Mechanisms of therapy resistance and relapse in AML

Scientific abstract

Acute myeloid leukemia (AML) is an aggressive blood cancer leading to complications related to bone marrow failure and organ infiltration. Treatment comprises high-dose chemotherapy to try to achieve remission followed by either more chemotherapy or a hematopoietic stem cell transplant (HSCT). Treatment resistance and relapse after remission are common and <25% of patients survive 5 years. Although current genetic approaches can help to estimate the risk of therapy resistance or relapse, much less is known about the molecular alterations that drive recalcitrance to therapy. The goal of this project is to define the molecular changes contributing to therapy resistance. Bone marrow or blood samples from AML patients at diagnosis or following treatment failure were subjected to bulk whole genome and transcriptome sequencing. Our results show an increase in the variant allele fraction of specific genetic mutations increases at relapse. Recurrent transcriptomic changes at relapse are aligned with an increase in these specific mutations, and associated with enrichment of a stem cell-like signature. These findings suggest that AML relapse is associated with an increase in leukemic stem cell-like activity triggered by activation of specific signaling pathways. Identification of these molecular aberrations now provide an opportunity to begin to select or discover more enduring therapies for AML treatment.

Plain language abstract

Acute myeloid leukemia (AML) is a fast-growing cancer of the blood that causes serious problems by damaging the bone marrow and spreading to other organs. Treatment usually starts with high-dose chemotherapy to try to bring about remission (a period where the cancer is not active), followed by either more chemotherapy or a stem cell transplant. However, many patients do not respond to treatment or the cancer returns after remission. Less than 25% of patients survive five years after diagnosis.

Current genetic tests can help estimate a patient's risk of relapse or resistance to treatment, but we still don't fully understand the molecular reasons why some cases of AML are harder to treat. The goal of this study was to find out what molecular changes cause AML to resist treatment.

We used bone marrow and blood samples from AML patients either at the time of diagnosis or after their treatment had failed. These samples were analyzed using whole genome and transcriptome sequencing, which look at all of a patient's DNA and gene activity. We found that certain genetic mutations became more common after the cancer came back. These changes in gene activity were linked to the increased presence of cancer cells that act like stem cells, which are known for their ability to survive chemotherapy and regenerate.

This suggests that AML relapse may be caused by a rise in stem cell-like cancer cells, driven by changes in specific molecular pathways. Understanding these changes opens the door to developing better, longer-lasting treatments that may help prevent relapse and improve survival for AML patients.