

Cellular and molecular biology of chronic myeloid leukemia

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INTRODUCTION

Chronic myeloid leukemia (CML, also known as chronic myelocytic or chronic myelogenous leukemia) is classified as one of the myeloproliferative neoplasms (MPN), along with polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). (See "Overview of the myeloproliferative neoplasms".)

MPNs share several distinct features:

- They are clonal disorders of hematopoiesis that arise in a hematopoietic stem or early progenitor cell.
- They are characterized by the dysregulated production of a particular lineage of mature myeloid cells with fairly normal differentiation.
- They exhibit a variable tendency to progress to acute leukemia.
- They share abnormalities of hemostasis and thrombosis.

The individual myeloproliferative neoplasms predominantly affect a single myeloid cell type, resulting in an excess of neutrophils in CML, erythrocytes in PV, and platelets in ET. However, there is considerable overlap between the clinical features as patients with CML, for example, often have thrombocytosis.

CML is almost invariably associated with an abnormal chromosome 22 known as the Philadelphia chromosome, often abbreviated as Ph, Ph(1), or Ph¹ [1,2]. The Philadelphia chromosome t(9;22) (q34;q11) results in the formation of a unique gene product (BCR-ABL1), which is a constitutively active tyrosine kinase. This deregulated tyrosine kinase is implicated in the development of CML and has become a primary target for the treatment of this disorder.

The cellular and molecular biology of CML will be reviewed here. The molecular genetics of this disorder, including the Philadelphia chromosome and its protein product, are discussed in more detail separately. (See "Molecular genetics of chronic myeloid leukemia".)

CELL OF ORIGIN

Normal counterpart — CML is a clonal myeloproliferative neoplasm derived from an abnormal multipotent hematopoietic stem cell (HSC) that has acquired the *BCR-ABL1* fusion gene, usually through t(9;22)(q34;q11), also known as the Philadelphia (Ph) chromosome [3].

The clonal nature of CML and other myeloproliferative neoplasms was confirmed in complementary clonality studies in women with CML utilizing isozymes of the X-chromosome linked enzyme glucose-6-phosphate dehydrogenase (G6PD) [4] or methylation-sensitive restriction fragment length polymorphisms in X-linked genes [5]. The derivation of this clonal population from a multipotent HSC was first supported by cytogenetic studies that demonstrated the Ph chromosome in granulocyte, monocyte, and erythroid precursors, megakaryocytes, and most B-lymphocytes from patients with CML [6].

Subsequent findings supported the role of a multipotent HSC as the cell of origin:

- *BCR-ABL1* mRNA can be found in CD34+ (progenitor) subpopulations from patients with CML [7].
- Leukemia stem cells in mice are Lin-c-Kit+Sca-1+, a known phenotype of HSCs [8].
- Approximately one-third of CD3+ T lymphocytes are Ph-positive in chronic phase CML [9].
- When CML progresses to acute phase, the blast cells may be of myeloid or lymphoid phenotype and are invariably found to carry the Ph chromosome, suggesting that they arise from the same leukemic clone as the chronic phase cells. Interestingly, peripheral blood T lymphocytes from patients with CML are often Ph-negative [10], perhaps because normal T cells are long-lived and preferentially responsive to the mitogen stimulation necessary for metaphase analysis.

- Although rare, several cases of Ph-positive T-lymphoid blast crisis have been reported [11], suggesting that the disease involves a multipotent cell capable of differentiating to T-lymphoid cells as well as myeloid and B-lymphoid cells.

In the aggregate, these studies strongly support the hypothesis that CML is a clonal malignancy involving the multipotential HSC. By contrast, CML in blast crisis appears to be derived from various BCR-ABL1 transformed progenitor cell populations, rather than a more primitive HSC [12,13]. (See 'Progression to acute phase CML' below.)

The leukemia stem cell — All leukemias, including CML, appear to be maintained by a pool of self-renewing malignant cells, as assessed by their ability to transfer the disease upon xenotransplantation into immunodeficient mice [14]. These leukemic stem cells (LSC, also leukemia-initiating cells) may be more immature than the majority of circulating leukemic cells, and are thought to have originated from cells with existing self-renewal capacity or from progenitors that have re-acquired this stem cell-like property [15]. (See "Pathogenesis of acute myeloid leukemia", section on 'Cell of origin').

LSCs may be identified in the laboratory by the following features [16]:

- LSCs engraft after transplantation and can be transplanted serially.
- Transplantation of LSCs in xenografts results in morphologic and immunophenotypic recapitulation of the CML tumor.

In chronic phase CML, the Ph chromosome translocation occurs for multilineage differentiation and self-renewal. The size of this HSC compartment, as defined by cell surface antigen expression, is normal, while committed myeloid progenitors and granulocyte-macrophage progenitors (CFU-GM) are significantly increased in number [17]. Studies in mouse model systems demonstrate that BCR-ABL1 does not confer self-renewal capacity to committed myeloid progenitors, and sustained CML-like leukemia cannot be produced by transplantation of BCR-ABL1 expressing committed progenitors into recipient mice [18]. This helps to explain why the Ph chromosome translocation is present in a multipotential HSC even though CML predominantly affects the neutrophil lineage: stem cell origin is required for maintenance of the disease in the bone marrow.

Interestingly, even though the BCR-ABL1 kinase is active in CML LSCs, CML LSCs exposed to tyrosine kinase inhibitors are not dependent upon BCR-ABL1 kinase activity for survival, but instead revert to dependence on cytokines that normally mediate survival and proliferation [19-23]. As such, efforts are ongoing to identify survival pathways in LSCs that may be targeted. As an example, initial studies in mice suggest that the B-lymphoid kinase (Blk) gene acts as a tumor suppressor in CML [24]. In these models, BCR-ABL1 acts through the transcriptional

regulator Myc to downregulate the *B/Ik* gene in LSCs. The restoration of *B/Ik* expression or the expression of other genes in the Blk pathway suppresses LSCs without impairing normal hematopoietic stem cells or hematopoiesis.

Several research groups have used mathematical modeling in an attempt to predict disease progression and control. As yet, the clinical utility of these measures is unknown. Studies of *BCR-ABL1* transcript dynamics in patients treated with imatinib have revealed an initial rapid decline in the majority of patients, followed by a slower rate of decrease. Mathematical models suggest that the first phase represents elimination of mature cells and committed progenitors, while the slower decline may reflect a gradual decrease in the LSC population [25,26]. Although patients who experience a more rapid decrease in the putative LSC population have superior overall survival [25], further prospective studies are necessary to determine if this parameter can be used to identify patients who might safely discontinue tyrosine kinase inhibitor (TKI) therapy [27]. A model of normal and CML hematopoiesis that incorporates feedback interactions among different cell populations in the bone marrow [28] predicts that the overall burden and the self-renewal probability of LSCs influences the response to TKI therapy, which is in agreement with clinical studies [29,30].

THE BCR-ABL1 FUSION PROTEIN

The protein product of the Philadelphia chromosome, the BCR-ABL1 fusion protein, is unique to the leukemic cells and is the fundamental cause of all the abnormalities observed in the Ph-positive leukemias. Understanding the functions of this protein and those encoded by the normal cellular genes involved in the Ph translocation, *ABL1* and *BCR*, is essential to elucidate the molecular pathophysiology of these leukemias [31-34]. (See "Molecular genetics of chronic myeloid leukemia".)

While much is known regarding the structure of the *BCR* and *ABL1* genes that come together to form the *BCR-ABL1* fusion gene, there is limited information on their normal function. The protein products of these genes have no intrinsic oncogenic properties. However, together they produce the BCR-ABL1 fusion protein that is essential for the development of CML.

BCR — The product of the *BCR* (breakpoint cluster region) gene is a ubiquitously expressed 1271 amino acid cytoplasmic phosphoprotein of 160 kDa molecular mass that has several known functional domains (figure 1):

- In the first exon-encoded sequences (amino acids 1-427), *BCR* contains a coiled-coil domain that mediates homo-oligomerization [35] and a novel serine kinase activity [36].

- The middle of the protein (amino acids 490 to 690; encoded by exons 3 to 10) contains a region of homology to the Dbl oncoprotein (with an associated pleckstrin homology domain) that functions as a guanine nucleotide exchange factor for Rho proteins [37].
- The C-terminus of BCR contains a domain with GTPase activating protein (GAP) homology and GAP activity toward the Rac and Cdc42 proteins [38]. The BCR gene has been inactivated in mice by homologous recombination; mice lacking BCR show an increased respiratory burst in their neutrophils as a result of loss of downregulation of p21Rac-mediated activation of neutrophil NADPH oxidase [39].

The normal function of the BCR gene product is not known and it has no intrinsic oncogenic properties.

ABL1 — The *ABL1* gene contains 11 exons with two alternative 5' exons, and produces two proteins (types Ia and Ib ABL1, also called types I and IV Abl in mice) of 1122 and 1142 amino acids, respectively, that differ in sequence only at their N-termini (figure 1). Type Ib ABL1 is covalently modified by myristoyl fatty acid at an N-terminal glycine residue [40].

The ABL1 proteins are similar to the Src family of non-receptor protein-tyrosine kinases and can phosphorylate cellular proteins on tyrosine residues. However, c-ABL1 has a large C-terminal domain of about 80 kDa that is not found in the Src proteins, which ends just after the catalytic domain. Thus, the c-ABL1 gene and a related gene (called *ABL*-related gene or *ARG/ABL2*) comprise a unique family, with recognizable orthologues in the genomes of *Caenorhabditis elegans* and *Drosophila*.

The normal function of the ABL1 proteins is unknown [41]. ABL1 is localized to the cell nucleus [42] and the F-actin cytoskeleton [43], and may be involved in the cell response to genotoxic [44] and oxidative stress [45], and in integrin [46] and platelet-derived growth factor (PDGF) signaling [47]. ABL1 tyrosine kinase activity is tightly controlled in the cell, and appears to be regulated at multiple levels by serine [48] and tyrosine [47,49] phosphorylation, by NH₂-terminal sequences [50], and by a cellular inhibitor that binds to the Src homology 3 (SH3) domain on ABL1 [45,51]. Mice lacking Abl1 exhibit poor postnatal viability from an unknown cause [52,53], and have defects in lymphoid development [54] and spermatogenesis [55].

BCR-ABL1 — There are several distinct BCR-ABL1 fusion proteins generated from the Ph chromosome translocation, depending on the site of the breakpoint on chromosome 22 (figure 1). Most patients with CML and one-third of those with Ph-positive B cell acute lymphoblastic leukemia (Ph+ B cell ALL) are characterized by p210^{BCR-ABL1}. Two-thirds of patients with Ph+ B cell ALL and a minority of patients with CML demonstrate p190^{BCR-ABL1}. The p230^{BCR-ABL1} is seen in chronic neutrophilic leukemia [56]. (See "Molecular genetics of chronic

myeloid leukemia", section on 'Distinct forms of BCR-ABL1 from alternative chromosome 22 breakpoints'.)

- The three principal forms of BCR-ABL1 (p190, p210, and p230 BCR-ABL1) contain all of ABL1 except the first exon-encoded sequence, including the entire ABL tyrosine kinase catalytic domain, but have different amounts of BCR sequence at the N-terminus (figure 1).
- All three forms of BCR-ABL1 contain the *Bcr* exon coiled-coil domain, but only p210 and p230 include the Dbl/pleckstrin homology domain from the central portion of BCR. The C-terminal GAP domain of BCR is not included in p190 and p210, but a portion is retained in the longer p230 fusion protein.
- All three forms of BCR-ABL1 have increased tyrosine kinase activity in vivo [57] and in vitro [58,59] relative to ABL1, due to the addition of *BCR* exon 1 sequences to *Abl*. When quantitated in an immune complex kinase assay, p190 has the highest intrinsic kinase activity, followed by p210 and p230 (about 10-, 6-, and 3-fold increased over that of c-ABL1, respectively) [58,59]. The different kinase activity of the BCR-ABL1 isoforms may in part account for the distinct leukemias associated with the different fusions and may predict responsiveness to therapy with tyrosine kinase inhibitors.

The precise mode of activation of ABL1 kinase activity by BCR is unknown, but may involve several distinct mechanisms including oligomerization of BCR-ABL1 via the coiled-coil domain [35], and interaction of BCR with the ABL1 Src homology 2 (SH2) domain [60], blocking the binding of an Abl inhibitor [45]. Unlike ABL1, BCR-ABL1 is localized exclusively in the cytoplasm of hematopoietic cells [61] in association with subcortical F-actin-rich structures [62]. BCR-ABL1 can be trapped in the nucleus by treatment of cells with a combination of an ABL1 kinase inhibitor and leptomycin-B, an inhibitor of nuclear export [63]. Removal of the ABL1 kinase inhibitor then induces apoptosis through activation of BCR-ABL1 kinase activity in the nucleus, which may have applications for in vitro purging of CML cells.

ESTABLISHMENT OF CHRONIC PHASE CML

Most patients with CML present with relatively indolent disease (termed chronic phase) characterized by splenomegaly and leukocytosis with a white blood cell differential showing virtually all cells of the neutrophilic series, from myeloblasts to mature neutrophils with peaks in the percent myelocytes and segmented neutrophils [3]. The granulocytes of chronic phase are morphologically normal, but cytochemically abnormal. This unusual phenotype is due to

distinct abnormalities in hematopoiesis [31,64]. The CML progenitors appear to have an alteration in the balance between self-renewal and differentiation that favors differentiation, an abnormality termed discordant maturation [65]. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia", section on 'Clinical manifestations'.)

While initial studies suggested that clonality in CML may occur before the acquisition of Philadelphia (Ph) chromosome [66], separate clonality studies demonstrated that Ph-negative CD34+ progenitors from patients with early chronic phase CML were polyclonal [67]. These results indicate that clonal hematopoiesis does not typically precede the acquisition of the Ph chromosome in the pathogenesis of CML and supports the leading hypothesis that the Ph chromosome is the inciting event in CML. Somatic mutations affecting *ASXL1*, *DNMT3A*, *RUNX1*, and *TET2* were reported in one-third of newly diagnosed CML patients, with analysis of individual hematopoietic colonies demonstrating that some mutations were present in Ph-negative cells [68]. These results suggest that the Ph chromosome translocation in some patients may arise upon a background of clonal hematopoiesis. (See "Clonal hematopoiesis of indeterminate potential (CHIP) and related disorders of clonal hematopoiesis".)

The development of chronic phase CML appears to be a direct result of BCR-ABL1 activity, which promotes its development by allowing:

- Uncontrolled proliferation of transformed cells (see 'Uncontrolled proliferation' below)
- Discordant maturation (see 'Discordant maturation' below)
- Escape from apoptosis (see 'Escape from apoptosis' below)
- Altered interaction with the cellular matrix (see 'Altered interaction with the cellular matrix' below)

The BCR and ABL1 proteins have no intrinsic oncogenic properties and cannot transform cells, even if overexpressed [40]. By contrast, the BCR-ABL1 protein has gained the ability to transform cell lines and primary cells in vitro, demonstrating that it is a classical oncogene [69]. The primary action of BCR-ABL1 in B-lymphoid progenitors appears to be stimulation of proliferation rather than oncogenic transformation [70], suggesting that multiple steps may be required for B-lymphoid transformation by BCR-ABL1. A multiple step model is also supported by studies in patients with known exposure to ionizing radiation [71,72] that have demonstrated a delay of several years between the initial mutational event (presumably, the acquisition of the Ph chromosome translocation in a stem cell) and the development of clinical symptoms that lead to the diagnosis of CML.

All forms of BCR-ABL1 can transform cytokine-dependent lymphoid [59,73] and myeloid [59,74] hematopoietic cell lines to become independent of cytokine for survival and proliferation. Although BCR-ABL1 can induce secretion of cytokines (including IL-3) in some cytokine-dependent hematopoietic cell lines [74,75], transformation of these cells by BCR-ABL1 does not require autocrine production of cytokine. BCR-ABL1 can also stimulate the growth of primary murine bone marrow-derived B-lymphoid progenitors in vitro, leading to the outgrowth of transformed pre-B cells that are independent of growth factors and stroma, and are leukemogenic upon transfer to syngeneic or immunodeficient recipient mice [76]. The p190 form of BCR-ABL1 is more potent than p210 in this growth stimulatory assay [77].

BCR-ABL1 signaling — BCR-ABL1 induces leukemogenesis through kinase dependent and kinase independent signaling pathways. Presumably, the specific cellular abnormalities observed in CML are the consequence of aberrant intracellular signaling. If this is correct, then an attempt can be made to correlate particular signaling pathways with specific cellular responses. Through the use of chemical inhibitors, dominant-negative mutants, and genetically deficient cells and mice, it has been possible to demonstrate that some of the signaling pathways are required for transformation and/or leukemogenesis by BCR-ABL1, validating these downstream pathways as targets for rational therapy of Ph-positive leukemia. However, there is considerable overlap and redundancy between the different pathways, and activation of multiple pathways is probably required for the complete leukemic phenotype in vivo [78].

Tyrosine kinase activity — BCR-ABL1 is a constitutively active tyrosine kinase. The tyrosine kinase activity of ABL1 is absolutely required for transformation by BCR-ABL1, as evidenced by the observation that mutations in the catalytic domain that inactivate kinase activity also abolish transformation [79]. Similarly, mutations in ABL1 that render the catalytic activity sensitive to temperature, inactivate transformation at the non-permissive temperature [80,81].

BCR-ABL1 induces tyrosine phosphorylation of a large number of cellular proteins in hematopoietic cells. As a result, a diverse group of intracellular signaling pathways is activated by BCR-ABL1 [82], in part through induction of protein complexes between tyrosine-phosphorylated proteins and SH2-containing proteins. Some of these pathways overlap with signaling induced by hematopoietic cytokines such as IL-3 [83].

A central role for the BCR-ABL1 tyrosine kinase in the pathogenesis of CML has been established by the therapeutic efficacy of small molecule inhibitors of the ABL1 tyrosine kinase. Specific BCR-ABL1 tyrosine kinase inhibitors decrease cellular proliferation of BCR-ABL1 expressing cells in vitro by more than 90 percent but have minimal effects on normal cells [84,85]. The applicability of these findings to humans was initially illustrated in a clinical trial in

which 31 of 31 patients with CML in chronic phase achieved clinical complete remission after receiving an orally active, specific inhibitor of the ABL1 protein tyrosine kinase.

Tyrosine kinase inhibitors have become the standard therapy for most patients with CML. While these agents have a high rate of long-term disease control, they are not able to cure CML. The inability of tyrosine kinase inhibitors to cure CML is thought to reflect a natural resistance of at least a population of leukemia stem cells to these agents [86,87]. (See "Overview of the treatment of chronic myeloid leukemia", section on 'Tyrosine kinase inhibitors (TKI)').

Kinase independent pathways — As mentioned above, signalling by BCR-ABL1 is thought to manifest through both kinase dependent and kinase independent pathways. Support for this comes from studies that have shown leukemia stem cells to be inherently resistant to tyrosine kinase inhibitors [20,86,87]. In addition, mutations of BCR-ABL1 have been identified that impair leukemogenesis despite preserving tyrosine kinase activity [88]. DNA microarray analyses of CML cells and other studies have implicated many kinase independent pathways in the pathogenesis of CML including [89-95]:

- Wnt/Beta-catenin pathway – Involved in the development of hematopoietic stem cells
- Hedgehog pathway – Critical for primitive hematopoiesis
- Alox5 pathway – Part of the oxidative stress response, inflammation, and other types of cancer development
- PTEN pathway – Regulates cell survival and growth
- FoxO pathway – Mediates cell-cycle arrest, stress resistance and apoptosis

The magnitude of effect of these kinase independent pathways is not well understood.

Uncontrolled proliferation — In established CML, the pool of Ph-positive committed myeloid progenitors in marrow and blood is greatly expanded due at least in part to increased proliferation. This was initially suggested by the predominance of Ph-positive bone marrow metaphases (90 to 100 percent) at diagnosis in most patients and later confirmed by in vivo labeling studies with tritiated thymidine [96]. However, the several year latency period in CML from mutation to disease development suggests that the relative magnitude of this advantage is quite small, as also evidenced by the following observations [71,72]:

- Normal stem cells persist in the bone marrow of patients with CML [97,98].
- Patients diagnosed early in the disease course exhibit significant residual Ph-negative hematopoiesis [99].

BCR-ABL1 has primary mitogenic activity and can stimulate cell cycle entry of hematopoietic cell lines and primary cells in the absence of growth factors [100,101]. While many signaling pathways participate, activation of the MAP kinase (MAPK) pathway appears to play a central role in the promotion of uncontrolled proliferation. BCR-ABL1 activates p21 RAS and the downstream RAF/MEK/MAPK pathway [100,102] that probably plays a role in mitogenesis, as evidenced by the observation that RAS is required for fibroblast and B-lymphoid transformation by BCR-ABL1 [103]. There are at least two independent mechanisms of RAS activation by BCR-ABL1: direct binding of the GRB2 adapter protein [88,104]; and activation of the SHC adapter protein by tyrosine phosphorylation [105]. The GRB2 binding site at BCR Tyr177 is required for myeloid and lymphoid leukemogenesis by BCR-ABL1 through distinct signaling pathways mediated by the GAB2 scaffolding/adapter protein [106]. The tyrosine phosphatase SHP2 is activated downstream of GAB2 and is required for BCR-ABL1 mediated myeloid and B-lymphoid transformation, and for activation of SRC family kinases and proliferation in BCR-ABL1⁺ pre-B cells [107].

The signaling activity of some RAS proteins requires association of the proteins with the plasma membrane. This in turn requires attachment of a farnesyl group (15-carbon lipid tail) to the protein, a reaction catalyzed by the enzyme, farnesyl transferase. Inhibition of this step by a farnesyl transferase inhibitor (FTI) is a potentially useful antineoplastic strategy in CML [108,109]. (See "Initial systemic chemotherapy for metastatic exocrine pancreatic cancer".)

BCR-ABL1 also has other important effects on pathways associated with uncontrolled proliferation:

- It activates the stress-activated protein kinase/Jun N-terminal kinase (SAPK/JNK) pathway [110], which contributes to fibroblast and B-lymphoid transformation [111].
- It is a potent activator of the JAK/STAT pathway [112-115]. JAK2 complexes with BCR-ABL1 via the ABL1 C-terminus and contributes to activation of the SRC kinase LYN [116], but neither the JAK2 binding site on BCR-ABL1 [117] nor JAK2 itself [118] is required for induction of CML-like leukemia in mice by BCR-ABL1. JAK2 kinase inhibitors decrease the proliferation and survival of cultured BCR-ABL1 expressing cells [119,120], but JAK2-deficient progenitors are equally sensitive to these drugs [118], indicating that targets other than JAK2 are responsible. The adapter protein AHI-1 mediates physical interaction between BCR-ABL1 and JAK2 in primitive CML progenitors, while combined treatment with imatinib and a JAK2 inhibitor (TG101209) increased apoptosis and decreased the leukemia-initiating activity of these progenitors in immunodeficient recipients (NSG mice) [121]. In addition to inhibiting JAK2 in CML stem cells, there is also a potential rationale for targeting JAK2 in the marrow microenvironment in CML [122,123].

- Activation of STAT5 contributes to transformation by BCR-ABL1 [124,125], at least in part through stimulation of proliferation [126,127]. The p190 form of BCR-ABL1 preferentially activates STAT6, which may contribute to the increased efficiency of B-lymphoid transformation by this isoform [114]. Agonists of peroxisome proliferator-activated receptor gamma (glitazones) have been shown to decrease STAT5 expression in CML cells and decrease the pool of leukemic stem cells in mouse models [128]. (See 'Retroviral transduction' below.)
- Both c-MYC [129] and cyclin D1 [130] are required for BCR-ABL1 induced mitogenesis and encourage cell cycle progression. (See "Pathobiology of mantle cell lymphoma", section on 'Cyclin D1 expression'.)

Ph+ myeloid progenitors (CFU-C) have the same requirement for and sensitivity to hematopoietic cytokines as normal CFU-C [131], and patients with CML do not typically have increased plasma levels of cytokines. Aberrant mRNA transcripts for interleukin (IL)-3 and granulocyte colony-stimulating factor (G-CSF) have been detected in the most primitive Ph+ progenitor/stem cells; neutralizing antibody experiments suggest that these cytokines contribute to autonomous growth and differentiation of these cells [132]. However, the IL-3 gene is not required for induction of CML-like myeloproliferative disease by BCR-ABL1 in a mouse model [133]. In comparison, primitive Ph+ progenitors appear to be insensitive to chemokines produced by marrow stroma, such as monocyte chemoattractant protein-1 (MCP-1), which inhibit the growth of normal progenitors [134]. However, the precise role of cytokines in the pathogenesis of CML requires further study. (See 'Mouse models of CML' below.)

Discordant maturation — The CML progenitors appear to have an alteration in the balance between self-renewal and differentiation that favors differentiation, an abnormality termed discordant maturation [65]. This observation is consistent with the finding that, in the chronic phase of CML, the size of the BCR-ABL1 containing, self-renewing, beta-catenin positive stem cells is normal, while that of the BCR-ABL1 containing, beta-catenin negative differentiating progenitor cells is expanded [12]. This suggests that, in the chronic phase, the mutant BCR-ABL1 protein affects a more critical function in progenitor cells than it does in the stem cells [135]. However, in the blast crisis of CML, the granulocyte-macrophage progenitors unexpectedly accumulate beta-catenin, normally found only in stem cells, and have appear to have self-renewing properties (see 'The leukemia stem cell' above and 'Progression to acute phase CML' below).

Escape from apoptosis — The survival of mature Ph+ neutrophils in patients with CML is only modestly prolonged and cannot account for the dramatic increase in granulocytes characteristic of the disease [136].

In vitro, cytokine-dependent hematopoietic cell lines expressing BCR-ABL1 are protected from apoptosis (the process of programmed cell death) upon cytokine withdrawal [73,74]. Ph+ cell lines are also resistant to apoptosis induced by radiation and cytotoxic chemotherapeutic agents [137]. In contrast to these findings in cell lines, conflicting results have been obtained in primary CD34+ CML cells. While one group found that CD34+ cells from patients with CML were resistant to apoptosis induced by serum withdrawal [138] or ionizing radiation [139], others have not observed prolonged survival of primary Ph+ CML cells relative to normal cells after serum deprivation or radiation [140,141]. These observations suggest that the antiapoptotic actions of BCR-ABL1 may be dependent on cell type; further studies are needed to determine the role of protection from apoptosis in the pathophysiology of CML.

The antiapoptotic activity of BCR-ABL1 is poorly understood. BCR-ABL1 blocks programmed cell death upstream of mitochondrial cytochrome c release and caspase activation [142,143]. Signaling pathways implicated in this survival function include Ras [144], Raf-1 [145], phosphatidylinositol 3-kinase [146] and its downstream effector Akt [147], STAT5, BCL-2 [148] and the related proteins BCL-xL and MCL-1 [149], and nuclear factor kappa B [150]. In a transgenic mouse model of CML, inhibitors of BCL-2 [151] or of the p53 antagonist MDM2 [152] sensitize BCR-ABL1+ stem/progenitors to ABL1 kinase inhibitors.

In normal cells, the anti-apoptotic protein Bcl-xL sequesters and inhibits the function of the pro-apoptotic Bcl-2 family members, including Bax and Bak. DNA damage triggers the nonenzymatic deamidation of Bcl-xL, thereby reducing its ability to control Bax/Bak activity and leading to apoptosis. However, the Bcl-xL deamidation pathway is inhibited in the myeloid cells of patients with CML and polycythemia vera [149]. This results in a blunted apoptotic response to DNA damage.

Altered interaction with the cellular matrix — CML cells have an altered cytoskeleton and decreased adhesion to microenvironmental substrates resulting in the inappropriate expansion of the myeloid cell compartment. However, some of the observed effects in cultured cells are paradoxical. As an example, BCR-ABL1 appears to stimulate rather than impair cell adhesion in cell lines [153]. The role of BCR-ABL1 induced abnormalities in the cell cytoskeleton and adhesion in Ph-positive leukemogenesis requires further study.

BCR-ABL1 binds to F-actin [62] and induces tyrosine phosphorylation and/or activation of several proteins associated with cytoskeletal structure and function. These include the GTP-binding protein Rac [154], the adapter proteins Crkl [155,156] and p62Dok [157], the scaffolding proteins Hef-1 [158] and Cas [159], the Cbl proto-oncoprotein [160], and the focal adhesion proteins paxillin, vinculin, tensin, and focal adhesion kinase (FAK) [161]. In cultured cells, BCR-

ABL1 expression induces multiple abnormalities of cytoskeletal function [162], cell adhesion [153] and chemotaxis/motility [163].

Primitive Ph+ hematopoietic progenitors from patients with CML show decreased adherence to bone marrow stroma [164] and fibronectin [165] due to a defect in beta-1 integrin function. Treatment with interferon-alfa [166-168], antisense oligodeoxynucleotides to BCR-ABL1 [169], or BCR-ABL1 tyrosine kinase inhibitors [170] all increase the adherence of CML progenitors to stroma or fibronectin and restore normal adhesion-dependent inhibition of proliferation [171]. CML cells expressing the imatinib-resistant BCR-ABL1 T315I mutant produce less fibronectin in the bone marrow microenvironment as a consequence of altered integrin-linked kinase/beta-3 integrin signaling [172], which may in part account for the more aggressive clinical course associated with this mutant BCR-ABL1 [173].

Defects in adherence may in part account for the increased circulation and unregulated proliferation of Ph+ progenitor/stem cells in CML [174]. Defective adherence may also explain the tendency of Ph+ progenitors to be lost from long-term marrow cultures in vitro [175], a phenomenon that has been exploited to purge CML marrow of malignant cells prior to autografting [176]. However, restoration of adherence of CML progenitors by interferon-alpha occurs within 48 hours in vitro, but does not explain the prolonged duration of therapy (weeks to months) required for hematologic responses to interferon-alpha in patients with CML. Similarly, it is not clear whether patients who fail to respond to interferon-alpha are also deficient in adhesion responses in vitro. Thus, the relevance of these adhesion defects to the pathophysiology of CML requires further investigation.

PROGRESSION TO ACUTE PHASE CML

As described above, CML usually progresses from a relatively indolent disease (termed chronic phase), easily controlled with oral chemotherapy, to a more aggressive disorder (accelerated phase), during which time disease control is more difficult to achieve. This transition from chronic phase to accelerated phase is often subtle and may not be easily detected. In virtually all patients treated with palliative chemotherapeutic agents (eg, busulfan, hydroxyurea) and in some patients treated with tyrosine kinase inhibitors, the disease culminates in an acute leukemia, termed "blast crisis." This phase, which is generally refractory to treatment, occurs approximately three to five years after the diagnosis of CML and 18 months after the onset of the accelerated phase. (See "Overview of the treatment of chronic myeloid leukemia", section on 'Pretreatment evaluation'.)

The progression of CML from chronic phase to accelerated phase or blast crisis is a complex, multistep process that is only partially understood. While some steps in this pathway have been elucidated, many remain unknown. Research into mechanisms of progression has been limited by a lack of appropriate models, although recent application of "Sleeping Beauty" transposon mutagenesis in a conditional *BCR-ABL1* transgenic model of CML has yielded a model of CML progression that may be useful for identification of relevant genetic events (see 'Mouse models of CML' below) [177]. While the Ph chromosome translocation may be the initiating event in CML, progression to blast crisis appears to require the acquisition of other chromosomal changes and/or dysregulation of differentiation-regulatory genes [2,178,179].

The following events appear to be necessary for the transformation of chronic phase CML into an acute phase of disease [180]:

- Constitutive expression of the BCR-ABL1 tyrosine kinase (see 'BCR-ABL1 activity' below)
- Differentiation arrest (see 'Differentiation arrest' below)
- Genetic instability and additional chromosomal abnormalities (see 'Genetic instability' below)
- Inactivation of tumor suppressor genes (see 'Inactivation of tumor suppressor genes' below)

The nature of the cell that underlies the transition of chronic phase CML to accelerated phase and/or myeloid blast crisis is uncertain, but appears to correspond to bone marrow granulocyte-macrophage progenitors (GMP) or other progenitor cell subsets [12]. Such transformed cells acquire self-renewal properties in vitro and possess leukemia-initiating activity in xenograft models.

The transformed cells of accelerated and/or myeloid blast phase exhibit increased expression, nuclear localization, and function of beta-catenin, a transcription factor in the WNT signaling pathway that has been implicated in self-renewal of normal HSCs [12,17]. This suggests that aberrant activation of the WNT pathway may be a central feature of disease progression in CML. Additional studies indicate that the Hedgehog (Hh) signaling pathway may also contribute to self-renewal of CML stem cells [181]. Together, these observations offer new opportunities for therapeutic intervention in CML through inhibition of WNT and Hh signaling.

BCR-ABL1 activity — Progression from chronic phase CML to accelerated phase or blast crisis requires the constitutive expression of the BCR-ABL1 protein. Quantitative analyses have supported the hypothesis that this progression may be induced by a rise in BCR-ABL1 activity:

- Tumor samples from advanced disease demonstrate higher levels of the *BCR-ABL1* mRNA and protein than that seen in chronic phase disease [182-184].
- There is a dose-dependent relationship for many of the leukemogenic effects of BCR-ABL1 on cells including uncontrolled proliferation and escape from apoptosis [184,185].
- Cell lines expressing high levels of BCR-ABL1 induce tumors more rapidly than those that have low levels of expression [184].

It is unclear if this increase in protein is due to an increase in production of BCR-ABL1, a decrease in protein degradation, or a combination of the two. In advanced CML and myeloid blast crisis, increased expression of the SET protein, an inhibitor of protein phosphatase 2A (PP2A), leads to decreased activity of PP2A and a corresponding increase in BCR-ABL1 signaling through tyrosine phosphorylation. Pharmacologic agents that reactivate PP2A decrease proliferation and survival of CML blast crisis cell lines and primary patient samples [186].

Differentiation arrest — Blast crisis in CML is characterized by a shift in the level of tumor differentiation to more immature forms. This failure of differentiation may be mediated through interactions between BCR-ABL1 and transcription factors or through a second genetic insult forming a dominant-negative transcription factor:

- The transcription factor C/EBPalpha is required for myeloid differentiation, and dominant-negative mutations in C/EBPalpha are found in a subset of AML patients [187]. Expression of C/EBPalpha is suppressed in blasts from patients with CML myeloid blast crisis, which could contribute to impaired myeloid differentiation [188,189]. The mechanism may involve binding of C/EBPalpha mRNA by the poly(rC)-binding protein hnRNPE2, with inhibition of translation. (See "Prognosis of acute myeloid leukemia", section on 'CEBPA gene'.)
- Deletions of the Ikaros (*IKZF1*) gene are detected in more than 80 percent of Ph-positive B-ALL, including lymphoid blast crisis of CML [190,191]. Ikaros is a zinc-finger transcription factor required for normal lymphoid development, and inactivation of IKAROS function in B-lymphoid precursors in mice blocks development at the large pre-B cell stage, contributing to the development of B-ALL [192]. (See "Classification, cytogenetics, and molecular genetics of acute lymphoblastic leukemia/lymphoma", section on 't(v;11q23.3)').
- A subset of patients with myeloid blast crisis acquire a t(3;21) translocation associated with fusion of AML1 and EVI1 transcription factors [193,194]. The leukemogenicity of the fusion gene has been demonstrated by expressing the gene in bone marrow cells; transplanting these cells into mice leads to the development of acute myeloid leukemia 5 to 13 months

later [195]. Co-expression of BCR-ABL1 and the AML1-EVI1 fusion protein in mouse bone marrow causes fatal hematologic disease in recipients by four months, with evidence of impaired myeloid differentiation, supporting a cooperating role between BCR-ABL1 and oncogenic transcription factors in progression to myeloid blast crisis [196]. (See "Molecular genetics of acute myeloid leukemia", section on 'NUP98/HOXA9 in t(7;11) and NUP98/DDX10 in inv(11)' and "Molecular genetics of acute myeloid leukemia", section on 'RUNX1/EAP, MDS1, EVI1 in t(3;21').)

Genetic instability — The malignant clone in CML is genetically unstable and acquires multiple genetic abnormalities during the progression from chronic phase to blast crisis. Studies in BCR-ABL1 expressing cell lines [197] and BCR-ABL1 transgenic mice [198] have suggested that BCR-ABL1 may directly induce karyotypic instability. An increased frequency of point mutations is also observed in BCR-ABL1 expressing cell lines [199]. (See 'Mouse models of CML' below.)

The mechanism of the putative BCR-ABL1 induced genetic instability is unknown. It may be related to an observed accentuation in cell cycle arrest at a G2/M checkpoint in BCR-ABL1 expressing cells in response to genotoxic damage [139,200], possibly via activation of STAT5 [201]. Increased homologous recombination mediated by Rad51 family members may also contribute to genetic instability and drug resistance in BCR-ABL1 expressing cells [202]. BCR-ABL1 expression stimulates the production of reactive oxygen species (ROS) in hematopoietic progenitors [203], and other studies suggest that ROS may contribute to the increased level of DNA damage and double-strand DNA breaks in BCR-ABL1 expressing cells [204].

Additional cytogenetic abnormalities develop in over 80 percent of patients with CML in accelerated and blast crisis phases, most commonly trisomy 8, trisomy 19, duplication of the Ph chromosome, and isochromosome 17q. At least some of these cytogenetic abnormalities have been characterized at the molecular level. (See 'Inactivation of tumor suppressor genes' below.)

Other cytogenetic abnormalities and abnormalities in gene expression have been noted but require further characterization:

- Mutations in two distinct RNA-binding proteins, Lin28 and Musashi, may contribute to CML disease progression in some patients. Further studies are necessary to elucidate the molecular mechanisms involved in each case.
 - Lin28 and the related protein Lin28B act by suppressing the maturation of miRNA let-7, which in turn may negatively regulate several signaling pathways in hematopoietic cells. Lin28 overexpression is observed in blast crisis CML and several other cancers, and is associated with a poor prognosis [205].

- The Musashi family protein MSI2, an RNA-binding protein that interferes with translation of target mRNAs and functions in cell fate determination during embryogenesis, is also overexpressed in advanced CML and acute myeloid leukemia, and is likewise associated with poor survival [206,207].
- Abnormalities of DNA methylation have also been observed in CML disease progression, including methylation of the calcitonin gene, the M-bcr region, and the ABL1 promoter region. In theory, CML patients might be monitored molecularly for evidence of disease progression, but this approach has not been successfully utilized clinically to date.

Inactivation of tumor suppressor genes — Some cases of CML that have progressed to blast crisis demonstrate loss of tumor suppressor genes. As examples:

- In myeloid blast crisis, 20 to 30 percent of patients have alterations (deletions and rearrangements) in the *TP53* tumor suppressor gene on chromosome 17p13 [208], although there may also be another tumor suppressor gene on 17p that is involved in disease progression. Direct support for a role of p53 comes from a transgenic animal model of p210BCR-ABL1 in which the loss of p53 was associated with initial signs resembling CML, followed by more rapid proliferation of blast cells and early death when compared with p210BCR-ABL1 mice with no abnormality in *TP53* [209].
- Amplification of *MYC* (on chromosome 8) and deletion of the *RB1* or p16INK4A/p14ARF (*CDKN2A*) tumor suppressor genes is more common in lymphoid blast crisis. Genetic studies in mouse model systems suggest that loss of the p19ARF tumor suppressor gene contributes directly to the transformation of immature B-lymphoid cells by *v-Abl* and *BCR-ABL1* [210-212]. Deletion of *CDKN2A* or the closely linked *CDKN2B* gene on chromosome 9p21 is frequent during progression of Ph⁺ B-ALL and is a poor prognostic factor [213].
- Large deletions of the derivative chromosome 9 are found in 15 to 20 percent of patients with chronic phase CML, appear to occur at the time of the Ph translocation, and are associated with decreased survival due to more rapid disease progression that is independent of other clinical features [214]. The mechanism is thought to involve deletion of one or more tumor suppressor genes adjacent to 9q34.1. Lack of expression of the reciprocal *ABL1-BCR* fusion gene is observed in a similar proportion of CML patients but does not correlate with deletions of der9q or with survival [215].

MOUSE MODELS OF CML

Although a great deal has been learned about the transforming and signaling properties of BCR-ABL1 from studies in cultured cells, these systems do not model the complex physiology of the bone marrow. A complete understanding of Ph-positive leukemia requires expression of the *BCR-ABL1* oncogene within the context of the hematopoietic system. The inbred laboratory mouse has been the species of choice for these efforts, which have focused on complementary methods for expression of BCR-ABL1 in the blood system [216]. There are three main methods of developing mouse models for CML [89]:

- Retroviral transduction of murine bone marrow ex vivo followed by transplantation
- Generation of transgenic strains of mice
- Xenograft non-obese diabetic severe combined immunodeficient (NOD/SCID) mouse

As yet there is no mouse model that provides a long chronic phase of CML-like disease followed by transformation to a blast crisis.

Retroviral transduction — The retroviral transduction mouse model was first introduced in the 1990s and has evolved to become the most frequently used *in vivo* model of CML [59,217-221]. A donor mouse is treated with fluorouracil and bone marrow is collected. This donor bone marrow is exposed ex vivo to a BCR-ABL1 transducing retrovirus and then transplanted into a lethally irradiated syngeneic recipient mouse. Recipients develop a number of distinct hematologic malignancies, including a myeloproliferative disease closely resembling human CML, and B-lymphoid leukemia similar to Ph-positive acute lymphoblastic leukemia.

The CML-like disease induced in mice by BCR-ABL1 is a very close pathophysiologic match to human CML:

- The target cell for retroviral transduction that gives rise to CML-like disease is an early progenitor/stem cell with multilineage repopulating ability [59].
- Recipient mice demonstrate splenomegaly, increased numbers of mature granulocytes circulating in the peripheral blood that express BCR-ABL, and bone marrow invasion by leukemic stem cells and progenitor cells [8].
- This CML-like disease is transplantable and undergoes evolution to acute leukemia, resembling blast crisis [222,223].

This model has provided support for BCR-ABL1 as the principal cause of these malignancies and has allowed for the *in vivo* study of BCR-ABL1 signaling, identification of novel genes involved in CML development, and testing of potential therapies [8,224,225].

Evolution to myeloid blast crisis can be mediated by the aberrant expression of several transcription factors, including NUP98-HOXA9, which is the product of a t(7;11) chromosomal

translocation [193]. A murine model of CML blast crisis can be induced by interactions between BCR/ABL and NUP98/HOXA9 and the transcriptional repressor hairy enhancer of split 1 (Hes1) [226].

Improvements in the generation of high titer retroviral stocks have permitted efficient induction of CML-like disease in mice, allowing the system to be used as an assay [59,220,221]. A direct comparison of the leukemogenic properties of the p190, p210, and p230 *BCR-ABL1* oncogenes in this model system indicates that all three forms of BCR-ABL1 induce a similar CML-like disease with equal efficiency, but that p190 is more potent than either p210 or p230 for lymphoid leukemogenesis [59]. These results suggest that the rarity of p190 in human chronic phase CML is due to infrequent *BCR* intron 1 breakpoints during the genesis of the Ph chromosome in stem cells; they do not support the hypothesis that p230 BCR-ABL1 induces a milder form of CML [227].

Donor bone marrow from mice with targeted mutations in signaling molecules can be used to test the role of a given pathway in BCR-ABL1 leukemogenesis. Although human CML progenitors express aberrant transcripts for IL-3 [132], bone marrow from mice with homozygous inactivation of the IL-3 gene can induce CML-like disease after transduction with BCR-ABL1 and transplantation [133], suggesting IL-3 is not required for the development of CML.

Although Src family kinases are activated by BCR-ABL1 [228], BCR-ABL1 can efficiently induce CML-like leukemia in bone marrow from mice lacking Lyn, Hck, and Fgr, the three principal Src kinases expressed in myeloid progenitors [229]. However, induction of B-lymphoid leukemia by BCR-ABL1 is attenuated by the lack of these three Src kinases [229]. These results suggest that Src family kinases may be rational therapeutic targets in Ph+ B-ALL and CML lymphoid blast crisis, but not in chronic phase CML. In agreement with this suggestion, siRNA knockdown of Lyn impaired survival in cells from CML lymphoid blast crisis patients to a greater extent than in myeloid cells [230].

The transcription factor STAT5 has also been implicated as an essential factor in the pathogenesis of BCR-ABL1 induced CML-like leukemia. Evidence for this role of STAT5 primarily comes from in vivo models that have demonstrated that CML-like leukemia cannot be induced in recipients of bone marrow from STAT5 mutant donors [124], although STAT5 may not be required for maintenance of CML stem cells or progression to blast crisis in this model [125]. (See 'Uncontrolled proliferation' above.)

Future use of this model system should provide a platform for drug testing [231] and investigation of immunological therapy of CML [232,233].

Transgenic models — The development of transgenic mouse models of CML was initially thwarted by findings that the constitutive tyrosine kinase activity of the BCR-ABL1 gene product caused toxicity [234] and embryonic lethality [235] in transgenic mice. Embryonic lethality was overcome by the use of minimally active promoters, particularly the metallothionein promoter or a tet-off (with expression controlled by tetracycline administration) system, to control the timing of BCR-ABL1 expression. This has allowed the development of transgenic mice expressing the p190 [236] and p210 [237,238] forms of BCR-ABL1. Despite wide expression of the transgene in both bone marrow and non-hematopoietic tissues, these mice exclusively develop acute lymphoid malignancies, demonstrating that BCR-ABL1 is a leukemia-specific oncogene [239,240]. Subsequently, the conditional expression of BCR-ABL1 in hematopoietic stem cells has resulted in a CML-like myeloproliferative disease [241].

Breeding the *BCR-ABL1* transgene into a *Bcr* null background has demonstrated that lymphoid leukemogenesis by BCR-ABL1 does not require the normal BCR gene product [242,243]. (See 'BCR' above.)

Characterization of transgenic mice before the development of overt leukemia has demonstrated early karyotypic instability in lymphoid cells, suggesting genetic instability is a primary consequence of BCR-ABL1 expression [198]. Comparison of the leukemogenic properties of the p190 and p210 forms of BCR-ABL1 in transgenic mice indicate that p210 mice develop B- and T-lymphoid leukemia of relatively long latency, while p190 mice develop exclusively B-lymphoid malignancy of shorter latency, supporting a distinct difference in lymphoid leukemogenesis by the two isoforms [237].

Conditional transgenic models of BCR-ABL1 have been developed that allow control of oncogene expression. In one model, conditional expression of BCR-ABL1 in lymphoid progenitors results in acute B-lymphoblastic leukemia [240]. Complete remission of leukemia was achieved by suppression of BCR-ABL1 expression, even after multiple rounds of induction and reversion. In addition, BCR-ABL1 has a profound antiapoptotic effect on primary malignant B-lymphoid cells *in vivo*. In a more recent model, conditional expression of BCR-ABL1 in hematopoietic stem cells results in CML-like myeloproliferative disease [241]. Both models have shown that continuous expression of BCR-ABL1 is required for maintenance of the leukemic phenotype *in vivo* [240,241].

Xenograft NOD/SCID model — The human xenograft non-obese diabetic severe combined immunodeficient (NOD/SCID) mouse model is a newer technique that may offer an environment more representative of the physiologic state of CML in humans. CD34+ cells are purified from the peripheral blood or bone marrow of patients with CML and transplanted into sublethally irradiated NOD/SCID mice [244,245]. Both normal and leukemic cells are found in

the bone marrow of the recipient mice. Although most recipient mice do not develop lethal CML-like disease, transplantation of cells from blast crisis results in the rapid increase in leukemic cells in the recipient [244].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Chronic myeloid leukemia (CML) in adults (Beyond the Basics)")
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SUMMARY

- Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm derived from an abnormal multipotent hematopoietic stem cell that has acquired the *BCR-ABL1* fusion gene, usually through t(9;22)(q34;q11), also known as the Philadelphia chromosome. (See 'Cell of origin' above.)
- All leukemias, including CML, appear to be maintained by a pool of self-renewing malignant cells called leukemic stem cells (LSC). CML LSC may be more immature than the majority of circulating leukemic cells and are thought to have originated from cells with existing self-renewal capacity or from progenitors that have re-acquired this stem cell-like property. (See 'The leukemia stem cell' above.)
 - The development of chronic phase CML appears to be a direct result of BCR-ABL1 activity, which promotes its development by allowing:

- Uncontrolled proliferation of transformed cells (see 'Uncontrolled proliferation' above)
- Discordant maturation (see 'Discordant maturation' above)
- Escape from apoptosis (see 'Escape from apoptosis' above)
- Altered interaction with the cellular matrix (see 'Altered interaction with the cellular matrix' above)
- The progression of CML from chronic phase to accelerated phase or blast crisis is a complex, multistep process that is only partially understood. The following events appear to be necessary for the transformation of chronic phase CML into an acute phase of disease:
 - Constitutive expression of the BCR-ABL1 tyrosine kinase (see 'BCR-ABL1 activity' above)
 - Differentiation arrest (see 'Differentiation arrest' above)
 - Genetic instability and additional chromosomal abnormalities (see 'Genetic instability' above)
 - Inactivation of tumor suppressor genes (see 'Inactivation of tumor suppressor genes' above)
- Mouse models have provided support for BCR-ABL1 as the principal cause of these malignancies and have allowed for the *in vivo* study of BCR-ABL1 signaling, identification of novel genes involved in CML development, and testing of potential therapies. (See 'Mouse models of CML' above.)

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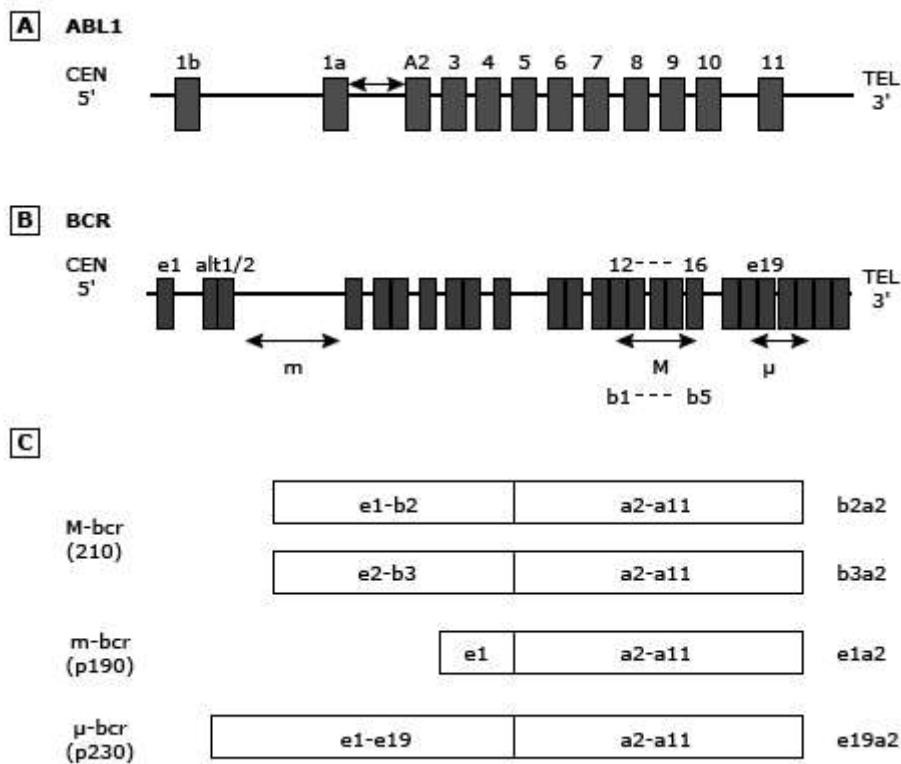
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GRAPHICS

ABL1 and BCR genes in chronic myeloid leukemia



A schematic representation of the ABL1 gene on chromosome 9 (A) and the BCR gene on chromosome 22 (B). All exons (red/blue boxes) have been scaled to the same size for clarity. Exon numbers are indicated above the coding sequence and the breakpoint cluster nomenclature is placed below the M-bcr (b1-b5). Introns are represented by the intervening lines. The various breakpoint regions are identified by double-headed arrows. The schematic fusion transcripts for the typical M-, m-, and μ -bcr are illustrated (C), while the translocation product is demonstrated on the right.

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