The genomic lesions that characterize acute lymphoblastic leukemia in childhood include recurrent translocations that result in the expression of fusion proteins that typically involve genes encoding tyrosine kinases, cytokine receptors, and transcription factors. These genetic rearrangements confer phenotypic hallmarks of malignant transformation, including unrestricted proliferation and a relative resistance to apoptosis. In this Minireview, we discuss the molecular mechanisms that link these fusions to the control of cell death. We examine how these fusion genes dysregulate the BCL-2 family of proteins, preventing activation of the apoptotic effectors, BAX and BAK, and promoting cell survival.

**Recurrent fusion genes in acute lymphoblastic leukemia**

Acute lymphoblastic leukemia (ALL)\(^2\) is the most common form of childhood malignancy. Therapy for ALL is one of the great success stories of modern chemotherapy, and overall cure rates are now >90% in developed countries, depending on molecular subtypes and clinical features (1). The extraordinary improvements in outcomes in ALL have unquestionably been driven by the treatment of patients on international collaborative clinical trials (2), which have made it possible to rapidly recruit sufficient numbers of patients to studies of new treatment regimes. The analysis of treatment responses, based on measurement of minimal residual disease, has allowed the early identification of treatment failure or relapse and the consequent adjustment of treatment intensity.

The next revolution in our understanding of ALL biology is being driven by many studies, involving thousands of patient samples, characterizing the genomic landscape of ALL through genome and transcriptome sequencing (3–7). This has led to the recognition of novel molecular subtypes of ALL, defined by the genomic lesions that drive them. Characterization of leukemic genomes provides insight into the key molecular pathways involved in ALL subtypes.

Many recently identified genomic lesions in ALL are fusion genes, arising from chromosomal translocations (8). These include fusions that activate tyrosine kinases, cytokine receptors, and transcription factors. The presence of these fusions has important prognostic and treatment implications. In this Minireview, we consider how these genomic lesions promote resistance to apoptosis in ALL.

**Gene fusions in ALL**

Chromosomal translocations, resulting in the expression of fusion genes, are a hallmark of B-cell malignancies. This likely arises as fusion partners are mistakenly juxtaposed during periods of genomic editing and recombination-activating gene (RAG1 and RAG2) activation or somatic hypermutation during B-cell development (9). Recurrent chromosomal translocations have been recognized and detected in ALL, initially by staining of metaphases and microscopy, and more recently by fluorescent in situ hybridization (FISH). The detection of a small number of recurrent translocations is a standard component of ALL diagnosis and risk assessment. For example, t(12;21) ETV6-RUNX1 and t(1;19) TCF3-PBX1 identify ALL associated with excellent outcomes, whereas TCF3-PBX1 is associated with a higher incidence of central nervous system involvement. Other fusions are associated with poor prognosis and are an indication for treatment intensification (8). This includes the mixed lineage leukemia-rearranged (MLL-r) leukemias, which are discussed later.

Fusions activating tyrosine kinases are particularly important in ALL, as they are potentially amenable to treatment with tyrosine kinase inhibitors (TKI’s). Imatinib, a small molecule ABL1 inhibitor, has dramatically altered the treatment paradigm for patients with Philadelphia chromosome positive (Ph+) B-ALL and chronic myeloid leukemia (CML) because it encodes the BCR-ABL1 fusion gene (10). The majority of Ph+ patients are now successfully treated with TKI-containing regimens, without the need for hematopoietic stem cell transplant. Philadelphia-like ALL (Ph-like ALL), characterized by a gene expression profile resembling Ph+ ALL but with the absence of BCR-ABL1, is also a fusion-driven
disease, and to date, rearrangements involving 13 kinases and cytokine receptors have been identified (4). The kinases activated in Ph-like ALL, which include ABL1, ABL2, and JAK2, can potentially be targeted with specific TKIs (4, 13).

Many ALL fusion genes block apoptosis

A key test that a fusion gene is a true driver of leukemia is its capacity to inhibit apoptosis induced by cytokine deprivation in cytokine-dependent cell lines (14, 15). This test and determining whether expression of the fusion in hematopoietic stem cells recapitulates the primary tumor when cells are transplanted into syngeneic mice are commonly used to establish genes as drivers of leukemia.

Not all leukemia fusions have the same capacity to block cytokine withdrawal-induced cell death. Fusions that activate tyrosine kinases or cytokine receptor signaling often have this function. Others, principally those that involve transcriptional regulators, readily cause leukemia in mice, but leukemic cells expressing such fusion genes remain cytokine-dependent when cultured ex vivo. Understanding the mechanisms by which fusions repress apoptosis has important therapeutic implications, as blocks in apoptosis are a mechanism of chemoresistance, including resistance to therapies targeting fusions (16, 17). The application of drugs that directly target cell death pathways, or inhibit the signaling pathways downstream of activated tyrosine kinases, may significantly enhance the efficacy of standard chemotherapy. The BCL-2 family of apoptosis regulators is key in this process, because they regulate the cell death responses repressed by leukemia fusion oncogenes (18).

BCL-2 family and cancer

Overexpression of members of the BCL-2 protein family that block apoptosis contributes to malignant transformation. This was first recognized as the mechanism of action of the recurrent translocation t(14;18) in follicular lymphoma (19–21). Amplification of pro-survival, BCL-2-like, genes MCL-1 and BCL-XL and deletion of pro-apoptotic genes BOK and PUMA are over-represented in the somatic copy number variations in over 3000 cancer specimens, across 26 human cancers, including ALL (22).

The BCL-2 family has been reviewed in detail elsewhere (15, 23, 24). However, for the purposes of this review, it is worth considering the key molecular events that regulate cellular commitment to apoptosis in cytokine withdrawal models. Both the cytokine signaling pathways on which cells normally depend and the cell survival pathways activated by kinase fusion genes converge on repressing the activation of the intrinsic apoptotic pathway regulated by the BCL-2 family (Fig. 1).

The BCL-2 family is functionally grouped into proteins that repress apoptosis, BCL-2, BCL-XL, BCL-w, MCL-1, and A1, and the proteins that promote apoptosis (pro-apoptotic) (23). The pro-apoptotic members are further subdivided into two groups, the BAX/BAK subfamily and the BH3-only subfamily, consisting of BIM, BAD, BID, BIK, BMF, PUMA, NOXA, and HRK (25). The pro-survival and BH3-only subgroups regulate the activation of BAX and BAK. Activation of BAX and BAK is the critical step in the commitment to apoptosis, as it is required to trigger mitochondrial outer membrane permeabi-
lization, initiating a cascade of programmed downstream events, including cytochrome c release, formation of the apoptosome by APAF-1, and activation of caspase-9 and the effector caspases, that characterize apoptotic cell death (Fig. 1) (24, 26–28).

The interleukin-3 (IL-3)-dependent cell lines are commonly used to test the capacity of ALL fusions to block apoptosis induced by cytokine deprivation (29). IL-3-dependent cell lines from gene-deleted mice have shown that the presence of at least one of BAX and BAK is absolutely required for cytokine withdrawal-induced apoptosis (30–32). When cytokine is removed from cultures of IL-3-dependent Ba/F3 cells lacking both BAX and BAK, cells remain viable for long periods, although they do not proliferate. When cytokine is restored, cells re-enter the cell cycle and divide again. Demonstrating that some ALL fusions can maintain cell survival in the absence of cytokine provides clear evidence that such leukemia fusion genes directly or indirectly prevent BAX and BAK activation (33, 34).

The molecular mechanisms of BAX and BAK activation are complex and are tightly regulated by the interactions between the BCL-2 protein family members. Mutational and structural analysis shows that BAX and BAK activation is initiated by conformational changes that, for example in the case of BAX, allow translocation and insertion into the outer mitochondrial membrane (35). For both BAX and BAK, the conformational changes expose interaction domains that favor first homodimerization and then the formation of higher order oligomeric structures that ultimately punch a hole in the mitochondrial membrane.

The BH3-only BCL-2 family members initiate BAX and BAK activation in two ways. Some BH3-only proteins directly engage BAX and BAK through an interaction between their BH3 domain and a hydrophobic groove on the surface of BAX and BAK (36, 37). Other BH3-only proteins do not directly bind BAX or BAK, but instead they repress the function of the anti-apoptotic BCL-2 family members through an analogous molecular interaction (37). Anti-apoptotic BCL-2 family members and BAX and BAK share significant structural homology, including the surface of the hydrophobic groove interaction site for the BH3 domain of the BH3-only proteins (25). Anti-apoptotic BCL-2 family proteins can thus “soak up” BH3-only proteins that might otherwise bind BAX or BAK. This is overwhelmed when the abundance of BH3-only proteins increases. The anti-apoptotic BCL-2 family members are also able to directly bind and inhibit activated monomeric BAX and BAK to inhibit apoptosis (24).

**Kinase-activating fusions and anti-apoptotic BCL-2 proteins**

Fusions involving tyrosine kinases in ALL typically result in the loss of regulatory domains, overexpression of the kinase domain, and the acquisition of coiled-coil domains or helix-loop-helix motifs that facilitate oligomerization and autophosphorylation of the kinase domain (38). This could be through the repression of BH3-only protein expression or increased expression of anti-apoptotic BCL-2 proteins. Both mechanisms may operate simultaneously.

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The regulation of MCL-1 protein abundance is important. MCL-1 is absolutely required for normal hematopoietic development (39). The half-life of MCL-1 is short, and it plays a key role in regulating apoptosis in response to cytokine receptor signaling, including interleukin-7 (IL-7)-dependent survival of T- and B-lymphocytes (40). In IL-3 or granulocyte-macrophage colony-stimulating factor (GM-CSF)-dependent hematopoietic cells, MCL-1 undergoes rapid proteasomal degradation soon after cytokine withdrawal (41). When cytokine is restored, MCL-1 expression is rapidly up-regulated. The most compelling evidence that kinase-activating fusions function to maintain MCL-1 expression and repress BH3-only proteins is from studies of the BCR-ABL1 fusion.

**BCR-ABL1 shifts the balance of BCL-2 family proteins in favor of cell survival**

There are three forms of the *BCR-ABL1* fusion gene, with alternate breakpoints in the breakpoint cluster region (BCR) gene. Each is associated with distinct subtypes of leukemia (42). The p210 BCR-ABL1 is the hallmark of CML; p185 is found in adult and pediatric B-ALL; and p230 is associated with neutrophilic CML (38). In *Arf*−/− B-ALL cells expressing p185 BCR-ABL1, there is selection against silencing of MCL-1 expression, unless apoptosis was blocked by BAX and BAK deletion, or overexpression of BCL-2 or BCL-XL (43, 44). This shows that MCL-1 is required to prevent BAX and BAK activation for the fusion to maintain cell viability. Treatment of these cells with imatinib induced a dose-dependent reduction in MCL-1 protein, but it had no effect on BCL-2 or BCL-XL expression (43).

In CML models, BCR-ABL1 appears to maintain MCL-1 expression through the activation of STAT3-dependent transcription. Deletion of STAT3 prevents BCR-ABL1 from initiating CML, and there is a correlation between STAT3 phosphorylation and resistance to imatinib (45, 46). These observations raise the possibility that inhibition of STAT3 phosphorylation, directly or indirectly, could synergize with imatinib treatment.

Other evidence supports repression of pro-apoptotic BH3-only proteins by BCR-ABL1. Imatinib treatment up-regulated expression of BIM and BAD in human CML cell lines (17). There is some indication that the presence of BCR-ABL1 drives ERK-mediated phosphorylation of BIM and subsequent BIM degradation (Fig. 2) (47, 48). However, the functional significance of BIM phosphorylation driven by leukemia fusion genes is not established (49).

The levels of other anti-apoptotic BCL-2 proteins may also be regulated by BCR-ABL1, which may raise the threshold that a death stimulus must reach before apoptosis can proceed. An intriguing line of evidence comes from experiments using BCL-2 inhibitor drugs (or BH3-mimetic drugs). ABT-737 is the prototype inhibitor with broad activity against BCL-2, BCL-XL, and BCL-W, but with no activity against MCL-1 (50). This drug enhanced imatinib cell killing and prolonged the survival of mice transplanted with Ph+ ALL (17, 51). Mechanistically, ABT-737 increases the pool of unbound BH3-only proteins, which in steady state are otherwise bound to and sequestered by BCL-2 and BCL-XL (17). Although ABT-737 treatment increased survival in some imatinib-treated Ph+ ALL xenografts, ABT-263 (navitoclax, identical activity...
to ABT-737) and ABT-199 (selectively inhibits BCL-2) were ineffective in another Ph+ ALL xenograft model (51, 52). Nevertheless, therapeutic combinations of TKIs and BH3 mimetics are of interest, as anti-apoptotic BCL-2 proteins other than MCL-1 can compensate for the loss of MCL-1 induced by TKIs.
Leonard et al. (53) highlighted the importance of the BCL-2/MCL-1 ratio in sensitivity to venetoclax. The high BCL-2/MCL-1 ratio (in a pediatric Ph+ ALL cell line) mediated sensitivity to venetoclax, whereas low expression of BCL-2 conferred resistance in another CML cell line. Combined treatment with venetoclax and the TKI dasatinib induced the highest levels of cell killing (53). Depletion or inhibition of the total BCL-2 anti-apoptotic protein pool lowers resistance to cell death. Thus, diminished expression of MCL-1, driven by inhibition of BCR-ABL1 kinase, together with direct inhibition of BCL-2 by BH3-mimetic drugs may drive ALL cells to activate their intrinsic apoptosis pathways (48). Similarly, a MEK inhibitor in human Ph+ cell lines was insufficient as a single agent to induce cell killing (48, 54). However, when combined with ABT-263 or ABT-199, cell killing was induced (48). These studies highlight the potential efficacy of combining tyrosine kinase and BCL-2 family inhibition to treat patients with BCR-ABL1-driven leukemia.

**JAK2 fusions and the role of BCL-XL**

JAK-STAT pathway-activating fusions in ALL are also associated with poor outcomes. Many Janus kinase 2 (JAK2) fusions with different fusion partners have been reported (4). In addition, fusions that increase expression of cytokine receptor-like factor 2 (CRLF2), most commonly with P2RY8 or as an IGH rearrangement, cooperate with activating JAK2 mutations to drive ALL (Fig. 2) (55). How these fusions regulate the apoptotic pathway is less well studied, but activating JAK2 mutations provides some insights. JAK2V617F is the causal mutation of polycythemia vera (PV) and is also found in a range of other myeloproliferative neoplasms. Like JAK2 fusions, JAK2V617F is constitutively activated (56). There is evidence supporting the hypothesis that activated JAK2 signaling leads to elevated expression of BCL-2, BCL-XL, and MCL-1. BCL-2 and BCL-XL expression is increased in PV patients with the JAK2V617F mutation, and higher JAK2V617F expression in erythroid precursor cells from PV patients was associated with increased sensitivity to ABT-737 treatment (57). RNA interference-induced knockdown of BIM decreased sensitivity to JAK2 inhibition, implying that JAK2 signaling also represses BIM, whereas MCL-1 knockdown increased apoptosis in JAK2V617F cells and increased sensitivity to JAK2 inhibition (58). Enforced expression of JAK2V617F increased MCL-1 expression by STAT3-dependent transcription (59). Together, this suggests that JAK2 signaling raises the apoptosis threshold by increasing expression of anti-apoptotic members of the BCL-2 family.

One might then predict synergy between JAK2 inhibitors and BH3-mimetic drugs. The combination of JAK2 inhibitors, such as ruxolitinib or AZD1480, with BH3-mimetics enhanced the limited efficacy of JAK inhibitors as single agents (60, 61). Waibel et al. (62) used an Eμ-TEL-JAK2 (ETV6-JAK2) mouse model of T-ALL to show that up-regulation of BCL-2/BCL-XL and down-regulation of BIM expression promote leukemic cell survival. BCL-2/BCL-XL inhibition (ABT-737), combined with JAK2 inhibition, induced the greatest therapeutic response, compared with either agent alone. Clearly, there are common mechanisms by which BCR-ABL1 fusions and JAK2 fusions maintain cell viability. This may apply to all leukemia fusions activating tyrosine kinase domains. They must all, in some way, regulate the activation of BAX and BAK, although the individual BCL-2 proteins and the pathways that connect the fusions to the apoptosis machinery may vary (63).

**ETV6-RUNX1 and cell survival**

The ETV6-RUNX1 fusion is present in up to 25% of pediatric B-ALL cases and is associated with favorable outcomes for patients (4, 64). The ETV6-RUNX1 fusion is not necessary to maintain leukemic cell viability, and it is not sufficient alone to cause a leukemia in murine transplant models (65, 66). There is substantial evidence to indicate that the ETV6-RUNX1 fusion can be detected antenatally in pre-leukemic clones. The full manifestation of ETV6-RUNX1-driven ALL therefore requires secondary changes that confer resistance to apoptosis (65).

The erythropoietin receptor (EPOR) is consistently overexpressed in ETV6-RUNX1-positive ALL (67, 68). EPOR is a homodimeric cytokine receptor that may also be expressed as a fusion in Ph-like ALL (4). Normal EPOR signaling requires binding of the EPO ligand to the receptor to induce signal transduction through JAK2 and STAT5 phosphorylation (69). Chromatin immunoprecipitation assays showed the ETV6-RUNX1 fusion bound to the promoter of EPOR, driving EPOR transcription. However, most data suggest that elevated expression of EPOR alone is not sufficient to activate signaling and that EPO ligand is also required. It may be that ETV6-RUNX1 drives unregulated EPOR signaling, STAT5 activation, and elevated BCL-XL expression (70). Another suggested survival mechanism may be a combination of STAT3 activation (which increases BCL-2 and BCL-XL expression) and c-MYC-dependent transcription (71).

**Infant MLL-r ALL**

Infant MLL-r ALL is often aggressive, and the outcomes remain poor despite intensified chemotherapy or allogeneic hematopoietic stem cell transplantation (74, 75). The MLL (KMT2A) gene is a histone methyltransferase located on chromosome 11q23. MLL-r ALL accounts for 80% of infant ALL, and more than 80 fusion partners have been identified. The most common are AF4, ENL, and AF9 (76, 77). KMT2A functions in a multiprotein transcriptional regulatory complex and is required for normal hematopoiesis (78). Among the key transcription targets regulated by KMT2A are the homeobox (HOX) genes and in particular the HOXA cluster. The transgenic expression of the MLL-AF9 fusion does not cause AML in HoxA9-deficient animals. MLL rearrangements may arise during fetal hematopoiesis and may be detected at birth, prior to the onset of disease (79). Although additional genetic mutations are uncommon in infant MLL-r ALL (3, 80), there are recognized associations with activating PI3K/RAS pathway mutations and FLT3 (79).

The common MLL translocations in infant ALL confer resistance to apoptosis (81). This may result from high BCL-2 expression (82). Although BCL-2 is not required for MLL-AF9 to initiate leukemia in murine models, deletion of BCL-2 delays disease onset and diminishes clonal proliferation (83). MLL-AF4 also specifically up-regulates the BCL-2 expression by DOT1L-mediated H3K79 methylation at the BCL-2 locus (84).
Transcriptional up-regulation of anti-apoptotic BCL-2 proteins by MLL rearrangements may inhibit glucocorticoid-dependent apoptosis. Glucocorticoids form the backbone of ALL treatment protocols. Approximately 30% of infant MLL-r ALL have poor glucocorticoid responses (75, 85). Glucocorticoid-induced apoptosis in lymphocytes proceeds via the BCL-2-regulated pathway and is absolutely dependent on BAX and BAK (86). Stam et al. (88) and others (87) showed increased expression of MCL-1 in prednisolone-resistant pediatric ALL samples, most notably MLL-r ALL. RNAi knockdown of MCL-1 in prednisolone-resistant MLL-r leukemia cells partially restores prednisolone killing (88). Epigenetic silencing of BIM in MLL-r ALL also contributes to glucocorticoid resistance (89, 90).

The role of BCL-2 in the viability of MLL-r leukemia suggests that including BCL-2 inhibition in treatment regimens may be effective. Data from the Pediatric Preclinical Testing Program showed the BH3 mimic navitoclax has significant anti-tumor activity, particularly in MLL-r ALL (91). Jayanthan et al. (92) also demonstrated that combining ABT-737 with a histone deacetylase inhibitor, proteasome inhibitor, multi-tyrosine kinase inhibitor, and anthracycline had additive effects. Venetoclax was also effective at killing MLL-r ALL leukemic cells. In MLL-r ALL xenografts, venetoclax was associated with a higher response rate of 50%, compared with 26% in non-MLL-ALL xenografts, suggesting that BCL-2 inhibition, in conjunction with chemotherapeutics, is effective in this sub-group (93, 94). These data support the trial of the introduction of BCL-2-inhibitor drugs into therapeutic regimens for MLL-r leukemias (84).

DOT1L is a critical component of the MLL-r transcriptional complex. Phase I trials of small molecule DOT1L inhibitors have shown promising molecular efficacy (95, 96). DOT1L inhibitors also sensitize MLL-r ALL to venetoclax (84), providing additional evidence that BCL-2 proteins play a role in MLL-r leukemia and that BCL-2 inhibition may improve clinical outcomes.

Exploiting other cell death pathways in ALL

Repressing BH3-only protein expression while maintaining expression of anti-apoptotic BCL-2 proteins is a common theme of ALL fusion function. Other genetically programmed cell death pathways, which do not necessarily contribute directly to fusion-driven ALL, may be clinically exploited to bypass blocks in apoptosis. Necroptosis, or programmed necrosis, is activated by diverse extrinsic stimuli but prominently by TNF receptor 1 signaling (97). The key molecules that mediate necroptosis include the RIP kinases (RIPK1 and RIPK3) and the mixed lineage kinase domain-like protein. The inhibitor of apoptosis proteins, cIAP1 and cIAP2, determines whether TNFR1 signaling activates necroptosis. When these are expressed, the necroptosis pathway is blocked (98). IAP inhibitor small molecule drugs bind to the IAPs and cause rapid proteasomal degradation and simultaneous up-regulation of TNF-activated TNFR1 signaling (99). The net effect is autonomous TNFR1-dependent necroptosis. In ALL, the IAP antagonists have shown single agent efficacy in a range of patient-derived xenograft models (100). The mechanism of action of IAP inhibitor drugs exploits pathways not primarily regulated by the leukemia driver fusions but that are intact even in highly resistant tumors.

Conclusion

The mechanisms by which oncogenic fusion genes promote survival converge on the BCL-2 family of proteins and the repression of BAX and BAK activation. These fusions promote cell survival by altering the balance of the BCL-2 family members to favor survival, repressing expression of pro-apoptotic BH3-only proteins, and up-regulating pro-survival BCL-2 family members. For fusions that activate tyrosine kinases, most interest has focused on how the signal transduction pathways initiated by the fusion impact on key anti-apoptotic proteins such as BCL-2 and MCL-1. Transcription factor fusions also regulate the levels of these same BCL-2 family proteins. Fusion-dependent up-regulation of BCL-2 or MCL-1 expression is a mechanism of drug resistance but also a therapeutic opportunity. Although drugs that inhibit BCL-2 (BH3 mimetics) have shown some efficacy in vitro, their use has yet to be implemented into ALL treatment protocols. The promise of this approach will be tested in upcoming clinical trials.

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