ELSEVIER

Blood 142 (2023) 4586

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

636.MYELODYSPLASTIC SYNDROMES-BASIC AND TRANSLATIONAL

Bcor Truncation Mutations Collaborate with a U2AF1 S34F Mutant to Promote Clonal Hematopoiesis and MDS

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Mutations in spliceosome genes such as U2AF1 have been identified across major cancer types, including myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Mutations involving the U2AF1 gene, mostly commonly involving amino acids 34 or 157 have been reported in up to 20% of patients with MDS. To investigate how mutant U2AF1 contribute to hematologic malignancy, we generated transgenic mice that expressed a mutant U2AF1 S34F mutant under control of hematopoietic specific Vav1 regulatory elements. Sanger sequencing demonstrated that expression of the mutant U2AF1 was similar to that of wild-type (WT) U2AF1 in bone marrow and spleen. U2AF1 S34F mice showed decreased long-term hematopoietic stem cells (HSC) compared with age matched wild type WT mice. Hematopoietic stem cell transplantation (HSCT) showed that U2AF1 S34F HSCs repopulated recipients less efficiently than WT HSCs, consistent with previous reports. However, U2AF1 S34F mice did not develop evidence of hematologic malignancy, suggesting that additional mutations were required to develop MDS or AML. BCOR, a corepressor for BCL6, has been reported to be frequently co-mutated in MDS patients with U2AF1 S34F, suggesting that these two mutations might collaborate to produce MDS. To test the hypothesis, we introduced a BCOR truncation mutation into hematopoietic stem and progenitor cells (HSPC) from U2AF1 S34F or WT mice, using CRISPR-Cas9, followed by transplant to WT recipient mice. Primary recipients of U2AF1 S34F and Bcor double mutant bone marrow (U2B) showed decreased engraftment compared to WT-Bcor mutant (WB) recipients, consistent with a competitive disadvantage of U2AF1 S34F HSPC observed previously by several labs. We performed secondary HSCT to evaluate the long-term repopulation pattern of U2B HSPC. Secondary transplant recipients from U2B primary mice showed anemia and leukopenia, consistent with MDS. U2B secondary recipients typically showed low engraftment initially (reflecting ineffective hematopoiesis) followed by gradually increasing proportion of U2B cells in the peripheral blood. At necropsy, all secondary recipients of U2B bone marrow showed evidence of clonal hematopoiesis involving cells with 1 or 2 distinct, unique Bcor truncation mutations. We then sequenced bone marrow DNA from the U2B mouse used as donor for the secondary transplant and identified 14 independent Bcor mutations. All 14 Bcor mutations were out of frame, and encoded a truncated Bcor protein, indicating that cells with a U2AF1 S34F and a Bcor truncation had a competitive advantage in vivo. These results suggest that loss of normal Bcor function can collaborate with a U2AF1 S34F mutant, resulting in clonal expansion of abnormal HSC.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-189251