New role of tumor suppressor STAT3β discovered in leukemia

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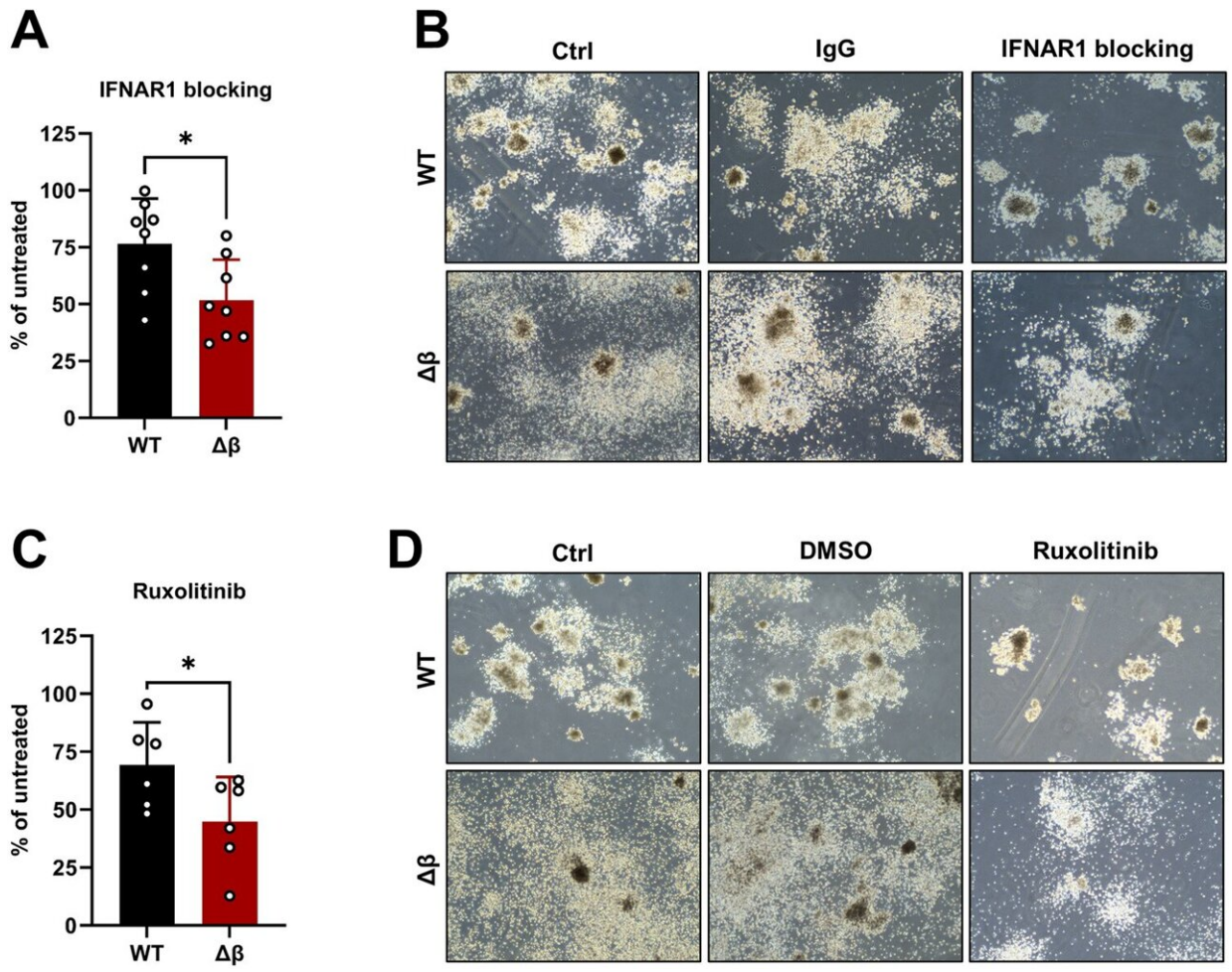

Interference with IFN signaling is a vulnerability of STAT3β-deficient cells. Credit: *Cell Death & Disease* (2024). DOI: 10.1038/s41419-024-06749-9

The protein STAT3β has a positive influence on the course of acute myeloid leukemia (AML) and could serve as a prognostic marker in the future. These are the outstanding results of a cancer research study at the Karl Landsteiner University of Health Sciences (KL Krems).

In the work published in *Cell Death & Disease*, an international research team succeeded in identifying the previously unknown effect of the protein on interferon-dependent signaling pathways. The results of the study suggest that knowledge of the amount of STAT3β could help to make novel personalized treatment choices for AML.

AML is a malignant disease of the hematopoietic system in which a wide range of different cellular and genetic alterations can be observed. This complexity poses an enormous challenge to the development of effective therapies.

One protein that is now receiving particular attention is STAT3 (Signal Transducer and Activator of Transcription 3). It exists in two forms (α and β), with the α form tending to promote tumors and the β form rather suppressing them.

An international research team from Austria, Hungary, and Italy, coordinated by KL Krems, has focused on the β form (STAT3β) and intensively investigated its tumor-suppressing role in AML—with promising results.

Better with more STAT3β

"We were able to show that STAT3β has a positive influence on the course of AML," says Prof. Dagmar Stoiber-Sakaguchi, Head of the Division of Pharmacology at KL Krems and head of the research team, succinctly summarizing its key findings.

Crucial to this discovery was the establishment of an animal model in which the expression of STAT3β in the leukemia cells was inhibited. This showed that the absence of the protein significantly shortened the survival time after the onset of AML—a clear indication of a protective effect of STAT3β or its function as a so-called tumor suppressor.

Further results of the study then indicated an interaction of STAT3β with interferon-dependent signaling pathways in the leukemia cells.

Sophie Edtmayer, Ph.D. student and first author of the study, says, "We were able to show by RNA sequencing analyses that the loss of STAT3β leads to an increase in interferon-dependent signals in the cells. This observation was also confirmed by a higher sensitivity of these cells to inhibitors of the interferon signaling pathways."

Practical application

"We then wanted to investigate the specific significance of our results for patients," Prof Stoiber-Sakaguchi explains. To this end, the Medical University of Graz provided leukemic cells from affected patients. These were used to analyze whether there is a correlation between the amount of STAT3β and the expression of interferon-activated genes as well as the survival time of those affected.

The results of this study were compelling, showing that lower levels of STAT3β were associated not only with increased expression of interferon-activated genes, but also with reduced survival. Prof Stoiber-Sakaguchi comments, "This finding suggests that STAT3β levels could be used to predict disease progression."

In fact, the team is already thinking ahead: the discovery of a link between low STAT3β, activation of interferon-dependent pathways and reduced survival suggests that therapeutic intervention in the interferon

pathways could have a positive effect on the course of AML—a promising result of this study coordinated by KL Krems.

More information: Sophie Edtmayer et al, A novel function of STAT3β in suppressing interferon response improves outcome in acute myeloid leukemia, *Cell Death & Disease* (2024). DOI: 10.1038/s41419-024-06749-9

Provided by Karl Landsteiner University