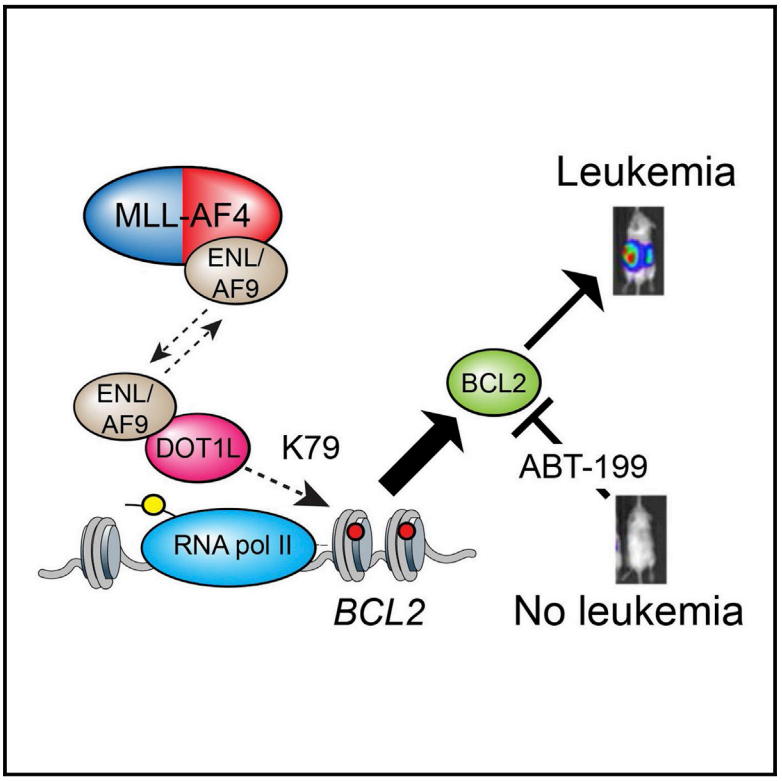
Article

Cell Reports

MLL-Rearranged Acute Lymphoblastic Leukemias Activate BCL-2 through H3K79 Methylation and Are Sensitive to the BCL-2-Specific Antagonist ABT-199

Graphical Abstract



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In Brief

Therapies designed to exploit specific molecular pathways in aggressive cancers are an exciting area of research. Mutations in the MLL gene cause aggressive incurable leukemias. Benito et al. show that MLL leukemias are highly sensitive to BCL-2 inhibitors, especially when combined with drugs that target mutant MLL complex activity.

Highlights

- *MLLr* ALL blasts express high levels of BCL-2, BAX, and BIM
- MLL/AF4 activates *BCL2* through H3K79 methylation
- *MLLr* ALL cells are exquisitely sensitive to BCL-2 antagonist ABT-199
- ABT-199 treatment synergizes with H3K79 methylation inhibitors on *MLLr* samples

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MLL-Rearranged Acute Lymphoblastic Leukemias Activate BCL-2 through H3K79 Methylation and Are Sensitive to the BCL-2-Specific Antagonist ABT-199

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SUMMARY

Targeted therapies designed to exploit specific molecular pathways in aggressive cancers are an exciting area of current research. *Mixed Lineage Leukemia* (*MLL*) mutations such as the t(4;11) translocation cause aggressive leukemias that are refractory to conventional treatment. The t(4;11) translocation produces an MLL/AF4 fusion protein that activates key target genes through both epigenetic and transcriptional elongation mechanisms. In this study, we show that t(4;11) patient cells express high levels of BCL-2 and are highly sensitive to treatment with the BCL-2-specific BH3 mimetic ABT-199. We demonstrate that MLL/AF4 specifically upregulates the *BCL-2* gene but not other BCL-2 family members via DOT1L-mediated H3K79me2/3. We use this information to show that a t(4;11) cell line is sensitive to a combination of ABT-199 and DOT1L inhibitors. In addition, ABT-199 synergizes with standard induction-type therapy in a xenotransplant model, advocating for the introduction of ABT-199 into therapeutic regimens for MLL-rearranged leukemias.

INTRODUCTION

Mixed-lineage-leukemia (*MLL*) is one of the most frequently translocated genes (*MLL*-rearranged or *MLLr*) in hematologic malignancies and produces aggressive leukemias where more targeted therapeutic approaches are particularly needed. Translocation t(4;11)(q21;q23) generates *MLL/AF4* and *AF4/MLL* fusion products, both of which function as transcriptional activators. The role of AF4/MLL in t(4;11) leukemias is controversial, as it has transformation potential (Bursen et al., 2010) but is not expressed in all t(4;11) patients (Andersson et al., 2015). Conversely, the MLL/AF4 fusion protein is expressed in all t(4;11) patients, and knockdowns of MLL/AF4, even in the presence of AF4/MLL, are sufficient to stop t(4;11) leukemias from growing (Thomas et al., 2005).

t(4;11) leukemias are diagnosed mainly as precursor B cell acute lymphoblastic leukemia (B-ALL) in both infants, children, and adults, and they predict poor long-term outcomes, even with aggressive chemotherapy or therapy combined with stem cell transplantation (Beldjord et al., 2014; Dreyer et al., 2015; Pieters et al., 2007). t(4;11) leukemias have very few cooperating mutations, especially in infants (Andersson et al., 2015), suggesting that MLL/AF4 is the primary driver of continued leukemogenesis. Therefore, understanding the function of the MLL/AF4 fusion protein and the genes that it regulates will be essential for the development of targeted t(4;11) therapies.