BLOOD eLetter - BMI1 and CDKN2A/B in BCR-ABL-driven leukemogenesis
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Re: "BMI1 collaborates with BCR-ABL in leukemic transformation of human CD34+ cells"

In exploring the interaction between BMI1 and BCR-ABL in ABL-dependent human leukemogenesis, Rizo et al., provide functional evidence that BMI1 represents a logical target for future anti-leukemic drug development. This interesting study raises a few important points:

1. It was asserted that 'little is known about molecular mechanisms underlying transformation of CML-CP to CML-BC'. Surprisingly, the CDKN2A/B locus (that encodes three tumor suppressor genes ARF, CDKN2A and CDKN2B) was overlooked in this Introduction, particularly as the encoded genes are well-recognized targets of BMI1-dependent transcriptional repression (1), and genomic deletion of this locus is frequently associated with the evolution of lymphoid CML-BC from CML-CP (2,3).

2. Co-expression of BMI-1 and BCR-ABL in human CD34+ CB cells was claimed as sufficient to induce transplantable leukemias in NOD-SCID mice. In view of incomplete penetrance of these leukemias (50%, 4 of 8 recipients), this claim over-states the magnitude of this genetic interaction. Rather, these experiments indicate that additional factors are required for leukemia development in this system. As a counterpoint, every BCR-ABL-expressing murine pre-B cell that lacks the Arf tumor suppressor gene (encoded by Cdkn2a, and transcriptionally repressed by Bmi1) is a leukemia-initiating cell, indicating that these two genetic events are sufficient to generate murine BCR-ABL-driven lymphoid leukemias (4).

3. The biological functions ascribed to BMI1 in leukemogenesis by Rizo et al., include bypassing of senescence, facilitation of symmetric cell division and protection against oxidative stress. In genetically-defined, BCR-ABL-driven lymphoid leukemia models, oncogene-induced Arf expression is tightly linked to a p53-dependent transcriptional response and apoptosis (5). While Bmi1 regulates expression of genes in addition to those at the Cdkn2a/b locus in normal hematopoiesis, BMI1’s significant attenuation of BCR-ABL-dependent ARF expression and subsequent ARF- and p53-dependent apoptosis, may also contribute to BMI1’s role in human ABL-driven leukemic transformation.

References:


Conflict of Interest: None declared