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Press release
For immediate publication

New therapeutic options discovered for malignant blood cancer: A study appearing in the journal Leukemia

Graz, 23 March 2023 – Leukemia is less a specific disease than an umbrella term for a variety of malignant changes in the hematopoietic or lymphatic systems of the body. The forms of therapy are as varied as the disease itself. One subtype of leukemia is the group of myeloproliferative neoplasms (MPNs). Each year just one or two cases are diagnosed per 100,000 inhabitants, making MPNs an extremely rare, chronic type of blood cancer. New therapeutic options for myeloproliferative neoplasms have been discovered at Med Uni Graz and published in the acclaimed journal "Leukemia."

Rare hematological cancers

Myeloproliferative neoplasms (MPN) originate in the hematopoietic stem cells in the bone marrow. These hematopoietic stem cells are normally responsible for forming healthy, functioning blood cells throughout an individual's life. Certain genetic changes such as mutations in the Janus kinase 2 (JAK2) and calreticulin (CALR) genes of hematopoietic stem cells can result in a disruption in normal hematopoiesis and the development of a myeloproliferative neoplasm through uncontrolled, excessive growth of mature blood cells (erythrocytes, granulocytes, thrombocytes). Those affected have a higher risk of blood clots and thus heart attacks, strokes or other embolisms. Complaints such as fatigue, night sweats and fever may also be very common in the context of these diseases. Thanks to the development of Janus kinase (JAK) inhibitors, a specific therapy for patients with a mutation in the JAK2 gene has been available for several years. There is still no targeted therapy for patients with a mutation in the CALR gene.

A recently published paper in the high-impact journal "Leukemia" by Johannes Foßelteder, a PhD student from Andreas Reinisch's working group at the Division of Haematology and Department of Blood Group Serology and Transfusion Medicine, describes impaired protein folding in the endoplasmic reticulum (ER) of hematopoietic stem cells as a new CALR mutation-specific pathomechanism. The endoplasmic reticulum is a network of branching ducts in the cell that plays an important role in the formation of substances such as proteins or fatty acids. The researchers show that this impaired protein folding also represents a new therapeutic target that can be used for specific treatment of patients with CALR mutations.

Decoding pathogenic mechanisms through precise genetic manipulation of healthy hematopoietic stem cells

The scientists were able to introduce the two most common CALR gene mutations into healthy human hematopoietic stem cells at the physical location of the gene using very precise CRISPR

gene editing. Hidden behind the awkward abbreviation CRISPR is a new molecular biology procedure that very specifically changes the building blocks of DNA in the genome. The genetic scissors can be used in nearly all living cells, and its precision is unique. The Graz researchers were able to shed light on the exact molecular pathogenic mechanisms that are triggered by the CALR mutation and contribute to the malignant degeneration of cells.

The final straw: Impaired protein folding — a new therapeutic target for treating CALR-mutated MPNs

Correct folding of newly formed proteins is a highly complex process that occurs in the endoplasmic reticulum (ER). The three-dimensional structure is essential to the correct functioning of proteins and the slightest error in the folding process can render the proteins useless. Incorrectly or incompletely folded proteins lead to the triggering of an alarm in the ER that is referred to as the unfolded protein response (UPR). Incorrectly folded proteins are either corrected or degraded. If these correction and degradation processes are overburdened by an excess of incorrectly folded proteins, the result is apoptosis, induced cell death.

This was the starting point for Andreas Reinisch and Johannes Foßelteder's team. Using their new cell model, the group discovered that mutations in the CALR gene negatively affect the regular protein folding processes in hematopoietic stem cells. Due to the accumulation of incorrectly folded proteins, the UPR is activated excessively in the CALR-mutated cells. In their study, the researchers were able to show that additional blocking of protein degradation (with proteasome inhibitors) or blocking of the UPR (blocking of the protein folding correction) produces too many incorrectly folded proteins and this is the final straw. The cells enter apoptosis and die.

Since proteasome inhibitors are already approved for other hematological diseases, these preclinical results could be transferred quickly.

Andreas Reinisch appears optimistic about the study findings: "Naturally we hope that these inhibitors will find their way into clinical use and provide promising therapeutic approaches for patients with CALR-mutated MPNs."

Contact and further information

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Profile: Andreas Reinisch

Andreas Reinisch studied medicine at Med Uni Graz and graduated from the PhD program Molecular Medicine in 2010. He then spent five years conducting research at Stanford University in California. In his research, he focuses on the development of leukemia at the genetic and molecular levels using modern CRISPR gene editing. He is employed by Med Uni Graz as a §99.5 tenure track professor.

Link to the publication:

Human gene-engineered calreticulin mutant stem cells recapitulate MPN hallmarks and identify targetable vulnerabilities
https://www.nature.com/articles/s41375-023-01848-6