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MEETING ABSTRACT

A3.3

STAT3β is a tumor suppressor in acute myeloid leukemia

Petra AIGNER[1], Tatsuaki MIZUTANI[1], Jaqueline HORVATH[1,2], Thomas EDER[1], Stefan HEBER[3], Karin LIND[4], Valentin JUST[1], Herwig P. MOLL[5], Assa YEROSLAVIZ[6], Michael J.M. FISCHER[3], Lukas KENNER[1,7,8], Balázs GYŐRFFY[9,10], Heinz SILL[4], Florian GREBIEN[1,11], Richard MORIGGL[1,12], Emilio CASANOVA[1,5] and Dagmar STOIBER[1,2,13,*]

[1]Ludwig Boltzmann Institute for Cancer Research, Vienna, Austria; [2]Institute of Pharmacology, Center for Physiology and Pharmacology, Comprehensive Cancer Center, Medical University of Vienna, Austria; [3]Institute of Physiology, Center for Physiology and Pharmacology, Medical University of Vienna, Austria; [4]Division of Hematology, Medical University of Graz, Austria; [5]Institute of Physiology, Center for Physiology and Pharmacology, Comprehensive Cancer Center, Medical University of Vienna, Austria; [6]Computational Systems Biochemistry group, Max Planck Institute for Biochemistry, Martinsried, Germany; [7]Clinical Institute of Pathology, Medical University of Vienna, Austria; [8]Unit of Pathology of Laboratory Animals, University of Veterinary Medicine, Vienna, Austria; [9]MTA TTK Lendület Cancer Biomarker Research Group, Institute of Enzymology, Hungarian Academy of Sciences, Budapest, Hungary; [10]Semmelweis University, 2nd Department of Pediatrics, Budapest, Hungary; [11]Institute of Medical Biochemistry, University of Veterinary Medicine, Vienna, Austria; [12]Institute of Animal Breeding and Genetics, University of Veterinary Medicine, Vienna, Austria; [13]Current affiliation: Department Pharmacology, Physiology and Microbiology, Division of Pharmacology, Karl Landsteiner University of Health Sciences, Krems, Austria

Background: Signal transducer and activator of transcription 3 (STAT3), a multifunctional regulator of transcription, is expressed in two alternatively spliced isoforms, full-length STAT3α and truncated STAT3β. Although formerly postulated as a dominant negative regulator, STAT3β has been attributed with STAT3α-independent functions and recently gained attention as a potent tumor suppressor in cancer. In acute myeloid leukemia (AML), STAT3 is frequently constitutively activated; however, the functions of STAT3 isoforms are unknown. Thus, the objective of this study was to gain improved understanding of STAT3β and its specific role in AML.

Methods: Samples, derived from AML patients at diagnosis, were analyzed for the *STAT3β/STAT3α* mRNA expression ratio and its correlation with clinical prognosis and overall survival. In addition, an inducible *Stat3β* transgenic mouse model was crossed with *Pten*-deficient mice, as a pre-described model for AML. In a second AML model, fetal liver-derived stem cells from *Stat3β* transgenic mice and wild-type littermates, transduced with an MLL-AF9 translocation, were transplanted in immunocompromised NOD scid gamma mice.

Results: Here, we demonstrate a correlation between higher *STAT3β/STAT3α* ratios in patient-derived AML samples and a favorable clinical prognosis as well as increased overall survival. In two separate AML mouse models, elevated levels of *Stat3β* resulted in severely reduced leukemogenesis, delayed leukemic infiltration and prolonged survival. Additionally performed RNA-seq analysis revealed a small set of genes that are specifically up- or down-regulated in *Stat3β* transgenic AML blasts. In particular, genes associated with cell-surface interactions at the vascular wall and mobilization were found to be regulated by STAT3β, *e.g. Sell* (L-selectin). *In vitro*, the antibody-mediated blocking of SELL successfully extinguished initial differences in colony-formation assays with *Stat3β* transgenic blasts.

Discussion: In conclusion, these findings indicate that STAT3β can serve as an anti-tumorigenic molecule and tumor suppressor in AML mouse models via the tumor-intrinsic regulation of novel target genes. Furthermore, the *STAT3β/STAT3α* mRNA expression ratio in AML patients correlates with clinical outcome and hence demonstrates potential as a future prognostic marker and might help to shape new treatment strategies.

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*Corresponding author e-mail: *dagmar.stoiber@kl.ac.at*