Animal models of BCR–ABL+ leukemias have provided important new knowledge about the molecular pathophysiology of these diseases, and answered questions that are difficult or impossible to address using BCR–ABL-expressing cell lines or primary Ph+ leukemia samples from patients. The power of mouse models lies in their ability to recapitulate precisely the phenotypes of BCR–ABL+ leukemias in vivo, but this comes at the price of significant complexity. Here I review recent studies of leukemias induced in mice by BCR–ABL with an emphasis on the intricate nature of these diseases and the need for careful pathological and molecular analysis.

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Introduction

The molecular biology of BCR–ABL and its protein product, the Bcr–Abl tyrosine kinase, have been intensively analysed in cell culture systems since the discovery of the fusion oncogene nearly 18 years ago. Through these studies, we know that Bcr–Abl has increased tyrosine kinase activity relative to c-Abl (Ilaria and Van Etten, 1995; Lugo et al., 1990) and has gained the ability to transform fibroblasts (Lugo and Witte, 1989), cytokine-dependent hematopoietic cell lines (Daley and Baltimore, 1988; Harirahan et al., 1988), and primary bone marrow B-lymphoid cells (McLaughlin et al., 1987). The primary structures of the Bcr and Abl polypeptides have been analyzed and dissected in great detail, with the elucidation of an oligomerization domain (McWhirter et al., 1993), Grb2 binding site (Pendergast et al., 1993b; Puil et al., 1994), serine kinase activity (Maru and Witte, 1991) and regulatory phosphorylation sites (Liu et al., 1996; Wu et al., 1998), SH2 binding domain (Pendergast et al., 1991) and Dbl homology in Bcr and description of N-terminal SH3 (Franz et al., 1989; Jackson and Baltimore, 1989; Van Etten et al., 1995), SH2 (Ilaria and Van Etten, 1995; Mayer et al., 1992) and catalytic domains (Pendergast et al., 1993a) and C-terminal adapter protein binding sites (Ren et al., 1994), nuclear localization signals (Wen et al., 1996) and DNA-binding (Kipreos and Wang, 1992) and actin-binding (McWhirter and Wang, 1993; Van Etten et al., 1994) domains in Abl. Studies in cultured cells have identified many signal transduction pathways activated by Bcr–Abl, including activation of Ras (Sawyers et al., 1995), MAPK (Cortez et al., 1997), JNK/SAPK (Raitano et al., 1995), phosphatidylinositol-3 kinase (Skorski et al., 1995a; Varticovski et al., 1991), NF-κB (Reuther et al., 1998), and STAT pathways (Carlesso et al., 1996; Ilaria and Van Etten, 1996; Shuai et al., 1996). Studies with inhibitors and dominant-negative mutants have suggested that several of these pathways contribute to transformation of fibroblasts or hematopoietic cells by Bcr–Abl in vitro (Dickens et al., 1997; Nieborowska-Skorska et al., 1999; Reuther et al., 1998; Sawyers et al., 1992, 1995; Raitano, 1995; Skorski et al., 1995a,b).

Although much has been learned about the biology of BCR–ABL through these studies, a complete understanding of the pathophysiology of BCR–ABL-associated leukemias requires the expression of the oncogene in the hematopoietic system of a living organism. This is because the complex nature of leukemia cannot be adequately modeled in any currently existing cell culture system. Although cell lines do exist that recapitulate some aspects of hematopoietic differentiation in vitro, these may not be appropriate systems for the analysis of BCR–ABL activity. For example, although the hallmark of human chronic myeloid leukemia (CML) is an overproduction of myeloid cells with preservation of myeloid differentiation, expression of BCR–ABL in 32D cells, which can undergo terminal granulocytic differentiation in response to G-CSF, blocks the ability of these cells to differentiate (Laneuville et al., 1991). Furthermore, while murine embryonic stem (ES) cells can undergo differentiation in vitro to all myeloid lineages, studies of BCR–ABL activity in ES cells have not provided major insights into leukemogenesis. Expression of BCR–ABL in ES cells alters the balance of in vitro erythroid differentiation towards myeloid and multipotential progenitors (Era and Witte, 2000) and permits multilineage engraftment of irradiated recipient mice by differentiated ES cells (Perlingeiro et al., 2001), but the hematologic disease that develops in recipients is not an accurate representation of human CML (Peters et al., 2001).

In order to express BCR–ABL directly in the hematopoietic system of mice, both transgenic and
retroviral transduction approaches have been employed. Despite a large effort, there is no realistic transgenic model of BCR–ABL-induced CML (Van Etten, 2001). However, the retroviral expression system does provide such a model, and will be the focus of this review.

An accurate and quantitative model of CML in mice

Human CML can be faithfully modeled in mice by retroviral transduction of the BCR–ABL gene into mouse bone marrow cells, followed by transplantation into irradiated syngeneic mice (Daley et al., 1990; Kelliher et al., 1999). When high-titer virus stock is employed, this procedure induces CML-like myeloproliferative leukemia in all recipients within 4 weeks after transplantation (Li et al., 1999; Pear et al., 1998; Zhang and Ren, 1998). Mice with BCR–ABL-induced CML-like disease exhibit massive polyclonal expansion of maturing myeloid cells, principally neutrophils, which express Bcr–Abl protein and infiltrate spleen, liver, and lungs. Although neutrophils are the predominant hematopoietic lineage overproduced in murine CML-like disease, macrophages, erythroid progenitors, B-lymphocytes and sometimes T-lymphocytes from diseased mice carry the same spectrum of BCR–ABL proviral clones as the granulocytes, demonstrating that the cells initiating the CML-like leukemia are early multipotential progenitors (Li et al., 1999). The CML-like disease is efficiently transferred by transplantation of bone marrow or spleen cells from a primary animal to irradiated secondary recipients (Li et al., 1999; Pear et al., 1998; Zhang and Ren, 1998). Interestingly, of the many different BCR–ABL-transduced clones that contribute to the leukemia in the primary mouse, only a small subset are capable of generating day 12 spleen colonies and of engrafting and inducing CML-like disease in secondary recipients (Li et al., 1999; Zhang and Ren, 1998), suggesting that the cells initiating CML-like disease are heterogeneous for self-renewal. Serial transplantation leads to evolution of the leukemic process into clonal acute myeloid or more often lymphoid leukemia, representative of blast crisis (Daley et al., 1991; Pear et al., 1998). Murine CML-like leukemia is therefore an accurate and faithful model of human CML that has proven useful for analysis of the molecular pathophysiology of this disease (Li et al., 2001; Li et al., 1999; Million and Van Etten, 2000; Roumiantsev et al., 2001).

Multiple distinct leukemias originate from BCR–ABL-transduced marrow

All recipients of BCR–ABL-transduced marrow develop CML-like disease when bone marrow donors are pretreated with 5-fluorouracil (5-FU) before harvest. This is consistent with the origin of these leukemias from early progenitor/stem cells, whose transduction is favored by 5-FU treatment. However, other BCR–ABL-transduced progenitors are present in the bone marrow population and can induce other forms of leukemia if recipients do not first succumb to CML-like disease. This can be seen with decreases in virus titer (Daley et al., 1990), alterations in transduction conditions (Elefanty and Cory, 1992), or by employing marrow from donors not treated with 5-FU (Li et al., 1999). These other malignancies include acute B-lymphoid and T-lymphoid leukemia/lymphoma, erythroleukemia, and histiocytic tumors (sarcomas) arising from the myelomonocytic lineage. The latter disease most closely resembles one of the human histiocytoses such as malignant histiocytic reticuloendotheliosis (Groopman and Golde, 1981), which does not typically have a Ph chromosome.

These multiple leukemias can compete within the bone marrow of recipient mice and lead to confusing clinicopathological syndromes under certain conditions. In recipients of BCR–ABL-transduced marrow from non-5-FU-treated donors, a mixture of CML-like myeloproliferative disease, B-cell acute lymphoblastic leukemia (B-ALL), and histiocytic sarcoma develops, with some recipients having two or even all three diseases simultaneously (Li et al., 1999). Such leukemic mice have the cardinal clinicopathological features of each disease independently and can be recognized by careful histological analysis and by the demonstration of distinct proviral clones in the different leukemic cells. The effect of competing leukemias can also be observed with mutations in BCR–ABL that attenuate the induction of CML-like disease, such as point mutations in the Src homology 2 (SH2) domain. The R1172K mutation in p210 BCR–ABL eliminates phosphotyrosine binding by SH2 (Ilaria and Van Etten, 1995) and recipients of p210 R1172K-transduced marrow all succumb to B-ALL (Roumiantsev et al., 2001), suggesting that the SH2 domain is absolutely required for induction of CML-like disease by BCR–ABL.

However, the cells initiating the B-ALL have restricted differentiation potential (Li et al., 1999) and phenotypic characteristics of early B-lymphoid progenitors (D Krause and RA Van Etten, unpublished observations). Depletion of these progenitors from the p210 R1172K-transduced marrow allows CML-like disease to reemerge in recipients after a delay, demonstrating that loss of Bcr–Abl SH2 function merely attenuates the development of CML-like leukemia but does not eliminate it (Roumiantsev et al., 2001). Defining the nature of the bone marrow progenitors that initiate distinct BCR–ABL-induced leukemias and developing methods to model each disease separately are major goals for future work. Importantly, B-ALL can be efficiently induced in the absence of CML-like disease by direct transduction and transplantation of marrow from non-5-FU-treated donor mice (Roumiantsev et al., 2001), allowing this BCR–ABL-induced disease, which is an accurate representation of human Ph + acute B-lymphoblastic leukemia, to be quantitatively modeled in mice.
Autocrine and paracrine effects in BCR–ABL leukemogenesis

Another intricacy of BCR–ABL-induced leukemia is that BCR–ABL can induce the secretion of multiple cytokines. This was appreciated initially from studies in the myeloid cytokine-dependent FDCP-1 cell line, where expression of BCR–ABL induces secretion of IL-3 in an SH2-dependent fashion (Anderson and Mladenovic, 1996; Hariharan et al., 1988). However, the ability of BCR–ABL to transform IL-3-dependent hematopoietic cell lines to become independent of exogenous IL-3 for survival and growth does not involve an autocrine mechanism (Daley and Baltimore, 1988; Hariharan et al., 1988; Ilaria and Van Etten, 1995).

In bone marrow transplant experiments, cytokine secretion by BCR–ABL-expressing cells can lead to expansion of hematopoietic cell populations in recipient mice that do not express the oncogene. A good example is the histiocytic sarcoma induced by BCR–ABL. Small areas of perivenular histiocytic infiltration are frequently observed in livers of mice with CML-like leukemia (Figure 1a), and analysis of proviral integration patterns demonstrates these cells are derived from the same multilineage progenitors that generate the neutrophils in this disease (Li et al., 1999). However, BCR–ABL-induced histiocytic malignancies can exist independently of classic myeloproliferative disease (Figure 1b), where they are characterized by slow accumulation of malignant macrophages that involve liver, mesentery, peritoneum and often associated with ascites (Daley et al., 1990; Elefanty et al., 1990). Mice with primary histiocytic sarcoma can exhibit increased levels (from 10–50 × 10^6 per mm^3) of neutrophils in the peripheral blood, suggestive of myeloproliferative disease; however, molecular analysis demonstrates that these neutrophils do not contain the retroviral provirus and hence are not a direct part of the malignant process (Daley et al., 1990; Elefanty et al., 1990; Scott et al., 1991). Mice with histiocytic sarcoma contain increased levels of circulating G-CSF and GM-CSF that are likely produced directly by these tumors and may responsible for the secondary increase in neutrophils (Elefanty et al., 1990). This illustrates that one must be extremely careful about diagnosing myeloproliferative disease in mice that harbor histiocytic sarcoma.

This phenomenon was responsible for some initial confusion about the leukemogenic properties of v-abl, the transforming gene of Abelson murine leukemia virus, when expressed in murine bone marrow. It was first reported that v-abl also induced CML-like disease in recipients of transduced marrow (Kellilher et al., 1990), and others subsequently described chronic myeloproliferative disease induced by v-abl in similar experiments (Chung et al., 1991; Han et al., 1991). However, these mice develop a complex mixture of B-lymphoid, mast cell, and histiocytic tumors and although some recipients have increased circulating neutrophils, genomic DNA from these cells lack the retroviral provirus and hence likely arise from paracrine stimulation by secreted cytokines (Scott et al., 1991). The inability of v-abl to induce CML-like myeloproliferative disease in the current high-efficiency retroviral bone marrow transduction/transplantation model system was confirmed by two recent studies (Gross and Ren, 2000; Million and Van Etten, 2000).

To complicate matters further, mice with BCR–ABL-induced CML-like disease exhibit a modest increase in circulating interleukin 3 (IL-3) (Li et al., 1999; Zhang and Ren, 1998), and perhaps in granulocyte-macrophage colony-stimulating factor (GM–CSF) as well (Zhang and Ren, 1998). The increase in IL-3 is particularly interesting because of the recent observation that primitive Ph^+ progenitors from human chronic phase CML patients express aberrant transcripts for IL-3 and exhibit autonomous in vitro growth that is partially inhibited by anti-IL-3 antibodies (Jiang et al., 1999). These observations
suggested that autocrine production of IL-3 might contribute to the pathogenesis of both human and murine CML. However, when mice with homozygous inactivation of the Il3 or both the Il3 and Gmcsf genes are used as donors in the retroviral bone marrow transduction/transplantation model, recipients of BCR–ABL-transduced marrow efficiently develop myeloproliferative disease (Li et al., 2001), demonstrating that neither cytokine is required for the pathogenesis of CML-like disease in this model system. Interestingly, increased circulating IL-3 is still observed in wild-type recipients of BCR–ABL-transduced marrow from Il3−/− donors but not when the host is of Il3−/− genotype (Figure 2), demonstrating that the source of increased IL-3 is the recipient, not the BCR–ABL-expressing donor cells (Li et al., 2001). Levels of circulating IL-3 are higher in recipients of marrow transduced with BCR–ABL retroviral vectors that co-express A. victoria green fluorescent protein (GFP) at high levels from an internal ribosome entry site than with vectors expressing a neomycin phosphotransferase gene at low levels from an internal promoter (Figure 2), while there is no increase in IL-3 in recipients of marrow transduced with an empty retrovirus. Collectively, these results suggest that the elevation in IL-3 represents an immunological reaction of the recipient to transplantation of bone marrow expressing a foreign protein.

The use of such bicistronic retroviral vectors, which co-express BCR–ABL and GFP from a single mRNA via an internal ribosome entry site (IRES), facilitates titering of retroviral stocks and allows the identification by flow cytometric analysis of transduced hematopoietic cells in diseased mice (Pear et al., 1998). The presence of a large fraction of GFP− myeloid cells in mice with BCR–ABL-induced CML-like disease has been taken as evidence of a significant paracrine effect in this model system (Zhang and Ren, 1998), but the persistence of this GFP CD11b+ myeloid population in Il3−/− Gmcsf−/− recipients of BCR–ABL-transduced marrow from donors of the same genotype (Tomasson et al., 2001) demonstrates that IL-3− or GM−CSF are not responsible. The majority of these GFP+ cells are probably accounted for by mechanisms other than paracrine stimulation of normal marrow progenitors. While it is fairly certain that GFP+ cells also express BCR–ABL, the converse is not true, and a large fraction of the GFP− cells must contain the retroviral provirus and may also express BCR–ABL. This follows from the observation that myeloid cells from these mice contain the BCR–ABL provirus at levels that are greater than or equal to one proviral copy per diploid genome (Li et al., 1999), and indeed Southern blotting of genomic DNA from purified GFP+ and GFP− myeloid cell populations from mice with myeloproliferative disease induced by an oncogenic receptor tyrosine kinase, activated FLT3, demonstrates equivalent levels of the provirus in the two populations (Kelly et al., 2002). The explanation for the lack of detection of GFP in provirus− cells may involve loss of GFP due to cell damage during in vitro manipulation (Tomasson et al., 2001) and possibly to genetic or epigenetic mechanisms that impair IRES function after proviral integration.

These examples demonstrate that autocrine and paracrine effects of BCR–ABL expression are an inevitable complication of in vivo leukemogenesis model systems that must be considered during the analysis of hematologic malignancies induced by BCR–ABL in mice.

![Figure 2](image-url) Recipients of BCR–ABL-transduced marrow produce IL-3 in reaction to GFP. Plasma IL-3 levels in transplanted mice were measured with an ELISA assay that detects nanogram quantities of this cytokine in biological fluids (Li et al., 2001). Leukemic recipients of BCR–ABL-transduced marrow (BCR–ABL (combined)) exhibit increased levels of circulating IL-3 relative to mice transplanted with untransduced marrow (control BMT) or with marrow transduced with empty vector (MSCVneo). Recipients of marrow transduced with retrovirus co-expressing high levels of A. Victoria green fluorescent protein (MSCV-IRES/GFP) exhibit significantly greater increases in circulating IL-3 than with BCR. Use of donors (BCR–ABL IL3 to WT) or recipients (BCR–ABL WT to IL3) with homozygous inactivation of the Il3 gene demonstrate that the source of IL-3 is the recipient, not the BCR–ABL-expressing donor cells.

Not all myeloproliferative disease is created equal: the case of Tel–Abl

Fatal myeloproliferative leukemia develops in recipients of bone marrow transduced with retroviruses expressing a wide variety of dysregulated tyrosine kinases in addition to Bcr–Abl, including Tel–Jak2 (Schwaller et al., 1998), Tel–PDGF/R (Tomasson et al., 2000), and activated FLT3 (Kelly et al., 2002). However, the human hematologic diseases associated with these different kinases have some distinct features from classical Ph+ CML, and careful histopathological and molecular analysis of the disease process in mice can yield valuable insights into differences in patho-
physiology. The leukemogenic activity of the Tel–Abl fusion tyrosine kinase provides a good illustration of this.

Fusion of the ABL gene to TEL (also called ETV6) on chromosome 12p13 has been reported in six patients with leukemia, three of whom had acute leukemia of B-lymphoid (Papadopoulos et al., 1995), T-lymphoid (van Limbergen et al., 2001) and undifferentiated myeloid (Golub et al., 1996) origin, the other three with atypical (Brunel et al., 1996) or typical (Andreasson et al., 1997; van Limbergen et al., 2001) CML.

TEL encodes a ubiquitously expressed 452 amino acid protein with homology to the Ets family of transcription factors (Golub et al., 1994). Two different TEL–ABL fusions have been observed; in the patients with B-ALL and atypical CML, the first four exons of TEL were fused to ABL exon 2, while the other four patients had TEL exons 1–5 fused to ABL exon 2. The resulting chimeric Tel–Abl proteins contain Tel amino acids 1–154 or 1–336, respectively, fused to the same 1104 COOH-terminal amino acids of c-Abl that is found in the Bcr–Abl fusion proteins. Both Tel–Abl fusion proteins share an NH2-terminal region of Tel (the PNT homology domain) that mediates homooligomerization (Golub et al., 1996; Jousset et al., 1997). The fact that Tel contains a coiled-coil oligomerization domain that is also required for activation of Bcr–Abl kinase activity and transformation (McWhirter et al., 1993) has led to the suggestion that oligomerization of Abl is the critical event in the pathogenesis of these leukemias, and that other functions of the NH2-terminal Abl fusion partner are unimportant. Consistent with this, Tel–Abl has been shown to transform Rat-1 fibroblasts (Golub et al., 1996), primary bone marrow B-lymphoid cells (Golub et al., 1996), and cytokine-dependent Ba/F3 hematopoietic cells (Golub et al., 1996; Hannemann et al., 1998) in vitro in a manner indistinguishable from Bcr–Abl. Furthermore, Tel–Abl and Bcr–Abl activate similar intracellular signaling pathways in cultured hematopoietic cells (Okuda et al., 1996; Voss et al., 2000).

However, when the ability of the larger Tel–Abl fusion protein to induce myeloid leukemia in mice was tested in the retroviral bone marrow transplantation model, several distinct differences with Bcr–Abl-induced myeloproliferative disease were noted (Million et al., 2002). Some recipients of TEL–ABL-transduced bone marrow succumbed to CML-like leukemia that was very similar to that induced by BCR–ABL but with a significant increase in disease latency. However, most TEL–ABL recipients died abruptly around 4–5 weeks post-transplantation with moderate leukocytosis and spleenomegaly (Figure 3a), but without evidence of the pulmonary myeloid infiltrates and hemorrhage that are the cause of morbidity and death in mice with classic CML-like disease. Histopathological evaluation of these mice revealed acute fatty liver and extensive neutrophilic infiltration and necrosis of the small bowel villi (Figure 3b,c). The hepatic picture is suggestive of endotoxin-induced injury, and indeed analysis of serum cytokine and chemistry profiles from premorbid mice revealed significant elevations in circulating endotoxin and TNFz with evidence of fulminant hepatic and renal failure (Figure 4). This distinctive fatal illness has been named small bowel syndrome (SBS). The precise pathophysiological mechanism of SBS and its distinct association with Tel–Abl are under investigation, but it is possible that abnormal homing of Tel–Abl expressing neutrophils to the gut and/or direct induction of TNFz expression by Tel–Abl are responsible (Figure 5). The relevance of Tel–Abl-induced SBS to human disease is suggested by the presence of ulcerative bowel disease in a patient with Tel–Abl-associated CML (van Limbergen et al., 2001).

A second distinct difference between BCR–ABL and TEL–ABL-induced leukemias is observed upon adoptive transfer of leukemic cells from primary diseased mice into secondary recipients. Similar to BCR–ABL, TEL–ABL-induced CML-like disease arises from multilineage progenitors capable of generating day 12 spleen colonies in secondary transplants, but neither TEL–ABL-induced CML-like disease nor SBS could be transferred to lethally irradiated recipient mice despite transplantation of large numbers of viable bone marrow and/or spleen cells (Million et al., 2002). In contrast, BCR–ABL-induced CML-like disease is successfully transferred to secondary recipients over 80% of the time under identical conditions. Most TEL–ABL secondary recipients succumbed to early or delayed graft failure, with others developing T-lymphoid or histiocytic tumors after long latent periods (Figure 6). Many of the former secondary mice had evidence of provirally marked cells in the spleen 2–3 weeks post-transplantation but these clones failed to radioprotect the recipients. These results suggest that TEL–ABL may act to expand a hematopoietic progenitor that lacks self-renewal as measured by secondary transplantation, or that TEL–ABL directly inhibits self-renewal of stem cells. Distinguishing between these possibilities will require further experiments and may have important implications for the treatment of these diseases by autologous stem cell transplantation.

Conclusions

The BCR–ABL+ leukemias are perhaps the most thoroughly understood of human malignancies, in part because of the development of accurate animal models for these diseases. In this review, I have tried to illustrate that the pathophysiology of these diseases must be understood in the most minute detail if the experimental results are to provide information useful for understanding human leukemia. A common mistake in analysis of murine leukemia experiments is to use survival as the primary endpoint of the study but fail to define precisely the cause of morbidity or death. As demonstrated by TEL–ABL, similar survival
Figure 3 A novel fatal syndrome of small bowel myeloid infiltration and hepatic steatosis in recipients of TEL–ABL-transduced bone marrow. (a) Comparison of peripheral blood leukocyte counts (upper panel) and spleen weights (bottom panel) at time of morbidity or death of mice with BCR–ABL- or TEL–ABL-induced CML-like disease versus TEL–ABL-induced small bowel syndrome (SBS). Mice with SBS exhibit increased circulating myeloid cells and modest splenomegaly relative to normal controls but significantly lower than mice with classic CML-like myeloproliferative disease. (b) Photomicrograph of H&E-stained small intestine of a mouse with SBS sacrificed at the time of morbidity. Serosal surface is oriented to the bottom with villous surface upwards. Note the extensive infiltration of villi with neutrophils with concomitant necrosis. Magnification 200×. (c) Photomicrograph of H&E-stained liver from mouse with SBS, demonstrating lack of cellular infiltrate but with extensive microvesicular change and hepatocellular apoptosis. Similar findings are present in all mice with SBS but to a varying degree. Insert shows oil red staining of this liver, demonstrating that the vacuolar change is due to the accumulation of neutral lipids such as triglycerides. Magnification 400×.

Figure 4 Increased circulating endotoxin and TNFα and hepatic and renal failure in mice with TEL–ABL-induced small bowel syndrome (SBS). Plasma endotoxin (far left) and TNFα (second from left) levels in mice with BCR–ABL- and TEL–ABL-induced CML-like disease were determined by commercial ELISA assays and compared with TEL–ABL-induced SBS and control recipients of untransduced marrow (normal Balb/c). Similarly, plasma glucose (third from left) and blood urea nitrogen (BUN, far right) levels were measured in these mice. Mice with SBS exhibit variable but significant increases in circulating endotoxin and TNFα, with marked hypoglycemia and increased BUN characteristic of severe liver and kidney dysfunction.

curves can result from very different pathological processes. Conversely, the case of BCR–ABL SH2 mutants shows that minor changes in the physiology of what is essentially the same leukemic process can result in disparate survival outcomes. Careful and creative application of these model systems should continue to provide important new knowledge about the pathophysiology of BCR–ABL+ leukemia that cannot be obtained from analysis of cell lines or primary leukemic cells.
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Figure 5 Possible pathophysiological mechanism of TEL–ABL-induced small bowel syndrome. Transplantation of TEL–ABL-transduced bone marrow into irradiated recipient mice (BMT) is followed by homing of Tel–Abl-expressing neutrophils to the small bowel with infiltration and necrosis. Because mice with TEL–ABL-induced CML-like disease do not exhibit significant infiltration of the small bowel despite large numbers of circulating Tel–Abl neutrophils, it is possible that transient alterations in expression of leukocyte homing receptors in the gut from the radiation employed in the conditioning regimen contribute to the disease. Destruction of the bowel mucosal barrier leads to endotoxemia and stimulates TNFα production by monocytes, which is directly responsible for hepatic fatty change and apoptosis, leading to shock and renal acute tubular necrosis (ATN). It is also possible that direct induction of TNFα expression by Tel–Abl-expressing hematopoietic cells contributes to the pathogenesis of SBS.

Figure 6 Neither TEL–ABL-induced CML-like disease nor SBS can be transferred to secondary recipients. Pie diagrams representing outcomes of transplantation of bone marrow and spleen cells from primary mice with BCR–ABL-induced CML-like disease (left), TEL–ABL-induced CML-like disease (middle panel), or TEL–ABL-induced SBS (right panel) into lethally irradiated secondary recipient mice. The phenotype of disease that developed in secondary recipients is indicated by the color code at the bottom.
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