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GATA2 HAPLOINSUFFICIENCY REDUCES AGED HEMATOPOIETIC STEM CELL FUNCTIONALITY IN MULTIPLE LINEAGES

Topic: 11. Bone marrow failure syndromes incl. PNH - Biology & Translational Research

Keywords: Aging, GATA-2, Hematopoietic stem cell, MDS/AML

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Background: Mutations in the *GATA2* transcription factor cause immunodeficiency syndromes, which can present with monocytopenia, B cell, NK cell and dendritic cell deficiencies and an increased lifetime risk for myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) of 80% at 40 years of age. The role of GATA2 haploinsufficiency in the MDS/AML progression is still poorly understood.

Aims: Because patients with *GATA2* mutations have increased lifetime risk of developing MDS/AML, we hypothesize that aging has a contributing factor in the development of MDS/AML in Gata2 haploinsufficiencies. Therefore, we have analysed *Gata2*$^{+/-}$ mice in aging to reveal the Gata2 dependent mechanisms in leukemic progression.

Methods: We aged *Gata2*$^{+/-}$ and WT mice and performed primary and secondary transplantations of the aged bone marrow to young, lethally irradiated, WT recipients. We have also performed transcriptome analysis on HSCs of the adult, aged and transplanted *Gata2*$^{+/-}$ and WT mice.

Results: We found that HSCs in *Gata2*$^{+/-}$ mice have lost their quiescence. 2 months after transplantation of the aged cells, *Gata2*$^{+/-}$ mice developed B cell cytopenia, which represents the most common feature of GATA2 haploinsufficiency in patients. B cell cytopenia was persistent also after the secondary transplantation. We observed a significantly reduced blood chimerism in *Gata2*$^{+/-}$ mice after secondary transplantation, which suggested HSC exhaustion. 5 months after the secondary transplantation, *Gata2*$^{+/-}$ mice developed neutropenia and monocytopenia in addition to B cell cytopenia.

Summary/Conclusion: These results indicate a reduced functionality of aged and transplanted *Gata2*$^{+/-}$ HSCs in multiple lineages. Currently, we are working on the identification of Gata2 haploinsufficiency phenotype and the analysis of transcriptomic changes in Gata2 haploinsufficient HSCs observed in our aged *Gata2*$^{+/-}$ mouse model. Additionally, we are working on understanding the clonality of HSCs in the aged *Gata2*$^{+/-}$ mice.

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