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New Findings on Acute Leukemias: Specific Mutations Provide Targets for More Targeted Therapies

Researchers at the NCT Heidelberg and the German Cancer Research Center (DKFZ) have, for the first time, systematically determined how specific mutations promote acute myeloid leukemias. The results show why IDH1- and IDH2-mutated leukemias develop differently despite similar molecular mechanisms—and open up new approaches for diagnostics and targeted therapies. The National Center for Tumor Diseases (NCT) Heidelberg is a joint institution of the German Cancer Research Center (DKFZ), the Heidelberg University Hospital (UKHD), the Heidelberg Medical Faculty of the Heidelberg University and the Thoraxklinik Heidelberg.

Mutations in the genes encoding the enzymes IDH1 and IDH2 have long been considered important molecular alterations in acute leukemias. Until now, it was assumed that alterations in both genes trigger largely similar disease mechanisms. Researchers at the National Center for Tumor Diseases (NCT) in Heidelberg and the German Cancer Research Center (DKFZ) have now, for the first time, systematically deciphered how IDH1 mutations contribute to the development of diseases of the blood-forming cells and acute leukemias. In doing so, they have provided important new insights into the biology of IDH1-mutated leukemias and will help improve their diagnosis and treatment in the future.

The researchers were able to show that leukemias with IDH1 and IDH2 mutations differ significantly despite many similarities. A key factor is that the two genes are active in different types of hematopoietic cells, and mutations therefore exert their disease-promoting effects in different blood progenitor cells. The study found that IDH1 mutations specifically block the normal maturation of infection-fighting white blood cells—known as neutrophils—in both animal models and affected patients. As a result, patients with IDH1-mutated leukemia experience a characteristic loss of these cells, which is not observed in IDH2-mutated leukemia. At the same time, the researchers were able to demonstrate that pharmacologically inhibiting only the mutated IDH1 enzyme was not sufficient to lift the maturation block. Only the combination with a drug that inhibits DNA methylation restored normal maturation.

Daniel Lipka, head of the Translational Cancer Epigenomics Section in the Department of Translational Medical Oncology at the DKFZ and the NCT Heidelberg, is the senior author of the study. He says: "Our results show for the first time why IDH1- and IDH2-mutated leukemias are distinct diseases and why clinically used targeted combination therapies can be effective in IDH1-mutated leukemias."

These findings could be particularly relevant for countries with limited access to modern molecular diagnostics. Since IDH1-mutated leukemias are often associated with significantly reduced neutrophil counts, patients with this characteristic could be identified through a simple blood test and specifically screened for corresponding mutations. This would enable more resource-efficient diagnostics and facilitate access to molecularly targeted therapies for affected patients.

In the long term, the researchers now plan to investigate additional molecular processes that contribute to disease development independently of the actual enzymatic activity of the IDH1 mutation. This could lead to new therapeutic approaches for early precursors of acute leukemias that help prevent disease progression.

Publication:

Mariam Hakobyan et. al. Mutant IDH1 blocks neutropoiesis by repressing myeloid progenitor programs; Blood;
DOI: 10.1182/blood.2025031268

Press release

16-Jul-2026
Source: German Cancer Research Center

Further information

- National Center for Tumor Diseases (NCT)
- German Cancer Research Center (DKFZ)