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MEETING ABSTRACT

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Unraveling the tumor-supressive role of STAT3β in acute myeloid leukemia

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Background: One major mediator of cytokine signaling is the signal transducer and activator of transcription 3 (STAT3). In acute myeloid leukemia (AML) patients, STAT3 is frequently found constitutively activated, which is associated with poorer overall survival. Apart from this, STAT3 exists in two distinct isoforms generated by alternative splicing, the full-length transcript STAT3α and the C-terminally truncated isoform STAT3β. While STAT3 in general is considered as an oncogenic driver in malignant diseases, STAT3β gained attention as a favorable prognostic marker and was shown to regulate gene transcription also in a STAT3α-independent manner. Analysis of AML patient samples revealed that a high *STAT3β/α* mRNA ratio is a favorable prognostic marker correlating with disease outcome. However, the underlying molecular mechanism remained elusive. In this study we provide novel insights into the STAT3 isoform-specific impact on AML development.
Methods: We use a combination of *in vivo* models and *in vitro* assays coupled to next-generation sequencing approaches. Briefly, hematopoietic stem cells were isolated from fetal livers of wild-type and STAT3β-deficient mice, and were retrovirally transduced with the human fusion-oncogene MLL-AF9. Transformed cells were used to study the STAT3 isoform-specific impact on different cellular mechanisms *in vitro*. Moreover, the cells were transplanted into immunocompromised animals to explore leukemic potential.
Results: Lack of STAT3β in murine AML blasts led to accelerated disease progression and poorer overall survival in immunocompromised mice despite of any proliferation advantage *in vitro*. Flow-cytometry-based analysis of infiltrated blasts revealed that leukemic cells lacking STAT3β are less committed to the myeloid lineage and less responsive to differentiation stimulus. By performing transcriptome analysis of leukemic cells isolated from organs of diseased animals we identified a strong enrichment of genes involved in interferon signaling in absence of STAT3β.
Discussion: Understanding the tumor-suppressive role of STAT3β is crucial to discover novel therapeutic targets in AML. We aim to validate STAT3β-specific targets that could serve as novel therapeutic targets. Especially patients with lower STAT3β levels and poor prognosis could benefit from these findings.

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