ELSEVIER

Blood 142 (2023) 5588–5589

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

501.HEMATOPOIETIC STEM AND PROGENITOR CELLS AND HEMATOPOIESIS: BASIC AND TRANSLATIONAL

Arid1b Loss Impairs Hematopoietic Stem Cell Function in Normal Hematopoiesis

Olivia Arnold, BS[1,2], *Theresa Bluemn, PhD*[1,2], *Cary Stelloh*[2], *Yongwei Zheng, PhD*[2], *Demin Wang, PhD*[3,4], *Sridhar Rao, MDPhD*[5,6,7,2], *Nan Zhu, PhD*[8,7]

[1]Medical College of Wisconsin, Milwaukee, WI
[2]Versiti Blood Research Institute, Milwaukee, WI
[3]The Blood Research Institute, Milwaukee, WI
[4]Department of Microbiology and Immunology, Medical College of Wisconsin, Milwaukee, WI
[5]Department of Pediatrics, Division of Hematology, Oncology, and Bone Marrow Transplantation, Children's Hospital of Wisconsin, Milwaukee
[6]Department of Pediatrics, Division of Hematology, Oncology, and Transplantation, Medical College of Wisconsin, Milwaukee, WI
[7]Cell Biology, Neurobiology, and Anatomy, Medical College of Wisconsin, Milwaukee, WI
[8]Versiti Blood Research Institute Milwaukee, Milwaukee, WI

Switch Sugar Non- Fermenting (SWI/SNF) nucleosome remodeling complexes are multi subunits complexes that utilize the energy from ATP to remodel chromatin, affecting cellular processes on chromatin including that of gene transcription. SWI/SNF complexes play important roles in normal development and differentiation as well as in oncogenesis. ARID1 proteins, ARID1A and ARID1B, are unique and mutually exclusive subunits of the canonical SWI/SNF complex BRG-1/BRM Associated Factor (BAF) complex. Arid1a is the most frequently mutated SWI/SNF subunit in cancers and plays a vital role in hematopoiesis. Arid1b is also frequently mutated in cancers, and its loss promotes Acute Myeloid Leukemia leukemogenesis. However, its role in normal hematopoiesis is not known.

In this study we used hematopoietic specific Cre strains, VavCre and Mx1Cre, to delete Arid1b in a mouse genetic model to study its role in normal hematopoiesis. Analysis of steady state hematopoiesis in the VavCre model showed no significant differences in complete blood count (CBC) between Arid1b $^{fl/fl}$VavCre+ and VavCre+ mice. Further, bone marrow (BM) cellularity was not significantly different between control and experimental mice. Flow cytometry analysis of the percentage of mature myeloid, B cell, or T cell populations in the peripheral blood (PB), BM, or spleen (SPL) did not show significant differences between Arid1b $^{fl/fl}$VavCre+ and VavCre+ control mice. Further, we did not observe any significant differences in percentages of hematopoietic stem and progenitor cells (HSPCs), including HSCs, common myeloid progenitors (CMPs), granulocyte macrophage progenitors (GMPs), megakaryocyte/erythrocyte progenitors (MEPs), and common lymphoid progenitors (CLPs) in the BM of Arid1b $^{fl/fl}$VavCre+ mice versus VavCre+ controls. Analysis of Mx1Cre model showed similar results. Taken together, these results suggest that Arid1b is dispensable for steady state hematopoiesis.

To assess the effect of loss Arid1b in a regenerative setting, we conducted non-competitive and competitive transplantation experiments in VavCre and Mx1Cre models. We transplanted BM cells from Arid1b $^{fl/fl}$Cre+ or Cre+ mice (CD45.2) into lethally irradiated recipient CD45.1 mice with (CD45.1 at 1:1 ratio) or without competitor cells for competitive or non-competitive transplantations respectively. In Mx1Cre model, deletion of Arid1b was induced 4 weeks after transplantation. We monitored donor chimerism in PB over time as well as in the BM and SPL at end point. In both VavCre and Mx1Cre non-competitive transplants, we did not observe significant differences in CBC or donor chimerism in mature cells between Arid1b $^{fl/fl}$Cre+ and control Cre+ mice in the PB over time. Further, no significant differences were observed between knockout and control mice in donor chimerism in mature cell populations in the BM or SPL, nor HSPC populations in the BM at end point (24-28 weeks). Deletion of Arid1b in the BM was confirmed. These results indicate that Arid1b loss does not affect regenerative potential of HSPCs in a non-competitive setting.

In our competitive transplants, we observed significant decreases in PB donor chimerism for both myeloid and B cell populations over time in Arid1b $^{fl/fl}$VavCre+ compared to VavCre+ controls. Further, we observed significant decreases in donor chimerism of mature myeloid cells and B cells in the BM and SPL, as well as HSCs, CMPs, GMPs, and MEPs in the BM of Arid1b $^{fl/fl}$VavCre+ mice compared to VavCre+ controls at endpoint. However, there seemed to be incomplete penetrance as the ob-

served phenotype varied in cohorts of different donor mice and was not significant in all cohorts. A similar phenotype was observed in the Mx1Cre model with the exception of a trend, albeit insignificant, towards a decrease in donor derived mature B cell populations in Arid1b $^{fl/fl}$Mx1Cre+ compared to Mx1Cre+ mice in PB, SPL, and BM and no significant difference in HSCs in the BM at end point (20 weeks). Deletion of Arid1b in the BM was confirmed in both models. Overall, our results suggest that Arid1b deficient HSCs can regenerate the hematopoietic system but have defects in competitive transplantations with incomplete penetrance. Further work is needed to address the observed incomplete penetrance phenotype in competitive transplantations, and to understand the mechanism behind the requirement of Arid1b in normal hematopoiesis.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-186386