Shedding new light on blood cancers

The University of Trento with Yale University and the CNR Institute of Biophysics of Trento open the way to therapeutic solutions that target the ability of cells to respond to stress. The international study has been published in Molecular Cell

Trento, 17 March 2022 – Blood cancers are very aggressive diseases with devastating consequences for the quality of life of patients. In many cases, for example in myelodysplastic syndromes and leukemias, patients have mutations in some proteins, called splicing factors, which lead to ineffective blood cell production. Research has long been engaged in identifying new therapeutic approaches to fight these types of cancers.

New hope comes from a study conducted by the University of Trento and Yale University, in collaboration with the CNR Institute of Biophysics of Trento and published in Molecular Cell: "Precision analysis of mutant U2AF1 activity reveals deployment of stress granules in myeloid malignancies" (DOI: https://doi.org/10.1016/j.molcel.2022.02.025).

The researchers have studied the biological processes of RNA. RNA molecules, transcribed from DNA, must be processed in order to function properly. During splicing, RNA molecules are cut and select pieces are glued back together with the help of proteins called splicing factors, among which protein U2AF1 (U2 Small Nuclear RNA Auxiliary Factor 1) plays an important role. RNA splicing is therefore a fundamental process to ensure cellular diversity. Mutations in U2AF1 and in other splicing factors, which are frequent in many types of tumors, generate mistakes in this process.

Toma Tebaldi, a researcher at the Department of Cellular, Computational and Integrative Biology of the University of Trento and Assistant Professor Adjunct at the Yale University School of Medicine, is co-last and co-corresponding author of the study: "The main discovery is that mutations in the U2AF1 splicing factor modify the composition and aggregation of the RNAs in the cell, and facilitate the formation of stress granules, aggregations of RNAs and proteins that form when cells are 'stressed'. Therefore, mutant cancer cells have a competitive advantage over 'normal' cells in stressful situations, such as tumors and the pharmacological treatments used to treat them".

Giulia Biancon (researcher at Yale) and Stephanie Halene (Professor of Hematology at Yale), the other prominent authors of the article, added: "The discovery that U2AF1 mutations increase the formation of stress granules opens new perspectives for the pharmacological treatment of myelodysplastic syndromes and leukemias. Identifying this mechanism has not been easy because it is not caused by a single large change to one RNA, but by the sum of many small changes in hundreds of RNAs. More generally, this mechanism could explain and help treat conditions characterized by mutations affecting other splicing factors".

The article is published with a cover image that is based on a painting by artist Antonietta Bellini. It is a metaphor of RNA biological processes that are the subject of the study.
Toma Tebaldi concluded: "The project began during my time at Yale and now continues at the Cibio Department of UniTrento thanks to funding from AIRC (the Italian foundation for cancer research) that made it possible to establish the laboratory of RNA and Disease Data Science in 2021".

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