taken together, these data indicate that ABL kinases likely play an important role in metabolic reprogramming in cancer cells; however, additional data are needed to solidify their role in this process.

Tumor Progression and Metastasis Driven by ABL Kinases

In addition to tumor initiation/proliferation, ABL kinases also regulate numerous processes that contribute to tumor progression, and in recent years, *in vivo* studies demonstrate that ABL kinases drive tumor metastasis/recurrence.

Regulation of cytoskeletal dynamics.

Actin polymerization is critical for cell polarity, which is essential for suppression of tumor initiation; actin reorganization is necessary for directed migration during tumor progression; and alteration of microtubule dynamics influences proliferation [76]. ABL kinases (particularly ABL2) regulate actin polymerization via effects on WAVE complexes and

cortactin, which activate the Arp2/3 complex to promote actin filament stabilization and branching, and ABL2 also controls microtubule bundling and assembly [18, 77]. ABL proteins bind WAVE2 directly and indirectly via Abi1 [78, 79]; the WAVE2 complex regulates ABL activity; and ABL kinases bidirectionally phosphorylate WAVE2 [80]. Ena/VASP proteins (Mena, EVL, VASP) cooperate with the WAVE complex to regulate the actin cytoskeleton, and lamellipodin is a binding partner [81]. In basal-like breast cancer cells, ABL-mediated phosphorylation of lamellipodin, which induces its binding to Scar/WAVE and Ena/VASP complexes, is critical for EGF-mediated directed migration and invasion [81]. In epithelial cells, ABL activation by HGF/MET induces RHOA-dependent actomyosin contractility, and migration/invasion in breast cancer models [54]. ABL kinases also promote migration and invasion of glioblastoma [67], melanoma [82, 69], prostate [83], cervical [45], and hepatocellular carcinoma cells [41, 84]. Invadopodia formation (actin-rich protrusions from the plasma membrane that catalyze matrix degradation) are critical for invasion. Activation of ABL2 promotes invadopodia maturation in breast cancer cells by binding/phosphorylating cortactin, and subsequent Arp2/3-mediated actin polymerization [85, 86, 77]. ABL2 also interacts with and phosphorylates MT1-MMP a critical regulator of invadopodia in breast cancer cells, whereas in melanoma cells, ABL1 and ABL2 induce *MMP-1*, *MMP-3* and *MT1-MMP* mRNA/protein expression and secretion [69, 87]. In colon cancer cells, NOTCH->disabled (DAB)-1 signaling activates ABL1, which phosphorylates the RHO-GEF, TRIO, a pro-invasive modulator of the actin cytoskeleton [57]. Finally, ABL1 also influences microtubule assembly by phosphorylating PLK1, which phosphorylates plus-end microtubule-binding proteins, which regulate cytokinesis [66].

Epithelial-Mesenchymal-Transition.

The epithelial-mesenchymal transition (EMT) is a critical step in invasion and metastasis of epithelial-derived cancers. Cells lose epithelial polarity, cell-cell junctions are dissolved, and cells acquire a mesenchymal phenotype characterized by increased migratory capacity and an enhanced ability to degrade extracellular matrix (ECM; e.g. basement membrane) [88]. EMT Is characterized by repression of epithelial markers (e.g. E-cadherin) and expression of mesenchymal markers (e.g. vimentin, EMT transcription factors-SNAIL1/2, ZEB1/2, TWIST1) [88]. Accumulating evidence suggest that ABL kinases play a critical role in EMT. ABL1 promotes PDGF-induced EMT in colon cancer cells and claudin (tight-junction protein)-induced EMT in hepatocellular carcinoma cells, via p65 (DDX5)/β-catenin and RAF/ERK/SNAIL2/ZEB1 pathways, respectively [89, 84, 90]. Moreover, inhibition of ABL1/geminin suppresses EMT in breast cancer [70]. Melanomas originate from neural crest-derived melanocytes, and thus, do not undergo classical EMT; however, they are highly plastic, and switch between differentiated and invasive states, which contributes to the high rate of metastasis and drug resistance [91]. This phenotypic shift is linked to $BRAF^{V600E}$-induced switch in expression of EMT transcription factors from ZEB2/SNAIL2, which display tumor suppressive properties to TWIST1/ZEB1, which induces invasion and tumor growth [92]. Importantly, ABL1 and ABL2 activity is required for $BRAF^{V600E}$-induction of the EMT-TF switch and subsequent invasion in melanoma [51].

Vesicular Trafficking.

Cancer cells are dependent on cell surface receptor signaling which is regulated by endocytosis and trafficking of the receptors to the cell surface, processes dependent on vesicle trafficking. Moreover, cathepsin pro-invasive proteases, which are synthesized in the rough endoplasmic reticulum are transported to early endosomes, initially processed in late endosomes, and full activated in lysosomes, where they cleave intracellular and membrane-bound proteins, and old organelles/long lived proteins (autophagy) [93]. ABL proteins regulate multiple processes that are dependent on vesicle trafficking as they prevent EGFR endocytosis/degradation (in 293T and COS7 cells); induce transferrin (in rat hepatocytes) and B-cell receptor endocytosis; induce clustering of acetylcholine receptors at the neuromuscular junction (mouse muscle cells); and regulate phagocytosis [8, 94]. ABL kinases also promote autophagy in alveolar carcinoma cells by inducing lysosome/autophagasome fusion [95]. Moreover, in breast cancer and melanoma cells, ABL kinases facilitate endosome maturation, which promotes trafficking of cathepsins and the NME1 metastasis suppressor (NM23-H1) to the lysosome, where NME1 is subsequently degraded by activated cathepsins [42]. Vesicular trafficking is also critical for protease secretion [93]. In cancer cells, cathepsin protein and mRNA is often dramatically increased, resulting in secretion of excess procathepsins which are subsequently activated in the tumor microenvironment and promote invasion and metastasis by directly and indirectly (e.g. via MMP activaton) degrading the ECM [96]. Importantly, ABL kinases dramatically induce cathepsin expression and secretion by increasing mRNA expression, nuclear translocation and DNA binding activity of key transcription factors (SP1, ETS1, RELA) [40].

Angiogenesis.

The process by which tumors co-opt endothelial cells to produce new blood vessels is a critical step in metastasis. In addition to promoting matrix degradation, and increasing motility, ABL proteins also impact on endothelial function. ABL kinases are activated by bFGF, and ABL inhibition prevents bFGF-induced human umbilical vein endothelial (HUVEC) tube formation [97]. Moreover, HUVEC cells expressing active ABL1 facilitate angiogenesis and subsequent tumor growth when they are co-injected with MDA-MB-231 breast cancer cells in a xenograft model [97]. NRP1, a non-catalytic receptor that binds VEGFR-2, is critical for endothelial cell signaling and angiogenesis. ABL1 forms a complex with NRP1, and NRP1 induces ABL1-mediated phosphorylation of paxillin to promote migration, vessel sprouting, and branching of retinal endothelial cells and retinal angiogenesis in a mouse model [98]. The VEGF-165 isoform, which binds VEGFR-2, has important roles in vascular permeability and vascular leakage, a key feature of tumor vasculature. The NRP1 cytoplasmic domain, promotes vascular leakage in a mouse model of neovascular disease by activating ABL1 within the VEGF-165 isoform complex [99]. Finally, data using conditional ABL1/ABL2 knockout mice demonstrate that the kinases are critical for TIE2/ANG1 -induced endothelial survival and VEGF-induced endothelial cell permeability [100, 101]. Taken together, these data suggest that targeting ABL kinases could potentially reduce angiogenesis and vascular leakage, thereby improving drug delivery to tumors; however, clearly more data in cancer models are needed to substantiate this hypothesis.

Metastasis and Recurrence.

ABL kinases not only promote invasion and EMT, processes critical for cancer progression, but they also drive metastasis, *in vivo*, and are associated with disease recurrence. ABL1 and ABL2 promote lung colonization of melanoma cells via MMP, NME1, and cathepsin-mediated pathways [69, 42, 40]. ABL2 promotes intravasation and spontaneous lung metastasis of MDA-MB-231 breast cancer cells [64]. ABL1 and ABL2 promote breast cancer osteolytic bone metastasis (using a MDA-MB-231 bone metastatic subline) via TAZ (Hippo pathway) and STAT5A signaling pathways that induce MMP-1 and IL-6 secretion [43]. Moreover, ABL1/ABL2 also induce NSCLC metastasis to bone, brain and other organs, and induce extravasation into the lung parenchyma via β-catenin and TAZ signaling pathways [102]. In colon cancer cells, ABL1 auto-activation induced by NOTCH-DAB1 drives metastasis of intestinal tumors in mice lacking *Apc* and *Aes* (an inhibitor of NOTCH signaling) [57]. Phosphorylated ABL1 also was identified as a protein associated with hepatocellular carcinoma early recurrence, using western blotting with primary tumor pools from 80 patients and 192 different antibodies [103]. Moreover, a recent study using a large population-based sample of primary breast cancers (discussed below; currently in-review) demonstrates that low/negative ABL1/ABL2 activities in primary luminal A breast cancers is associated with eventual recurrence/metastasis, and ABL1/ABL2 activities are subsequently elevated in the matched recurrent/metastatic samples [104].

Therapeutic Resistance.

Accumulating evidence suggests that ABL kinase activation drives therapeutic resistance to targeted and cytotoxic agents. In breast cancer, ABL1 promotes resistance to tamoxifen, fulvestrant (downregulates ERα), aromatase inhibitors, lapatinib (EGFR/Her-2 inhibitor), as well as to conventional chemotherapeutics such as doxorubicin [105–108]. Importantly, an ABL1 kinase domain mutation also was identified in a primary breast cancer post-chemotherapy (doxorubicin) sample compared to the pre-treatment sample (ABL1-P253H) [109]. ABL kinase activation also has been linked to radioresistance in head and neck cancer as β1-integrin depletion activates ABL kinases, and combination β1-integrins/ABL targeting induces radiosensitization [110]. Finally, using an unbiased siRNA-based screen, ABL1 also was identified as a determinant of resistance to cetuxumab-mediated antibody-dependent cytotoxicity in epidermoid cancer lines expressing EGFR [111].

Regulation of Downstream Signaling

ABL kinases activate downstream signaling pathways to promote solid tumor proliferation, survival, migration/invasion, and metastasis, and many of these signaling pathways ultimately converge on the induction/activation of transcription factors. These pathways include: STAT3/MMP-1 (melanoma)[69], STAT5/TAZ/IL-6/MMP-1 (breast)[43], TAZ/β-catenin (NSCLC)[102], BRAF/ERK (melanoma)[51], Scar/WAVE/Ena/VASP (breast)[112, 113], cortactin/Arp2/3 (breast) [85], geminin (breast) [70, 71], PLK-1 (cervical) [66], PCNA (breast) [114], SNAIL,TWIST/ZEB1 (breast, melanoma, hepatocellular carcinoma)[80, 90, 84, 91], cathepsin/NME1, (melanoma, breast)[42], SP1/ETS1/NF-κB/cathepsin (melanoma) [40], PKCδ/MMP-2 (hepatocellular carcinoma) [84], p68/β-catenin (prostate, colorectal)

[115, 89], and TRIO-RHOA (colon)[57]. Common mechanisms underlying activation of these pathways are described below.

Regulation of Enzymatic Activity and Complex Formation.

ABL1-dependent phosphorylation of TRIO on Y2681, stimulates its RHOA GEF activity in colon cancer cells *[57].* ABL-dependent RAC/RHO activation also has been identified in breast cancer, and although the mechanisms haven't been established, GEF phosphorylation (SOS, VAV, C3G) is a common mechanism of ABL-dependent RAC/RHO activation in a variety of cell types [62, 116–119]. In addition to influencing enzymatic activity, ABL-dependent phosphorylation also induces the formation of signaling complexes such as those involving WAVE/cortactin/Arp2/3, lamellipodin/Scar/WAVE and lamellipodin/Ena/VASP [81, 85, 86, 77]

Protein Stability.

An emerging ABL-dependent downstream signaling mechanism involves regulation of protein stability. In NSCLC cells, ABL kinases reduce the interaction of TAZ and β-catenin with β-TrCP, an E3 ubiquitin ligase that induces degradation of the transcription factors [102]. In the case of β-catenin, ABL kinases activate AKT, which enhances GSK3β activity, thereby dissolving the destruction complex (AXIN-GSK3β-CK2, etc.), reducing interaction with β-TrCP, and increasing β-catenin stability [102]. ABL1 also phosphorylates and stabilizes geminin and PLK-1; although the mechanisms have not yet been defined [71, 66].

Transcription Factor Expression and DNA Binding Activity.

In addition to altering the protein stability of transcription factors, ABL kinases also induce transcription factor mRNA expression. In breast cancer cells, ABL1/ABL2 induce *TAZ* and *STAT5A* mRNAs, whereas in melanoma cells, they induce *SP1* and *ETS1* mRNAs; however, the mechanisms of upregulation have not yet been established [43, 40]. In some melanoma cells, ABL kinases increase *RELA* mRNA expression via a kinase-independent pathway [6, 120], whereas in other lines ABL1/ABL2 do not alter *RELA* expression, and instead induce its nuclear translocation via a kinase-dependent mechanism [40]. Importantly, the authors also provide the first evidence that ABL1 and ABL2 dramatically increase the DNA binding activities of *SP1, ETS1*, and *RELA* to cathepsin promoters in melanoma cells [40].

Do ABL1 and ABL2 have redundant and/or unique functions in solid tumors?

Due to the similarity in structure of the N-termini and divergence of the C-termini, one would predict that ABL1 and ABL2 may have overlapping as well as unique functions. Unfortunately, most publications to date have focused on either ABL1 or ABL2 and have not examined the role of both proteins in their studies. However, a few studies have queried both proteins and identified unique functions or pathways. For example, ABL2 (but not ABL1) promotes proliferation of some breast cancer cells (BT-549) [49]. However, in other lines (MDA-MB-231), ABL2 (but not ABL1) inhibits proliferation and tumor size, but induces invasion and metastasis by generating actin barbed ends in invadopodia and

stimulating cortactin phosphorylation [85, 64]. Koleske and colleagues suggest that the differences in ABL1 and ABL2 function in invadopodia generation are due to their differential SH2 domain-mediated binding affinities for cortactin [86]. In another report, silencing ABL1 increases ABL2 expression and as a result, does not reduce bone metastasis using a MDA-MB-231 bone metastasis variant [43]. However, an shRNA targeting ABL1 and ABL2 produced better anti-metastatic effects than targeting ABL2 alone and reintroduction of either ABL1 or ABL2 was sufficient to rescue the phenotype [43]. These data indicate critical compensation between ABL1 and ABL2 and highlight the need to investigate the role of both proteins. In melanoma cells, although both ABL1 and ABL2 are required for invasion, they do so via distinct pathways: ABL1 drives STAT3-dependent induction of MMP-1, whereas ABL2 induces MMP-3 and MT1-MMP independent of STAT3 [69].

Tumor Suppressive Roles in Solid Tumors

ABL1 was initially identified as a tumor suppressor based on overexpression studies in COS7, NIH3T3 and Rat-1 cells [121]; however, their oncogenic functions now are well-established [reviewed in [5–8]]. Interestingly, data in solid tumors suggest ABL1 may have oncogenic or tumor suppressive roles depending on the cellular context. Understanding these opposing roles is key to identifying tumor types/subsets that are likely to benefit from anti-ABL therapies.

Prostate Cancer and GBM.

ABL1/2 promote invasion and prostate cancer aggressiveness [46, 115, 122]; however, other data suggest they inhibit progression. For example, upregulation of miR-20a in aggressive prostate cancers promotes migration and invasion of PC-3/DU145 cells by inhibiting ABL2 expression [83]. Likewise, depletion of integrin α3β1 increases RHOA/YAP/TAZ activation and prostate cancer invasion/metastasis by inhibiting ABL1/ABL2 signaling [123]. Similarly, although ABL1 activation promotes invasion in some GBM models [52], permanent silencing of ABL1 in PC-3 cells increases invasiveness, although it also simultaneously inhibits proliferation, tumor growth, and stem cell features [67]. Thus, ABL kinases may promote or inhibit invasion depending on the signal and may act to switch cells between invasive and proliferative states.

Breast Cancer.

Despite overwhelming evidence that ABL kinases promote breast cancer development and progression [48, 43, 71, 124, 81, 42, 54, 56, 125, 65, 114, 106, 70, 87, 63], there also is a growing body of evidence suggesting they also may have tumor suppressive roles, in some instances. For example, EphB4 activation of ABL kinases inhibits MDA-MB-435 proliferation, invasion and tumor growth (using imatinib)[126]. Similarly, overexpression of the Ras effector protein Rin1, an ABL1 activator, suppresses MDA-MB-231 invasiveness, and expression of a mutant form that inhibits ABL1 function, cannot suppress invasion [127]. These results contrast with reports showing that silencing ABL1/ABL2 prevents MDA-MB-231 cell invasion [87, 81, 128, 56], and EphB4 activation of ABL kinases in human embryonic neural stem cells promotes self-renewal and proliferation [129]. These

data are consistent with the notion that ABL kinases promote proliferation/invasion downstream of factors that induce these processes and inhibit proliferation/invasion in response to molecules that oppose these processes, thus, likely integrating the signals [69]. Interestingly, silencing ABL2 (ABL1 was not investigated) increases proliferation and MDA-MB-231 xenograft tumor size but prevents invasion/metastasis [64], similar to the opposing functions described above for ABL1 in GBM cells [67]. Thus, ABL kinases also may regulate the switch between proliferative and invasive states to facilitate motility and prevent proliferation during EMT, and induce proliferation and suppress motility once cells arrive at the metastatic site (MET)[69].

Indeed, ABL kinases promote EMT in response to some signals (described earlier) and induce MET in other instances. For example, Schiemman and colleagues demonstrate that inhibition of ABL kinases in nontumorigenic, murine NuMG cells paradoxically promotes EMT, whereas expression of a constitutively activated ABL1 form, in mesenchymal murine 4T1 breast cancer cells, induces MET [130]. Moreover, in a subsequent report, the authors show that expression of constitutively active ABL1 in 4T1 cells induces TGF-β secretion and subsequent reactivation/expression of TP53 (p53), and low levels of *ABL1* mRNA were associated with reduced relapse-free survival in basal-like breast cancer patients [131]. These results contrast with other data demonstrating that high *ABL1* mRNA levels correlate with bone metastases [43], and ABL1/ABL2 kinase activities (assessed using immunohistochemistry-IHC and phospho-CRKL antibody; read-out of activity)[42, 69] are increased in basal-like breast cancers as compared to other subtypes [42]. In a follow-up study, Schiemann and colleagues found that ABL1 is predominantly nuclear and acts as a tumor suppressor in breast cancer cells harboring wild-type p53 (e.g. luminal A MCF-7 cells), and is cytoplasmic and oncogenic in p53 mutant cells (e.g. basal-like MDA-MB-231 cells)[48, 132]. Moreover, expression of TTK, which causes ABL1 cytoplasmic retention [58], is reduced in MCF-7 cells and elevated in MDA-MB-231 cells, and expression of TTK into MCF-7 cells induces 3D growth, whereas TTK knockout in MDA-MB-231 cells inhibits 3D growth and sensitizes cells to DPH- (activates ABL1) induced growth inhibition [132]. The authors indicate that these differences between the subtypes are likely mediated by p53, and suggest that nuclear ABL1 acts as a tumor suppressor in p53-wild-type breast cancers (luminal A) and cytoplasmic ABL1 is oncogenic in p53-mutant breast cancers (basal-like) [132]. However, p53 was not definitively linked to TTK/14-3-3-mediated cytoplasmic retention of ABL1 [132].

A manuscript currently under review also demonstrates striking differences between ABL kinase activities in ER^+/PR^+ and triple-negative subtypes. The researchers tested whether ABL kinase activities are altered during breast cancer progression using a population-based sample of breast cancer cases (patients diagnosed/treated from 2000–2007; n=475) [104]. Interestingly, ABL1/ABL2 activities (pCRKL, IHC), were low/negative in ER^+/PR^+ tumors (at the time of diagnosis) from patients who eventually developed a recurrence/metastasis as compared to primary tumors (at diagnosis) from patients who did not recur [104]. Moreover, ABL1/ABL2 activities were dramatically elevated in the matched recurrent samples [104]. In contrast, in the basal-like, triple-negative subtype, there was a trend towards elevated ABL1/ABL2 activities in the primary tumors from patients that recurred as compared to those that did not recur, and ABL1/ABL2 activities were further increased in 3/4 recurrent/

metastatic samples. These data indicate that early in the disease process, ABL kinases likely induce EMT in the basal-like subtype but prevent EMT in the ER^+/PR^+ subtype. Moreover, once cells have reached the metastatic/recurrent site, ABL1/ABL2 activation is likely critical for proliferation/survival of both subtypes. Future experiments are needed to determine whether p53 status and ABL1 subcellular localization drive the differences observed between the subtypes. Moreover, additional studies are needed to confirm the exciting possibility that low/negative pCRKL staining in ER^+/PR^+ tumors (or high pCRKL staining in basal-like tumors) are biomarkers for breast cancer recurrence.

Clinical Targeting in Solid Tumors.

Although ABL inhibitors are utilized in solid tumors to block activation of other targets such as KIT, PDGFR, or SFKs; only a few clinical trials have been initiated with the purpose of specifically targeting ABL kinases. ABL001 is being tested for patients with advanced solid tumors (NCT03292783); cetuximab+nilotinib has been initiated for colon cancer (NCT01871311); and nilotinib+paclitaxel (NCT02379416) is being tested for patients with relapsed solid tumors. However, unfortunately, these trials have not limited participation to patients with tumors expressing activated ABL kinases. It isn't possible to accurately assess the efficacy of targeting ABL kinases, without using a targeted patient population, since tumors lacking ABL kinase activation are unlikely to respond (or may respond in an opposite manner), and ABL kinases are not activated in all tumors of a particular type. A Phase I/II trial using imatinib+panitumumab (EGFR inhibitor) did allocate patients to the study arm on the basis of activation/phosphorylation of imatinib (1^{st} generation TKI) targets using reverse phase protein microarray (RPPA) on laser capture microdissected samples [133]. Although the trial was small, and no benefit was noted, it does provide a methodology for identifying a targeted population [133].

Conclusions

Emerging evidence indicates that ABL kinases play important roles in solid tumors, and drive tumor proliferation and metastasis. Since numerous drugs targeting ABL kinases are either FDA-approved or are in clinical development for leukemia, repurposing these drugs for use in solid tumors is extremely attractive. However, since ABL kinases may serve as key nodes that integrate pro -and anti-proliferative and as well as EMT/MET states in some tumor types (e.g. breast cancer, GBM), more research is needed to understand their roles in these opposing processes. Over the past year, significant progress has been made towards this goal; however, additional studies clearly are needed. Moreover, biomarkers are required to define patient populations that may benefit from anti-ABL therapy, such as phosphorylation of key downstream targets (e.g. pCRKL) protein upregulation (if sufficient to drive the disease), ABL1/ABL2 mRNA signature, or development of highly specific anti-ABL1/ABL2 phospho-specific antibodies (current available antibodies crossreact with RTKs).

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References:

1. Plattner R, Irvin BJ, Guo S, Blackburn K, Kazlauskas A, Abraham RT et al. A New Link Between the c-Abl Tyrosine Kinase and Phosphoinositide Signaling via PLC-g1. Nat Cell Biol 2003;5(4): 309–19. [PubMed: 12652307]
2. Plattner R, Kadlec L, DeMali KA, Kazlauskas A, Pendergast AM. c-Abl is activated by growth factors and Src family kinases and has a role in the cellular response to PDGF. Genes Dev 1999;13(18):2400–11. [PubMed: 10500097]
3. Plattner R, Pendergast AM. Activation and signaling of the Abl tyrosine kinase: bidirectional link with phosphoinositide signaling. Cell Cycle 2003;2(4):273–4. [PubMed: 12851468]
4. Sirvent A, Benistant C, Roche S. Cytoplasmic signalling by the c-Abl tyrosine kinase in normal and cancer cells. Biol Cell 2008;100(11):617–31. [PubMed: 18851712]
5. Greuber EK, Smith-Pearson P, Wang J, Pendergast AM. Role of ABL family kinases in cancer: from leukaemia to solid tumours. Nat Rev Cancer 2013;13(8):559–71. doi:10.1038/nrc3563 nrc3563 [pii]. [PubMed: 23842646]
6. Ganguly SS, Plattner R. Activation of Abl family kinases in solid tumors. Genes Cancer 2012;3(5–6):414–25. doi:10.1177/1947601912458586 10.1177_1947601912458586 [pii]. [PubMed: 23226579]
7. Wang J, Pendergast AM. The Emerging Role of ABL Kinases in Solid Tumors. Trends Cancer 2015;1(2):110–23. doi:10.1016/j.trecan.2015.07.004. [PubMed: 26645050]
8. Khatri A, Wang J, Pendergast AM. Multifunctional Abl kinases in health and disease. J Cell Sci 2016;129(1):9–16. doi:10.1242/jcs.175521. [PubMed: 26729027]
9. Miller AL, Wang Y, Mooseker MS, Koleske AJ. The Abl-related gene (Arg) requires its F-actin-microtubule cross-linking activity to regulate lamellipodial dynamics during fibroblast adhesion. J Cell Biol 2004;165(3):407–19. [PubMed: 15138293]
10. Lamontanara AJ, Georgeon S, Tria G, Svergun DI, Hantschel O. The SH2 domain of Abl kinases regulates kinase autophosphorylation by controlling activation loop accessibility. Nat Commun 2014;5:5470. doi:10.1038/ncomms6470. [PubMed: 25399951]
11. Wang JY The capable ABL: what is its biological function? Mol Cell Biol 2014;34(7):1188–97. doi:10.1128/MCB.01454-13. [PubMed: 24421390]
12. Plattner R, Koleske AJ, Kazlauskas A, Pendergast AM. Bidirectional Signaling Links the Abelson Kinases to the Platelet-Derived Growth Factor Receptor. Mol Cell Biol 2004;24(6):2573–83. [PubMed: 14993293]
13. Tokonzaba E, Capelluto DG, Kutateladze TG, Overduin M. Phosphoinositide, phosphopeptide and pyridone interactions of the Abl SH2 domain. Chem Biol Drug Des 2006;67(3):230–7. doi: 10.1111/j.1747-0285.2006.00361.x. [PubMed: 16611216]
14. Dai Z, Pendergast AM. Abi-2, a novel SH3-containing protein interacts with the c-Abl tyrosine kinase and modulates c-Abl transforming activity. Genes Dev 1995;9(21):2569–82. [PubMed: 7590236]
15. Shi Y, Alin K, Goff S. Abl-interactor-1, a novel SH3 protein binding to the carboxy -terminal portion of the Abl protein, suppressed v-Abl transforming activity. Genes Dev 1995;9:2583–97. [PubMed: 7590237]
16. Lin J, Sun T, Ji L, Deng W, Roth J, Minna J et al. Oncogenic activation of c-Abl in non-small cell lung cancer cells lacking FUS1 expression: inhibition of c-Abl by the tumor suppressor gene product Fus1. Oncogene 2007;26(49):6989–96. [PubMed: 17486070]
17. Wen ST, Van Etten RA. The PAG gene product, a stress-induced protein with antioxidant properties, is an Abl SH3-binding protein and a physiological inhibitor of c -Abl tyrosine kinase activity. Genes Dev 1997;11:2456–67. [PubMed: 9334312]
18. Colicelli J ABL tyrosine kinases: evolution of function, regulation, and specificity. Sci Signal 2010;3(139):re6. doi:scisignal.3139re6 [pii] 10.1126/scisignal.3139re6.
19. Zheng W, Lennartsson J, Hendriks W, Heldin CH, Hellberg C. The LAR protein tyrosine phosphatase enables PDGF beta-receptor activation through attenuation of the c-Abl kinase activity. Cell Signal 2011;23(6):1050–6. doi:S0898–6568(11)00037–4 [pii] 10.1016/j.cellsig. 2011.01.024. [PubMed: 21300149]

20. Cong F, Spenser S, Cote JF, Wu Y, Tremblay ML, Lasky LA et al. Cytoskeletal protein PSTPIP1 directs the PEST-type protein tyrosine phosphatase to the c-Abl kinase to mediate Abl dephosphorylation. Mol Cell 2000;6:1413–23. [PubMed: 11163214]

21. Brasher BB, Van Etten RA. c-Abl has high intrinsic tyrosine kinase activity that is stimulated by mutation of the Src homology 3 domain and by autophosphorylation at two distinct regulatory tyrosines. J Biol Chem 2000;275(45):35631–7. [PubMed: 10964922]

22. Taagepera S, McDonald D, Loeb JE, Whitaker LL, McElroy AK, Wang JYJ et al. Nuclear-cytoplasmic shuttling of c-Abl tyrosine kinase. Proc Natl Acad Sci USA 1998;95:7457–62. [PubMed: 9636171]

23. Vigneri P, Wang JY. Induction of apoptosis in chronic myelogenous leukemia cells through nuclear entrapment of BCR-ABL tyrosine kinase. Nat Med 2001;7(2):228–34. [PubMed: 11175855]

24. Yi CR, Rosenberg N. Gag influences transformation by Abelson murine leukemia virus and suppresses nuclear localization of the v-Abl protein. J Virol 2007;81(17):9461–8. doi:10.1128/JVI.00735-07. [PubMed: 17596313]

25. Furstoss O, Dorey K, Simon V, Barila D, Superti-Furga G, Roche S. c-Abl is an effector of Src for growth factor-induced c-*myc* expression and DNA synthesis. EMBO J 2002;21(4):514–24. [PubMed: 11847100]

26. Soverini S, De Benedittis C, Papayannidis C, Paolini S, Venturi C, Iacobucci I et al. Drug resistance and BCR-ABL kinase domain mutations in Philadelphia chromosome -positive acute lymphoblastic leukemia from the imatinib to the second-generation tyrosine kinase inhibitor era: The main changes are in the type of mutations, but not in the frequency of mutation involvement. Cancer 2014;120(7):1002–9. doi:10.1002/cncr.28522. [PubMed: 24382642]

27. Patel AB, O'Hare T, Deininger MW. Mechanisms of Resistance to ABL Kinase Inhibition in Chronic Myeloid Leukemia and the Development of Next Generation ABL Kinase Inhibitors. Hematol Oncol Clin North Am 2017;31(4):589–612. doi:10.1016/j.hoc.2017.04.007. [PubMed: 28673390]

28. Choi HG, Ren P, Adrian F, Sun F, Lee HS, Wang X et al. A type-II kinase inhibitor capable of inhibiting the T315I "gatekeeper" mutant of Bcr-Abl. J Med Chem 2010;53(15):5439–48. doi:10.1021/jm901808w. [PubMed: 20604564]

29. Lu X, Zhang Z, Ren X, Pan X, Wang D, Zhuang X et al. Hybrid pyrimidine alkynyls inhibit the clinically resistance related Bcr-Abl(T315I) mutant. Bioorg Med Chem Lett 2015;25(17):3458–63. doi:10.1016/j.bmcl.2015.07.006. [PubMed: 26195136]

30. Choi Y, Seeliger MA, Panjarian SB, Kim H, Deng X, Sim T et al. N-myristoylated c -Abl tyrosine kinase localizes to the endoplasmic reticulum upon binding to an allosteric inhibitor. J Biol Chem 2009;284(42):29005–14. doi:10.1074/jbc.M109.026633 M109.026633 [pii]. [PubMed: 19679652]

31. Deng X, Okram B, Ding Q, Zhang J, Choi Y, Adrian FJ et al. Expanding the diversity of allosteric bcr-abl inhibitors. J Med Chem 2010;53(19):6934–46. doi:10.1021/jm100555f. [PubMed: 20828158]

32. Kim HJ, Yoon HJ, Choi JY, Lee IK, Kim SY. The tyrosine kinase inhibitor GNF-2 suppresses osteoclast formation and activity. J Leukoc Biol 2014;95(2):337–45. doi:10.1189/jlb.0713356 jlb.0713356 [pii]. [PubMed: 24130113]

33. Zhang J, Adrian FJ, Jahnke W, Cowan-Jacob SW, Li AG, Iacob RE et al. Targeting Bcr-Abl by combining allosteric with ATP-binding-site inhibitors. Nature 2010;463(7280):501–6. doi:10.1038/nature08675 nature08675 [pii]. [PubMed: 20072125]

*34. Wylie AA, Schoepfer J, Jahnke W, Cowan-Jacob SW, Loo A, Furet P et al. The allosteric inhibitor ABL001 enables dual targeting of BCR-ABL1. Nature 2017;543(7647):733–7. doi:10.1038/nature21702 nature21702 [pii]. This manuscript describes the development of a new ABL allosteric inhibitor, ABL001 [PubMed: 28329763]

35. Lee BJ, Shah NP. Identification and characterization of activating ABL1 1b kinase mutations: impact on sensitivity to ATP-competitive and allosteric ABL1 inhibitors. Leukemia 2017;31(5):1096–107. doi:10.1038/leu.2016.353. [PubMed: 27890928]

36. Gupta S, Li J, Kemeny G, Bitting RL, Beaver J, Somarelli JA et al. Whole Genomic Copy Number Alterations in Circulating Tumor Cells from Men with Abiraterone or Enzalutamide-Resistant

Metastatic Castration-Resistant Prostate Cancer. Clin Cancer Res 2017;23(5):1346–57. doi: 10.1158/1078-0432.CCR-16-1211. [PubMed: 27601596]

37. Pichler R, Fritz J, Tulchiner G, Klinglmair G, Soleiman A, Horninger W et al. Increased accuracy of a novel mRNA-based urine test for bladder cancer surveillance. BJU Int 2018;121(1):29–37. doi:10.1111/bju.14019. [PubMed: 28941000]
38. Wallace E, Higuchi R, Satya M, McCann L, Sin MLY, Bridge JA et al. Development of a 90-Minute Integrated Noninvasive Urinary Assay for Bladder Cancer Detection. J Urol 2017. doi: 10.1016/j.juro.2017.09.141.
39. Pendergast AM, Muller AJ, Havlik MH, Clark R, McCormick F, Witte ON. Evidence for regulation of the human ABL tyrosine kinase by a cellular inhibitor. Proc Natl Acad Sci U S A 1991;88(13):5927–31. [PubMed: 1712111]
*40. Tripathi R, Fiore LS, Richards DL, Yang Y, Liu J, Wang C et al. Abl and Arg mediate cysteine cathepsin secretion to facilitate melanoma invasion and metastasis. Sci Signal 2018;11(518). doi: 10.1126/scisignal.aao0422. This paper shows that ABL kinases induce cathepsin secretion by inducing expression, nuclear translocation and DNA binding of SP1, ETS1, and RELA transcription factors, and additionally, that ABL kinases promote invasion and lung metastasis by inducing cathepsin secretion.
41. Xing QT, Qu CM, Wang G. Overexpression of Abl2 predicts poor prognosis in heptocellular carcinomas and is associated with cancer cell migration and invasion. Onco Targets Ther 2014;7:881–5. doi:10.2147/OTT.S62348. [PubMed: 24940071]
42. Fiore LS, Ganguly S, Sledziona J, Cibull ML, Wang C, Richards DL et al. c-Abl and Arg induce cathepsin-mediated lysosomal degradation of the NM23-H1 metastasis suppressor in invasive cancer. Oncogene 2014;33(36):4508–20. [PubMed: 24096484]
43. Wang J, Rouse C, Jasper JS, Pendergast AM. ABL kinases promote breast cancer osteolytic metastasis by modulating tumor-bone interactions through TAZ and STAT5 signaling. Sci Signal 2016;9(413):ra12. doi:10.1126/scisignal.aad3210 9/413/ra12 [pii].
44. Sun Y, Chen C, Zhang P, Xie H, Hou L, Hui Z et al. Reduced miR-3127–5p expression promotes NSCLC proliferation/invasion and contributes to dasatinib sensitivity via the c-Abl/Ras/ERK pathway. Sci Rep 2014;4:6527. doi:10.1038/srep06527. [PubMed: 25284075]
45. Qin X, Wan Y, Wang S, Xue M. MicroRNA-125a-5p modulates human cervical carcinoma proliferation and migration by targeting ABL2. Drug Des Devel Ther 2016;10:71–9. doi:10.2147/DDDT.S93104.
46. Arora S, Saini S, Fukuhara S, Majid S, Shahryari V, Yamamura S et al. MicroRNA −4723 inhibits prostate cancer growth through inactivation of the Abelson family of nonreceptor protein tyrosine kinases. PLoS One 2013;8(11):e78023. doi:10.1371/journal.pone.0078023 PONE-D-13–21956 [pii]. [PubMed: 24223753]
47. Srinivasan D, Kaetzel DM, Plattner R. Reciprocal regulation of Abl and receptor tyrosine kinases. Cell Signal 2009;21(7):1143–50. [PubMed: 19275932]
48. Srinivasan D, Plattner R. Activation of Abl tyrosine kinases promotes invasion of aggressive breast cancer cells. Cancer Res 2006;66(11):5648–55. [PubMed: 16740702]
49. Srinivasan D, Sims JT, Plattner R. Aggressive breast cancer cells are dependent on activated Abl kinases for proliferation, anchorage-independent growth and survival. Oncogene 2008;27(8):1095–105. [PubMed: 17700528]
50. An R, Wang Y, Voeller D, Gower A, Kim IK, Zhang YW et al. CRKL mediates EML4 -ALK signaling and is a potential therapeutic target for ALK-rearranged lung adenocarcinoma. Oncotarget 2016;7(20):29199–210. doi:10.18632/oncotarget.8638. [PubMed: 27078848]
**51. Jain A, Tripathi R, Turpin CP, Wang C, Plattner R. Abl kinase regulation by BRAF/ERK and cooperation with Akt in melanoma. Oncogene 2017;36(32):4585–96. doi:10.1038/onc.2017.76. This publication demonstrates that mutant BRAF plays a role in ABL kinase activation in melanoma, and shows that ABL kinases play critical roles in BRAF-mediated proliferation and invasion and induce an EMT transcription factor switch. [PubMed: 28368422]
**52. Kumar S, Lu B, Dixit U, Hossain S, Liu Y, Li J et al. Reciprocal regulation of Abl kinase by Crk Y251 and Abi1 controls invasive phenotypes in glioblastoma. Oncotarget 2015;6(35):37792–807. doi:10.18632/oncotarget.6096. This manuscript demonstrates that the ABL negative regulator,

Abi-1, competes with the ABL downstream substrate, CRK in GBM cells, and thus GBMs harboring low levels of Abi1 and high levels of phosphorylated CRK may serve as a biomarker for GBMs that likely respond to imatinib. [PubMed: 26473374]

53. Zhao H, Chen MS, Lo YH, Waltz SE, Wang J, Ho PC et al. The Ron receptor tyrosine kinase activates c-Abl to promote cell proliferation through tyrosine phosphorylation of PCNA in breast cancer. Oncogene 2014;33(11):1429–37. doi:10.1038/onc.2013.84. [PubMed: 23542172]
54. Li R, Knight JF, Park M, Pendergast AM. Abl Kinases Regulate HGF/Met Signaling Required for Epithelial Cell Scattering, Tubulogenesis and Motility. PLoS One 2015;10(5):e0124960. doi: 10.1371/journal.pone.0124960 PONE-D-15-01659 [pii]. [PubMed: 25946048]
55. Hung AC, Lo S, Hou MF, Lee YC, Tsai CH, Chen YY et al. Extracellular Visfatin -Promoted Malignant Behavior in Breast Cancer Is Mediated Through c-Abl and STAT3 Activation. Clin Cancer Res 2016;22(17):4478–90. doi:10.1158/1078-0432.CCR-15-2704. [PubMed: 27036136]
56. Genna A, Lapetina S, Lukic N, Twafra S, Meirson T, Sharma VP et al. Pyk2 and FAK differentially regulate invadopodia formation and function in breast cancer cells. J Cell Biol 2018;217(1):375–95. doi:10.1083/jcb.201702184. [PubMed: 29133485]
**57. Sonoshita M, Itatani Y, Kakizaki F, Sakimura K, Terashima T, Katsuyama Y et al. Promotion of colorectal cancer invasion and metastasis through activation of NOTCH -DAB1-ABL-RHOGEF protein TRIO. Cancer Discov 2015;5(2):198–211. doi:10.1158/2159-8290.CD-14-0595. This paper identifies a novel pathway in colon cancer cells by demonstrating that NOTCH-DAB1 causes auto-activation of ABL1, which then promotes colorectal cancer invasion and metastasis, *in vitro*, and *in vivo* by activating the RHOA GEF, TRIO. [PubMed: 25432929]
58. Yoshida K, Yamaguchi T, Natsume T, Kufe D, Miki Y. JNK phosphorylation of 14–3-3 proteins regulates nuclear targeting of c-Abl in the apoptotic response to DNA damage. Nat Cell Biol 2005;7(3):278–85. [PubMed: 15696159]
**59. Testoni E, Stephenson NL, Torres Ayuso P, Marusiak AA, Trotter EW, Hudson A et al. Somatically mutated ABL1 is an actionable and essential NSCLC survival gene. EMBO Mol Med 2016;8(2):105–16. doi:10.15252/emmm.201505456. This is the first demonstration that ABL1 mutations identified in primary tumors or solid tumor cell lines are driver mutations. [PubMed: 26758680]
60. Nix NM, Brown KS. Ceritinib for ALK-Rearrangement-Positive Non-Small Cell Lung Cancer. J Adv Pract Oncol 2015;6(2):156–60. [PubMed: 26649248]
61. Matt S, Hofmann TG. The DNA damage-induced cell death response: a roadmap to kill cancer cells. Cell Mol Life Sci 2016;73(15):2829–50. doi:10.1007/s00018-016-2130-4. [PubMed: 26791483]
62. Sirvent A, Boureux A, Simon V, Leroy C, Roche S. The tyrosine kinase Abl is required for Src-transforming activity in mouse fibroblasts and human breast cancer cells. Oncogene 2007;26(52): 7313–23. [PubMed: 17533370]
63. He X, Zheng Z, Song T, Wei C, Ma H, Ma Q et al. c-Abl regulates estrogen receptor alpha transcription activity through its stabilization by phosphorylation. Oncogene 2010;29(15):2238–51. doi:onc2009513 [pii] 10.1038/onc.2009.513. [PubMed: 20101225]
64. Gil-Henn H, Patsialou A, Wang Y, Warren MS, Condeelis JS, Koleske AJ. Arg/Abl2 promotes invasion and attenuates proliferation of breast cancer in vivo. Oncogene 2013;32(21):2622–30. doi:10.1038/onc.2012.284 onc2012284 [pii]. [PubMed: 22777352]
65. Wang YL, Overstreet AM, Chen MS, Wang J, Zhao HJ, Ho PC et al. Combined inhibition of EGFR and c-ABL suppresses the growth of triple-negative breast cancer growth through inhibition of HOTAIR. Oncotarget 2015;6(13):11150–61. doi:3441 [pii] 10.18632/oncotarget.3441. [PubMed: 25883211]
*66. Yang X, Chen G, Li W, Peng C, Zhu Y, Yang X et al. Cervical Cancer Growth Is Regulated by a c-ABL-PLK1 Signaling Axis. Cancer Res 2017;77(5):1142–54. doi: 10.1158/0008-5472.CAN-16-1378. This manuscript demonstrates that ABL1 regulates proliferation of cervical cancer cells by promoting the stabilization of PLK-1 an essential regulator of microtubule dynamics. [PubMed: 27899378]
67. Lamballe F, Toscano S, Conti F, Arechederra M, Baeza N, Figarella-Branger D et al. Coordination of signalling networks and tumorigenic properties by ABL in glioblastoma cells. Oncotarget 2016;7(46):74747–67. doi:10.18632/oncotarget.12546. [PubMed: 27732969]

68. Furlan A, Stagni V, Hussain A, Richelme S, Conti F, Prodosmo A et al. Abl interconnects oncogenic Met and p53 core pathways in cancer cells. Cell Death Differ 2011;18(10):1608–16. doi:cdd201123 [pii] 10.1038/cdd.2011.23. [PubMed: 21455220]

69. Ganguly SS, Fiore LS, Sims JT, Friend JW, Srinivasan D, Thacker MA et al. c-Abl and Arg are activated in human primary melanomas, promote melanoma cell invasion via distinct pathways, and drive metastatic progression. Oncogene 2012;31(14):1804 −16. [PubMed: 21892207]

70. Ananthula S, Sinha A, El Gassim M, Batth S, Marshall GD, Jr., Gardner LH et al. Geminin overexpression-dependent recruitment and crosstalk with mesenchymal stem cells enhance aggressiveness in triple negative breast cancers. Oncotarget 2016;7(15):20869–89. doi:10.18632/oncotarget.8029. [PubMed: 26989079]

71. Blanchard Z, Mullins N, Ellipeddi P, Lage JM, McKinney S, El-Etriby R et al. Geminin overexpression promotes imatinib sensitive breast cancer: a novel treatment approach for aggressive breast cancers, including a subset of triple negative. PLoS One 2014;9(4):e95663. doi:10.1371/journal.pone.0095663. [PubMed: 24789045]

72. El Sayed SM, Mahmoud AA, El Sawy SA, Abdelaal EA, Fouad AM, Yousif RS et al. Warburg effect increases steady-state ROS condition in cancer cells through decreasing their antioxidant capacities (anticancer effects of 3-bromopyruvate through antagonizing Warburg effect). Med Hypotheses 2013;81(5):866–70. doi:10.1016/j.mehy.2013.08.024. [PubMed: 24071366]

**73. Sourbier C, Ricketts CJ, Matsumoto S, Crooks DR, Liao PJ, Mannes PZ et al. Targeting ABL1-mediated oxidative stress adaptation in fumarate hydratase-deficient cancer. Cancer Cell 2014;26(6):840–50. doi:10.1016/j.ccell.2014.10.005 S1535-6108(14)00409-7 [pii]. This paper is the first to link ABL kinase activation to metabolic reprogramming in solid tumor cells. They show that fumurate accumulation activates ABL1 which promotes aerobic glycolysis by inducing a mTOR-HIF1α pathway and induces NRF2, which protects cells from ROS-induced injury. [PubMed: 25490448]

74. Huang T, Zhou F, Wang-Johanning F, Nan K, Wei Y. Depression accelerates the development of gastric cancer through reactive oxygen speciesactivated ABL1 (Review). Oncol Rep 2016;36(5):2435–43. doi:10.3892/or.2016.5127. [PubMed: 27666407]

75. Dong Q, Li C, Qu X, Cao C, Liu X. Global Regulation of Differential Gene Expression by c-Abl/Arg Oncogenic Kinases. Med Sci Monit 2017;23:2625–35. [PubMed: 28555614]

76. Li R, Pendergast AM. Arg kinase regulates epithelial cell polarity by targeting beta1 -integrin and small GTPase pathways. Curr Biol 2011;21(18):1534–42. doi:S0960 −9822(11)00899–2 [pii] 10.1016/j.cub.2011.08.023. [PubMed: 21906945]

77. Courtemanche N, Gifford SM, Simpson MA, Pollard TD, Koleske AJ. Abl2/Abl -related gene stabilizes actin filaments, stimulates actin branching by actin-related protein 2/3 complex, and promotes actin filament severing by cofilin. J Biol Chem 2015;290(7):4038–46. doi:10.1074/jbc.M114.608117. [PubMed: 25540195]

78. Stuart JR, Gonzalez FH, Kawai H, Yuan ZM. C-ABL interacts with the wave2 signaling complex to induce membrane ruffling and cell spreading. J Biol Chem 2006.

79. Leng Y, Zhang J, Badour K, Arpaia E, Freeman S, Cheung P et al. Abelson -interactor-1 promotes WAVE2 membrane translocation and Abelson-mediated tyrosine phosphorylation required for WAVE2 activation. Proc Natl Acad Sci U S A 2005;102(4):1098–103. doi:10.1073/pnas.0409120102. [PubMed: 15657136]

80. Bryce NS, Reynolds AB, Koleske AJ, Weaver AM. WAVE2 regulates epithelial morphology and cadherin isoform switching through regulation of Twist and Abl. PLoS One 2013;8(5):e64533. doi:10.1371/journal.pone.0064533 PONE-D-11-07007 [pii]. [PubMed: 23691243]

81. Carmona G, Perera U, Gillett C, Naba A, Law AL, Sharma VP et al. Lamellipodin promotes invasive 3D cancer cell migration via regulated interactions with Ena/VASP and SCAR/WAVE. Oncogene 2016;35(39):5155–69. doi:10.1038/onc.2016.47. [PubMed: 26996666]

82. Zhang C, Yang C, Wang R, Jiao Y, Ampah KK, Wang X et al. c-Abl Kinase Is a Regulator of alphabeta Integrin Mediated Melanoma A375 Cell Migration. PLoS One 2013;8(6):e66108. doi:10.1371/journal.pone.0066108 PONE-D-13-06227 [pii]. [PubMed: 23805201]

83. Qiang XF, Zhang ZW, Liu Q, Sun N, Pan LL, Shen J et al. miR-20a promotes Prostate cancer invasion and migration through targeting ABL2. J Cell Biochem 2014. doi:10.1002/jcb.24778.

84. Yoon CH, Kim MJ, Park MJ, Park IC, Hwang SG, An S et al. Claudin-1 acts through c-Abl-protein kinase Cdelta (PKCdelta) signaling and has a causal role in the acquisition of invasive capacity in human liver cells. J Biol Chem 2010;285(1):226–33. doi:M109.054189 [pii] 10.1074/jbc.M109.054189. [PubMed: 19897486]
85. Mader CC, Oser M, Magalhaes MA, Bravo-Cordero J, Condeelis JS, Koleske AJ et al. An EGFR-Src-Arg-cortactin pathway mediates functional maturation of invadopodia and breast cancer cell invasion. Cancer Res 2011;71(5):1730–41. doi:0008–5472.CAN −10–1432 [pii] 10.1158/0008–5472.CAN-10–1432. [PubMed: 21257711]
86. Gifford SM, Liu W, Mader CC, Halo TL, Machida K, Boggon TJ et al. Two amino acid residues confer different binding affinities of Abelson family kinase SRC homology 2 domains for phosphorylated cortactin. J Biol Chem 2014;289(28):19704–13. doi:10.1074/jbc.M114.556480. [PubMed: 24891505]
87. Smith-Pearson PS, Greuber EK, Yogalingam G, Pendergast AM. Abl kinases are required for invadopodia formation and chemokine-induced invasion. J Biol Chem 2010;285(51):40201–11. doi:M110.147330 [pii] 10.1074/jbc.M110.147330. [PubMed: 20937825]
88. Mittal V Epithelial Mesenchymal Transition in Tumor Metastasis. Annu Rev Pathol 2018;13:395–412. doi:10.1146/annurev-pathol-020117-043854. [PubMed: 29414248]
89. Yang L, Lin C, Liu ZR. P68 RNA helicase mediates PDGF-induced epithelial mesenchymal transition by displacing Axin from beta-catenin. Cell 2006;127(1):139–55. doi:S0092–8674(06)01158–5 [pii] 10.1016/j.cell.2006.08.036. [PubMed: 17018282]
90. Suh Y, Yoon CH, Kim RK, Lim EJ, Oh YS, Hwang SG et al. Claudin-1 induces epithelial-mesenchymal transition through activation of the c-Abl-ERK signaling pathway in human liver cells. Oncogene 2013;32(41):4873–82. doi:10.1038/onc.2012.505. [PubMed: 23160379]
91. Vandamme N, Berx G. Melanoma cells revive an embryonic transcriptional network to dictate phenotypic heterogeneity. Front Oncol 2014;4:352. doi:10.3389/fonc.2014.00352. [PubMed: 25538895]
92. Caramel J, Papadogeorgakis E, Hill L, Browne GJ, Richard G, Wierinckx A et al. A switch in the expression of embryonic EMT-inducers drives the development of malignant melanoma. Cancer Cell 2013;24(4):466–80. doi:10.1016/j.ccr.2013.08.018 S1535-6108(13)00364-4 [pii]. [PubMed: 24075834]
93. Turk V, Stoka V, Vasiljeva O, Renko M, Sun T, Turk B et al. Cysteine cathepsins: from structure, function and regulation to new frontiers. Biochim Biophys Acta 2012;1824(1):68–88. doi:10.1016/j.bbapap.2011.10.002 S1570-9639(11)00270-6 [pii]. [PubMed: 22024571]
94. Cao H, Schroeder B, Chen J, Schott MB, McNiven MA. The Endocytic Fate of the Transferrin Receptor Is Regulated by c-Abl Kinase. J Biol Chem 2016;291(32):16424 −37. doi:10.1074/jbc.M116.724997. [PubMed: 27226592]
95. Yogalingam G, Pendergast AM. Abl kinases regulate autophagy by promoting the trafficking and function of lysosomal components. J Biol Chem 2008;283(51):35941–53. doi:M804543200 [pii] 10.1074/jbc.M804543200. [PubMed: 18945674]
96. Olson OC, Joyce JA. Cysteine cathepsin proteases: regulators of cancer progression and therapeutic response. Nat Rev Cancer 2015;15(12):712–29. doi:10.1038/nrc4027 nrc4027 [pii]. [PubMed: 26597527]
97. Yan W, Bentley B, Shao R. Distinct angiogenic mediators are required for basic fibroblast growth factor -and vascular endothelial growth factor-induced angiogenesis: the role of cytoplasmic tyrosine kinase c-Abl in tumor angiogenesis. Mol Biol Cell 2008;19(5):2278–88. doi:10.1091/mbc.E07-10-1068 E07-10-1068 [pii]. [PubMed: 18353972]
98. Raimondi C Neuropilin-1 enforces extracellular matrix signalling via ABL1 to promote angiogenesis. Biochem Soc Trans 2014;42(5):1429–34. doi:10.1042/BST20140141. [PubMed: 25233427]
99. Fantin A, Lampropoulou A, Senatore V, Brash JT, Prahst C, Lange CA et al. VEGF165-induced vascular permeability requires NRP1 for ABL-mediated SRC family kinase activation. J Exp Med 2017;214(4):1049–64. doi:10.1084/jem.20160311. [PubMed: 28289053]

100. Chislock EM, Pendergast AM. Abl family kinases regulate endothelial barrier function in vitro and in mice. PLoS One 2013;8(12):e85231. doi:10.1371/journal.pone.0085231. [PubMed: 24367707]

101. Chislock EM, Ring C, Pendergast AM. Abl kinases are required for vascular function, Tie2 expression, and angiopoietin-1-mediated survival. Proc Natl Acad Sci U S A 2013;110(30): 12432–7. doi:10.1073/pnas.1304188110. [PubMed: 23840065]

*102. Gu JJ, Rouse C, Xu X, Wang J, Onaitis MW, Pendergast AM. Inactivation of ABL kinases suppresses non-small cell lung cancer metastasis. JCI Insight 2016;1(21):e89647. doi:10.1172/jci.insight.89647 89647 [pii]. This manuscript demonstrates that ABL kinases induces non-small cell lung cancer metastasis to brain, bone, and other organ sites, and induces extravasation of cells into the lung parenchyma by stabilizing β-catenin and TAZ transcription factors. [PubMed: 28018973]

103. Morofuji N, Ojima H, Hiraoka N, Okusaka T, Esaki M, Nara S et al. Antibody-based proteomics to identify an apoptosis signature for early recurrence of hepatocellular carcinoma. Clin Proteomics 2016;13:28. doi:10.1186/s12014-016-9130-0. [PubMed: 27799868]

104. He C, Plattner R, Rangnekar VM, Zhou BP, Liu C, Stewart RL et al. Potential protein markers for breast cancer recurrence: a retrospective cohort study using the Kentucky Cancer Registry. (in review)

105. Sims JT, Ganguly SS, Bennett H, Friend WJ, J T, Plattner R. Imatinib reverses doxorubicin resistance by affecting activation of STAT3-dependent NF-κB and HSP27/p38/AKT pathways and by inhibiting ABCB1. PLoS One 2013;8(1):e55509. [PubMed: 23383209]

106. Zhao H, Ou-Yang F, Chen IF, Hou MF, Yuan SS, Chang HL et al. Enhanced Resistance to Tamoxifen by the c-ABL Proto-oncogene in Breast Cancer. Neoplasia 2010;12(3):214–23. [PubMed: 20234815]

107. Zhao H, Lo YH, Yu L, Wang SC. Overcoming resistance to fulvestrant (ICI182,780) by Downregulating the c-ABL Proto-Oncogene in breast cancer. Mol Carcinog 2011;50(5):383–9. doi:10.1002/mc.20721. [PubMed: 21480391]

108. Weigel MT, Banerjee S, Arnedos M, Salter J, A'Hern R, Dowsett M et al. Enhanced expression of the PDGFR/Abl signaling pathway in aromatase inhibitor-resistant breast cancer. Ann Oncol 2013;24(1):126–33. doi:10.1093/annonc/mds240 mds240 [pii]. [PubMed: 22865780]

109. Tan SH, Sapari NS, Miao H, Hartman M, Loh M, Chng WJ et al. High-Throughput Mutation Profiling Changes before and 3 Weeks after Chemotherapy in Newly Diagnosed Breast Cancer Patients. PLoS One 2015;10(12):e0142466. doi:10.1371/journal.pone.0142466. [PubMed: 26630576]

110. Koppenhagen P, Dickreuter E, Cordes N. Head and neck cancer cell radiosensitization upon dual targeting of c-Abl and beta1-integrin. Radiother Oncol 2017;124(3):370–8. doi:10.1016/j.radonc.2017.05.011. [PubMed: 28578803]

111. Murray JC, Aldeghaither D, Wang S, Nasto RE, Jablonski SA, Tang Y et al. c-Abl modulates tumor cell sensitivity to antibody-dependent cellular cytotoxicity. Cancer Immunol Res 2014;2(12):1186–98. doi:10.1158/2326-6066.CIR-14-0083. [PubMed: 25300860]

112. Michael M, Vehlow A, Navarro C, Krause M. c-Abl, Lamellipodin, and Ena/VASP proteins cooperate in dorsal ruffling of fibroblasts and axonal morphogenesis. Curr Biol 2010;20(9):783–91. doi:S0960–9822(10)00374-X [pii] 10.1016/j.cub.2010.03.048. [PubMed: 20417104]

113. Sossey-Alaoui K, Li X, Cowell JK. c-Abl-mediated phosphorylation of WAVE3 is required for lamellipodia formation and cell migration. J Biol Chem 2007;282(36):26257–65. doi:M701484200 [pii] 10.1074/jbc.M701484200. [PubMed: 17623672]

114. Zhao H, Ho PC, Lo YH, Espejo A, Bedford MT, Hung MC et al. Interaction of proliferation cell nuclear antigen (PCNA) with c-Abl in cell proliferation and response to DNA damages in breast cancer. PLoS One 2012;7(1):e29416. doi:10.1371/journal.pone.0029416 PONE-D-11-10311 [pii]. [PubMed: 22238610]

115. Iqbal S, Zhang S, Driss A, Liu ZR, Kim HR, Wang Y et al. PDGF upregulates Mcl-1 through activation of beta-catenin and HIF-1alpha-dependent signaling in human prostate cancer cells. PLoS One 2012;7(1):e30764. doi:10.1371/journal.pone.0030764 PONE-D-11-11411 [pii]. [PubMed: 22276222]

116. Sini P, Cannas A, Koleske AJ, Di Fiore PP, Scita G. Abl-dependent tyrosine phosphorylation of Sos-1 mediates growth-factor-induced Rac activation. Nat Cell Biol 2004;6(3):268–74. [PubMed: 15039778]
117. Cui L, Chen C, Xu T, Zhang J, Shang X, Luo J et al. c-Abl kinase is required for beta 2 integrin-mediated neutrophil adhesion. J Immunol 2009;182(5):3233–42. doi:10.4049/jimmunol.0802621. [PubMed: 19234221]
118. Tong H, Zhao B, Shi H, Ba X, Wang X, Jiang Y et al. c-Abl tyrosine kinase plays a critical role in beta2 integrin-dependent neutrophil migration by regulating Vav1 activity. J Leukoc Biol 2013;93(4):611–22. doi:10.1189/jlb.1012487 jlb.1012487 [pii]. [PubMed: 23325923]
119. Baruzzi A, Remelli S, Lorenzetto E, Sega M, Chignola R, Berton G. Sos1 Regulates Macrophage Podosome Assembly and Macrophage Invasive Capacity. J Immunol 2015;195(10):4900–12. doi: 10.4049/jimmunol.1500579. [PubMed: 26447228]
120. Gonfloni S Defying c-Abl signaling circuits through small allosteric compounds. Front Genet 2014;5:392. doi:10.3389/fgene.2014.00392. [PubMed: 25429298]
121. Sawyers CL, McLaughlin J, Goga A, Havlik M, Witte O. The nuclear tyrosine kinase c-Abl negatively regulates cell growth. Cell 1994;77:121–31. [PubMed: 7512450]
122. Balan V, Nangia-Makker P, Kho DH, Wang Y, Raz A. Tyrosine-phosphorylated Galectin-3 Protein Is Resistant to Prostate-specific Antigen (PSA) Cleavage. J Biol Chem 2012;287(8): 5192–8. doi:C111.331686 [pii] 10.1074/jbc.C111.331686. [PubMed: 22232548]
123. Varzavand A, Hacker W, Ma D, Gibson-Corley K, Hawayek M, Tayh OJ et al. alpha3beta1 Integrin Suppresses Prostate Cancer Metastasis via Regulation of the Hippo Pathway. Cancer Res 2016;76(22):6577–87. doi:10.1158/0008-5472.CAN-16-1483. [PubMed: 27680681]
124. Li X, Ma Q, Wang J, Liu X, Yang Y, Zhao H et al. c-Abl and Arg tyrosine kinases regulate lysosomal degradation of the oncoprotein Galectin-3. Cell Death Differ 2010;17(8):1277–87. doi:cdd20108 [pii] 10.1038/cdd.2010.8. [PubMed: 20150913]
125. Lo YH, Ho PC, Zhao H, Wang SC. Inhibition of c-ABL sensitizes breast cancer cells to the dual ErbB receptor tyrosine kinase inhibitor lapatinib (GW572016). Anticancer Res 2011;31(3):789–95. doi:31/3/789 [pii]. [PubMed: 21498698]
126. Noren NK, Foos G, Hauser CA, Pasquale EB. The EphB4 receptor suppresses breast cancer cell tumorigenicity through an Abl-Crk pathway. Nat Cell Biol 2006;8(8):815–25. [PubMed: 16862147]
127. Milstein M, Mooser CK, Hu H, Fejzo M, Slamon D, Goodglick L et al. RIN1 is a breast tumor suppressor gene. Cancer Res 2007;67(24):11510–6. doi:67/24/11510 [pii] 10.1158/0008-5472.CAN-07-1147. [PubMed: 18089779]
128. Chevalier C, Cannet A, Descamps S, Sirvent A, Simon V, Roche S et al. ABL tyrosine kinase inhibition variable effects on the invasive properties of different triple negative breast cancer cell lines. PLoS One 2015;10(3):e0118854. doi:10.1371/journal.pone.0118854. [PubMed: 25803821]
129. Liu T, Zeng X, Sun F, Hou H, Guan Y, Guo D et al. EphB4 Regulates Self -Renewal, Proliferation and Neuronal Differentiation of Human Embryonic Neural Stem Cells in Vitro. Cell Physiol Biochem 2017;41(2):819–34. doi:10.1159/000459693. [PubMed: 28214829]
130. Allington TM, Galliher-Beckley AJ, Schiemann WP. Activated Abl kinase inhibits oncogenic transforming growth factor-beta signaling and tumorigenesis in mammary tumors. FASEB J 2009;23(12):4231–43. doi:fj.09–138412 [pii] 10.1096/fj.09-138412. [PubMed: 19690215]
131. Morrison CD, Allington TM, Thompson CL, Gilmore HL, Chang JC, Keri RA et al. c -Abl inhibits breast cancer tumorigenesis through reactivation of p53-mediated p21 expression. Oncotarget 2016;7(45):72777–94. doi:10.18632/oncotarget.11909 11909 [pii]. [PubMed: 27626309]
132. Morrison CD, Chang JC, Keri RA, Schiemann WP. Mutant p53 dictates the oncogenic activity of c-Abl in triple-negative breast cancers. Cell Death Dis 2017;8(6):e2899. doi:10.1038/cddis. 2017.294 cddis2017294 [pii]. [PubMed: 28661474]
133. Pierobon M, Silvestri A, Spira A, Reeder A, Pin E, Banks S et al. Pilot phase I/II personalized therapy trial for metastatic colorectal cancer: evaluating the feasibility of protein pathway activation mapping for stratifying patients to therapy with imatinib and panitumumab. J Proteome Res 2014;13(6):2846–55. doi:10.1021/pr401267m. [PubMed: 24787230]