What makes blood stem cells transform? Regulation of RNA splicing may be an answer

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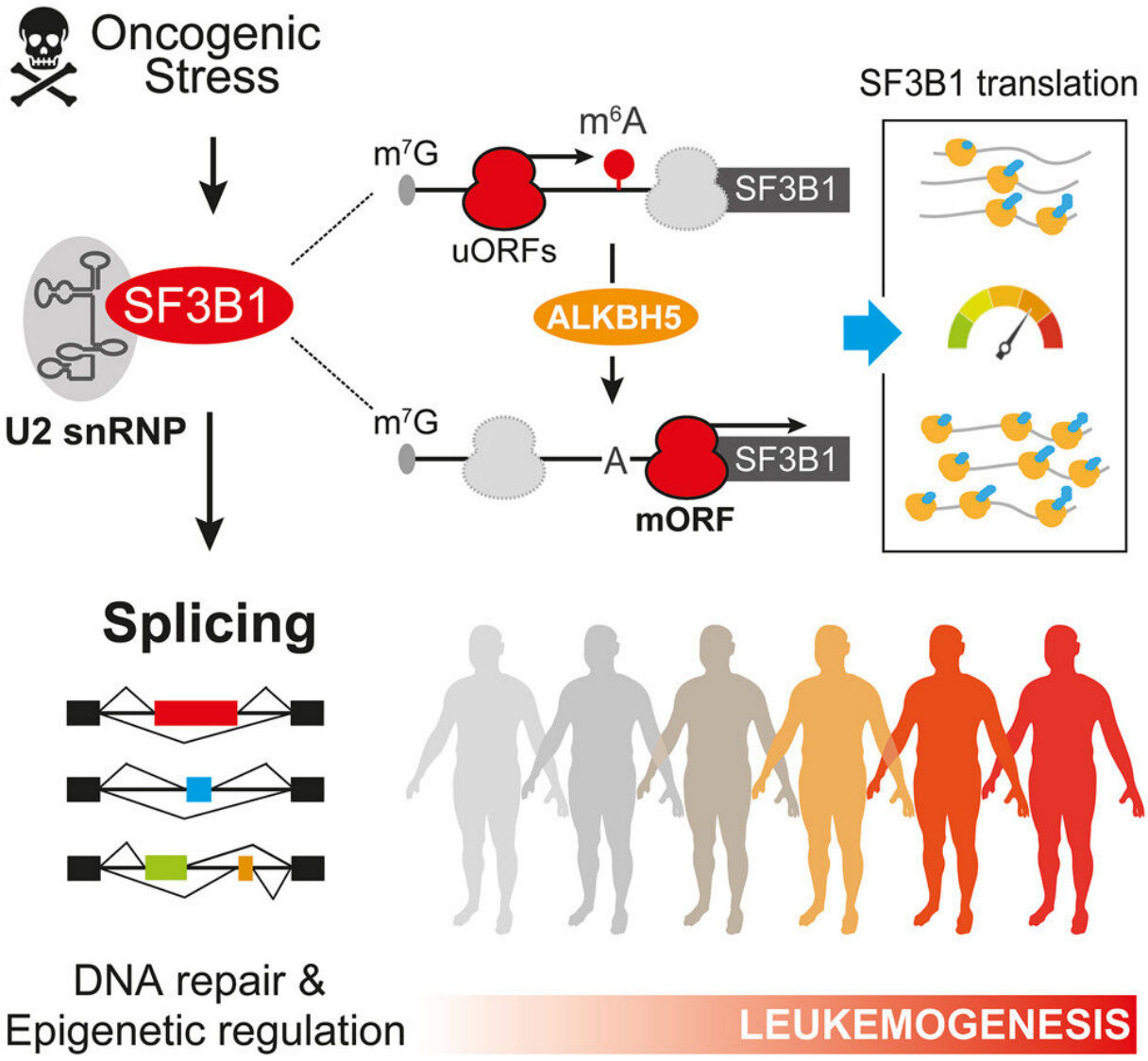

Graphical abstract. Credit: *Molecular Cell* (2023). DOI: 10.1016/j.molcel.2023.02.024

Researchers at Lund University Faculty of Medicine have determined a novel mechanism linking the metabolism of ribonucleic acids, RNA, to the development of leukemia in myelodysplastic syndrome (MDS) patients. In a study published in the journal *Molecular Cell*, they explain what makes hematopoietic stem cells acquire malignant traits in cancer.

RNA splicing is a major nexus of gene expression regulation, shaping cellular identity during development, frequently altered in human cancers. This process is mediated by a complex molecular machinery known as the spliceosome, which enables the production of multiple and functionally distinct proteins from single genes.

A team of researchers led by Dr. Cristian Bellodi recently discovered a hardwired genetic control mechanism modulating individual spliceosomal components, known as splicing factors, in cells harboring oncogenic lesions common in human cancers.

This work highlighted core splicing proteins, including SF3B1, frequently mutated in various cancers. Splicing factor mutations are particularly prevalent in MDS, a group of heterogeneous hematological disorders characterized by defective blood stem cells and a high risk of leukemia development. "Accumulating evidence is highlighting a role for aberrant splicing in cancer even in the absence of splicing factors mutations. However, little is known about the contribution of the non-mutated splicing factors in tumor evolution," explain the researchers.

The team began by investigating how the levels of non-mutated SF3B1, a core spliceosome component, contribute to the MDS disease. With Prof. Eva Hellström-Lindberg's group at the Karolinska Institute, Maciej Cieśla and coworkers discovered dynamic regulation of SF3B1 levels during the malignant transformation from MDS to leukemia.

"Strikingly, we found that SF3B1 protein accumulates in MDS patients to ensure genome integrity via splicing regulation. Blocking this mechanism drastically accelerates progression to aggressive leukemia," remarks Maciej Cieśla, a postdoctoral fellow in the RNA and Stem Cell Biology group at Lund University Stem Cell Center and first author of the study, now a group leader at IMOL, Poland.

The authors further investigated the molecular determinants controlling the SF3B1 production during the transition to leukemia. These studies led to the breakthrough discovery that SF3B1 synthesis depends on a single RNA chemical modification mark, known as N6-methyladenosine, m6A, deposited on its messenger RNA.

"We found that the presence of m6A RNA modification provides a 'stop signal' that regulates SF3B1 production, a critical event that impacts accumulation of DNA damage in leukemic cells," explains Cieśla.

"Our results revealing a new critical connection between RNA metabolism and genome integrity in leukemic stem cells, provide important insights into the complex underlying mechanisms fueling cancer development in MDS patients. Our findings are particularly timely, as increasing evidence indicates that RNA modification and splicing alterations represent new therapeutic vulnerabilities for treating hematological and solid cancer patients," concludes Cristian Bellodi, Associate Professor, Division of Molecular Hematology and Lund Stem Cell Center, Lund University.

More information: Maciej Cieśla et al, m6A-driven SF3B1 translation control steers splicing to direct genome integrity and leukemogenesis, *Molecular Cell* (2023). DOI: 10.1016/j.molcel.2023.02.024