ELSEVIER

Blood 142 (2023) 2751

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

602.MYELOID ONCOGENESIS: BASIC

The Oncoprotein SKI As a Driver in KMT2A-MLLT3/NRasG12D-Positive Acute Myeloid Leukemia

Miriam Frech, PhD[1], *Janine Schaprian*[1], *Miriam Ems*[1], *Sabine Teichler, PhD*[1], *Uta-Maria Bauer, PhD*[2], *Andreas Neubauer, MD*[3]

[1] Clinic for Hematology, Oncology, Immunology, and Center for Tumor Biology and Immunology (ZTI), Philipps University Marburg, Marburg, Germany
[2] Institute for Molecular Biology and Tumor Research (IMT), Philipps University Marburg, Marburg, Germany
[3] Department of Hematology, Oncology and Immunology, Phillips-University Marburg, Marburg, Germany, Marburg, Germany

KMT2A-rearranged acute myeloid leukemias (AML) have an intermediate to adverse prognosis. It was shown in a mouse model that the oncogene Myb contributes to AML maintenance in the KMT2A-MLLT3/NRasG12D genetic background (Zuber *et al.*, 2011). Interestingly, the Myb-regulated genetic network mostly overlaps with KMT2A-MLLT3 target genes, especially with leukemic stem cell-associated gene sets. However, canonical KMT2A target genes are not included. Hence, MYB seems not to act as a co-factor for KMT2A complexes. SKI is a nuclear co-regulator and an oncoprotein, which is overexpressed in AML and several solid tumors (Bonnon & Atanasoski, 2012). Overexpression (OE) of SKI is prognostic in AML and correlates with shorter overall survival. Our group showed that SKI OE in AML is partially regulated by MYB (Frech *et al.*, 2018). As a MYB target gene, we wanted to know if SKI can mediate MYB oncogenic activity in KMT2A-MLLT3/NRasG12D-positive AML.
We adopted the Zuber mouse model and performed an shRNA-mediated Ski knockdown (KD) in murine KMT2A-MLLT3/NRasG12D-positive AML cells (RN2). Mice were transplanted with RN2 cells carrying two different anti-Ski shRNAs or an anti-Renilla shRNA as control. The expansion of RN2 cells in mice was monitored by luciferase-based bioimaging. Upon disease onset, shRNA expression was induced by doxycycline treatment. The course of the disease was further monitored by bioimaging. Bone marrow cells were isolated and analyzed via flow cytometry. The expression of KMT2A target genes was analyzed by RT-qPCR in doxycycline-induced RN2 cells.
Ski KD induced a decreased viability of the RN2 cells *in vitro*. Moreover, SKI KD led to the eradication of RN2 cells in the mice *in vivo* and was associated with longer overall survival (log-rank $p<0.0005$). In line with the SKI OE mouse model of Singbrant *et al.* (2014), Ski KD led vice versa in our model to a decrease of myeloid cells and an increase of B cells. In contrast to Myb KD in the RN2 cells, Ski KD led to a lower expression of canonical KMT2A target genes, implicating that Ski may be part of KMT2A complexes in AML.
In summary, SKI seems to be crucial for KMT2A-MLLT3/NRasG12D-driven AML and may be a potential target for new therapeutic strategies.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-184750