Assembling defenses against therapy-resistant leukemic stem cells: Bcl6 joins the ranks

Francesca Pellicano and Tessa L. Holyoake

The resistance of leukemic stem cells in response to targeted therapies such as tyrosine kinase inhibitors (TKIs) relies on the cooperative activity of multiple signaling pathways and molecules, including TGFβ, AKT, and FOXO transcription factors (TFs). B cell lymphoma 6 (BCL6) is a transcriptional repressor whose translocation or mutation is associated with diffuse large BCL. New data now show that BCL6 is critical for the maintenance of leukemias driven by the BCR-ABL translocation (Philadelphia chromosome), suggesting that BCL6 is a novel, targetable member of the complex signaling pathways critical for leukemic stem cell survival.

Chronic myeloid leukemia (CML) arises from a translocation event within a normal hematopoietic stem cell (HSC) that results in a protein fusion between the tyrosine kinase (TK) ABL and the breakpoint cluster region (BCR) encoded on chromosome 22. The resulting fusion gene encodes for BCR-ABL, a constitutively active kinase that drives disease pathogenesis by increasing the production of mature and immature myeloid cells (Rowley, 1973). Over the last 10 yr, highly effective ABL TKIs have been developed (Druker et al., 1996). However, CML stem cells are inherently insensitive to these inhibitors, suggesting that CML is unlikely to be cured using TKIs alone and that combination therapy with agents able to induce apoptosis in CML stem cells in a selective manner will be required for disease eradication (Graham et al., 2002; Bhatia et al., 2003; Mahon et al., 2010). With growing evidence that BCR-ABL$^+$ CML stem cells are dependent on several key survival pathways, this scenario may now be achievable, thus offering the possibility of developing novel therapeutic approaches.

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BCL6: A key player in CML stem cell survival

Recent studies have added BCL6, a repressive zinc finger TF, to a small team of players in the resistance of BCR-ABL$^+$ stem cells to TKI treatment. Duy et al. (2011) generated a model for Philadelphia$^+$ (Ph$^+$) pre–B cell acute lymphoblastic leukemia (ALL) and found that BCL6 is critical for the survival of stem cells. In Ph$^+$ ALL cells, BCL6 was up-regulated in response to TKI, allowing the cells to survive treatment. Furthermore, BCR-ABL–transformed B lymphoblasts lacking BCL6 were not able to induce leukemia in immunodeficient mice. Treatment with the TKI imatinib was more effective in BCL6$^{-/-}$ BCR-ABL$^+$ ALL than in their BCL6$^{+/+}$ counterparts, suggesting a protective role for BCL6 in ALL stem cells treated with TKIs (Duy et al., 2011).

In this issue, Hurtz et al. demonstrate that BCL6 up-regulation by TKI maintains the self-renewal capacity of CML-initiating cells by inducing Forkhead box 3a (FOXO3a) signaling and by repressing Arf and p53. In CML, BCL6 expression was repressed at the mRNA and protein level in a BCR-ABL–dependent manner and was reactivated upon treatment with TKI, particularly in primary CD34$^+$ and primitive CD34$^+$38$^-$ cell subpopulations. Sensitivity to imatinib was greatly increased in primitive mouse hematopoietic cells (Lin$^-$Sca$^-$1$^+$c-Kit$^+$; LSK) that were retrovirally transduced with BCR-ABL but lacked BCL6, suggesting that BCL6 was required for drug resistance in these cells. BCL6 was also required for maintenance of these cells, as BCL6$^{-/-}$ CML cells rapidly underwent apoptosis. Furthermore, a dominant-negative form of BCL6 suppressed leukemogenesis in vivo, and p53 was identified as a key transcriptional target of BCL6. In fact, p53 was required for the dominant-negative form of BCL6 to suppress colony formation in vitro. Together, these data provide evidence that BCL6 functions to protect CML stem cells from TKI treatment, at least in part, by suppressing the Arf–p53 pathway.

First-string players in leukemic stem cell (LSC) survival

Several important factors have recently been investigated as potential key players in LSC survival. Some of these belong to the same signaling pathway as BCL6, whereas others are less directly involved; among the former are FOXO3a and phosphatase and tensin homologue (PTEN).

FOXO3a is a member of the FOXO TF family, which induces BCL6 expression in the BCR-ABL$^+$ cell line BV173 (Fernández de Mattos et al., 2004). The studies by Duy et al. (2011) and Hurtz et al. (2011) both suggest that FOXO TFs are upstream inducers of BCL6, specifically FOXO4 in Ph$^+$ ALL and FOXO3a in CML. The FOXO TFs, among other activators of BCL6, are negatively regulated by BCR-ABL through the PI3K–AKT

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pathway (Brunet et al., 1999). In Ph$^+$ cells, these TFs are normally inactive and localized to the cytoplasm; however, TKI-mediated inhibition of BCR-ABL leads to their activation and cell cycle arrest (Komatsu et al., 2003). BCL6 up-regulation after TKI treatment, as demonstrated in the recent studies, provides one possible explanation for why and how CML-initiating cells persist in patients despite long-term TKI treatment. It has been shown that FOXO TFs are important for the maintenance of both normal and CML stem cells (Tothova et al., 2007; Naka et al., 2010). In the specific case of FOXO3a, a syngeneic murine transduction/transplantation system that reproduces CML-like disease was used to show that FOXO3a is essential for the maintenance of CML stem cells (Naka et al., 2010). In that study, deletion of FOXO3a abrogated the ability of CML stem cells to generate disease. The authors also suggested that TGF-β, through inhibition of AKT activity, was responsible for FOXO3a activation. Nevertheless, no downstream effectors of FOXO3a were suggested to explain the FOXO3a-mediated maintenance of CML stem cells. Hurtz et al. (2011) provide a missing piece of this puzzle, and it is now possible to hypothesize a more complete signaling cascade leading from TGF-β through AKT to BCL6/p53 that maintains the survival of LSCs (Fig. 1).

Another player in the BCL6 signaling pathway is the tumor suppressor gene PTEN (Stambolic et al., 1998). PTEN is critical in adult hematopoietic cells, and its deletion leads to transplantable ALL in association with induction of p16^{Ink4a} and p53 (Yilmaz et al., 2006; Lee et al., 2010). The PI3K–AKT–FOXO pathway is negatively regulated by PTEN, and in the Duy et al. (2011) and Hurtz et al. (2011) studies, conditional deletion of PTEN abrogated the ability of Ph$^+$ ALL and CML cells to up-regulate BCL6 in response to TKI treatment. Another group also showed a critical role for PTEN in both CML and Ph$^+$ ALL (Peng et al., 2010), as PTEN was down-regulated by BCR-ABL in LSCs, and its deletion led to accelerated leukemia development. However, PTEN overexpression delayed the development of CML and Ph$^+$ ALL and prolonged survival of leukemic mice. It is likely that PTEN drives this survival effect by regulating its downstream protein AKT (Fig. 1).

Collectively, these studies reveal several potentially targetable proteins in a single signaling pathway, including TGF-β, AKT, and BCL6 (Fig. 1). Naka et al. (2010) used a combination of TGF-β inhibition by Ly364947 and TKI treatment and found that CML was completely eradicated in the transduction/transplantation mouse model. Duy et al. (2011) inactivated BCL6 with the retro-inverso BCL6 peptide inhibitor RI-BPI, resulting in delayed progression of Ph$^+$ ALL. In addition, treatment with a combination of imatinib and RI-BPI prevented acquisition of TKI resistance in the long term and potentiated the effect of TKI on refractory ALL cells. In the CML model, RI-BPI targeted primary leukemic CD34$^+$ cells, including the more primitive CD34$^+$38$^-$ population, and interfered with initiation of CML. Whereas RI-BPI alone did not significantly affect CML cell viability in vitro, it strongly enhanced the effect of imatinib. Survival of the K562 CML cell line was significantly inhibited and apoptosis was effectively induced when mTOR, a downstream target of AKT, was inhibited by rapamycin (Peng et al., 2010). Rapamycin also blocked ALL leukemogenesis induced by PTEN deletion in HSCs, suggesting that mTOR, like BCL6, is an important player in LSC survival (Lee et al., 2010). In keeping with a role for mTOR in LSC survival, the dual mTORC2/mTORC1 inhibitor OSI-027 has been shown to target progenitors from CML patients (Carayol et al., 2010). Interestingly, the tumor

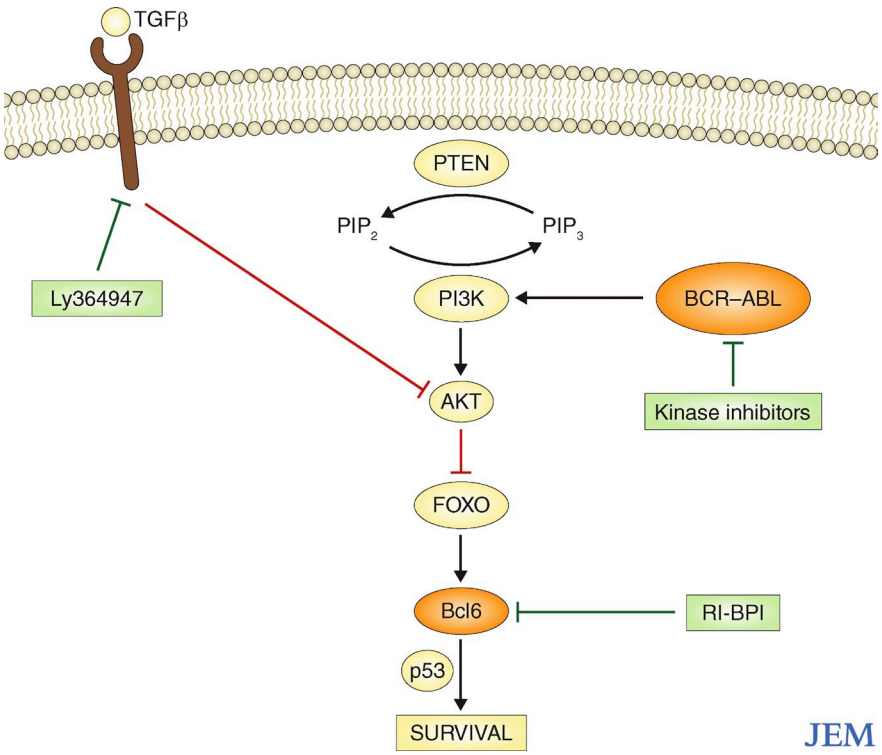

Figure 1. PI3K, AKT, FOXO, and BCL6 are key players in Ph$^+$ stem cell survival. Ph$^+$ ALL and CML are dependent on signals emanating from BCR-ABL through the PI3K–AKT pathway that may be driven by TGF-β via inhibition of AKT. BCL6 acts downstream of FOXO TFs and appears to represent a critical missing piece of the signaling pathway that leads to cancer stem cell survival. This signaling cascade offers potential for therapeutic modulation at various levels, including BCR-ABL inhibition by kinase inhibitors, TGFβ inhibition by Ly364947, and Bcl6 inhibition by RI-BPI.

suppressor promyelocytic leukemia (PML), which is highly expressed in HSCs and maintains quiescence in CML stem cells (Ito et al., 2008), binds to and negatively regulates mTOR (Bernardi et al., 2006). In Ito et al.'s study (2008), degradation and therefore inhibition of PML by an arsenic-based agent, As_2O_3, drove LSCs into cycle and sensitized them to killing by cytarabine. As_2O_3 has already been proven safe and nontoxic in clinical trials in acute leukemia, and is now widely used for this purpose. Furthermore, a phase I/II study of As_2O_3 in combination with imatinib has just been completed for patients with resistant CML in chronic phase (unpublished data).

The second string: Alox5, JAK2, etc.

Beyond PI3K signaling, several pathways also play a meaningful role in LSC survival. These include the arachidonate 5-lipoxygenase–macrophage scavenger receptor 1 (Alox5–Msr1) and protein phosphatase 2A–Janus TK2 (PP2A–JAK2) signaling pathways (Neviani et al., 2005, 2007; Chen et al., 2009). Alox5 is up-regulated by BCR-ABL in a kinase-independent fashion and regulates CML stem cells (Chen et al., 2009). In a mouse model of CML, Alox5 deficiency resulted in impaired LSC function and an inability to propagate CML. Alox5 deficiency appeared to exert its function via the inhibition of the downstream mediator Msr1, a protein that is highly expressed in normal hematopoietic cells but down-regulated in CML (Chen et al., 2011). Msr1 deletion on the Alox5-null background reversed the phenotype, leading to development of CML and aggravating LSCfunction, indicating Msr1 as a tumor suppressor. A specific inhibitor of Alox5, Zileuton, targeted LSCs, both alone and in combination with imatinib, and prolonged the survival of mice with CML-like disease (Chen et al., 2011).

The tumor suppressor PP2A, a serine threonine phosphatase that regulates cell survival and proliferation, was shown to be inactivated in CML progenitors because of BCR-ABL–induced up-regulation of the PP2A inhibitor protein SET (Neviani et al., 2005, 2007). By inducing PP2A phosphatase activity, it was possible to target CML stem cells, regardless of their sensitivity to TKIs. The sphingosine analogue FTY720 and newer, less immunosuppressive analogues are potent PP2A activators that inhibit BCR-ABL phosphorylation and suppress the growth of imatinib-sensitive and -resistant cell lines and primary CML cells. FTY720 suppressed the clonogenic potential of CML stem and progenitor cells, and impaired their self-renewal and long-term repopulating potential (Neviani et al., 2007). FTY720 also induced apoptosis of quiescent human CML stem cells and resulted in a marked reduction in the number of long-term BCR-ABL$^+$ stem cells in a CML mouse model (SCL-tTA/BCR-ABL/GFP). Interestingly, recent evidence suggests that JAK2, a cytokine signaling intermediate, has a role in activating SET downstream of BCR-ABL (Samanta et al., 2009). In CML, BCR-ABL activates JAK2 in the absence of ligand binding (Ilaria and Van Etten, 1996; Austin et al., 1997), and JAK2 inhibition leads to reactivation of PP2A (Neubauer et al., 1998; Samanta et al., 2009). This activation of JAK2 is important for BCR-ABL–driven leukemogenesis and the maintenance of CML stem and progenitor cells (Xie et al., 2002). However, the exact role of JAK2 in the survival of CML stem cells requires further investigation. It is known that BCR-ABL forms a complex with JAK2, leading to enhanced stability and activity of the BCR-ABL protein. This interaction appears to be mediated by Abelson helper integration site 1, an oncogene that alone enhances the oncogenic activity of BCR-ABL, contributing to the resistance of CML stem and progenitor cells to TKI treatment (Zhou et al., 2008). In keeping with a role for JAK2 activity in CML stem cell survival, a potent and specific JAK2 inhibitor (AG490; LC Laboratories) inhibited survival of imatinib-sensitive and -resistant CML cell lines, as well as cells derived from CML patients (Samanta et al., 2009).

Conclusions

Overall, the data strongly suggest that LSCs in both Ph$^+$ ALL and CML are dependent on signals emanating from the PI3K–AKT pathway that are at least partially mediated by TGF-β. Several points in this signaling cascade offer the potential for therapeutic modulation, including TGF-β itself. Because PTEN, FOXO3a, and BCL6 all belong to the same pathway, it is tempting to speculate that an effective TGF-β inhibitor may be sufficient as a single agent; however, this might be associated with unacceptable toxicity to normal tissues that depend on TGF-β for survival. Therefore, the potential to inhibit the pathway at different points is extremely exciting. For these reasons, it is also wise to continue to investigate other factors that have shown potential clinical relevance in CML, such as Alox5, PP2A, and JAK2.

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