Why leukemic stem cells not harmed by chemotherapy begin to grow and produce AML cells after treatment

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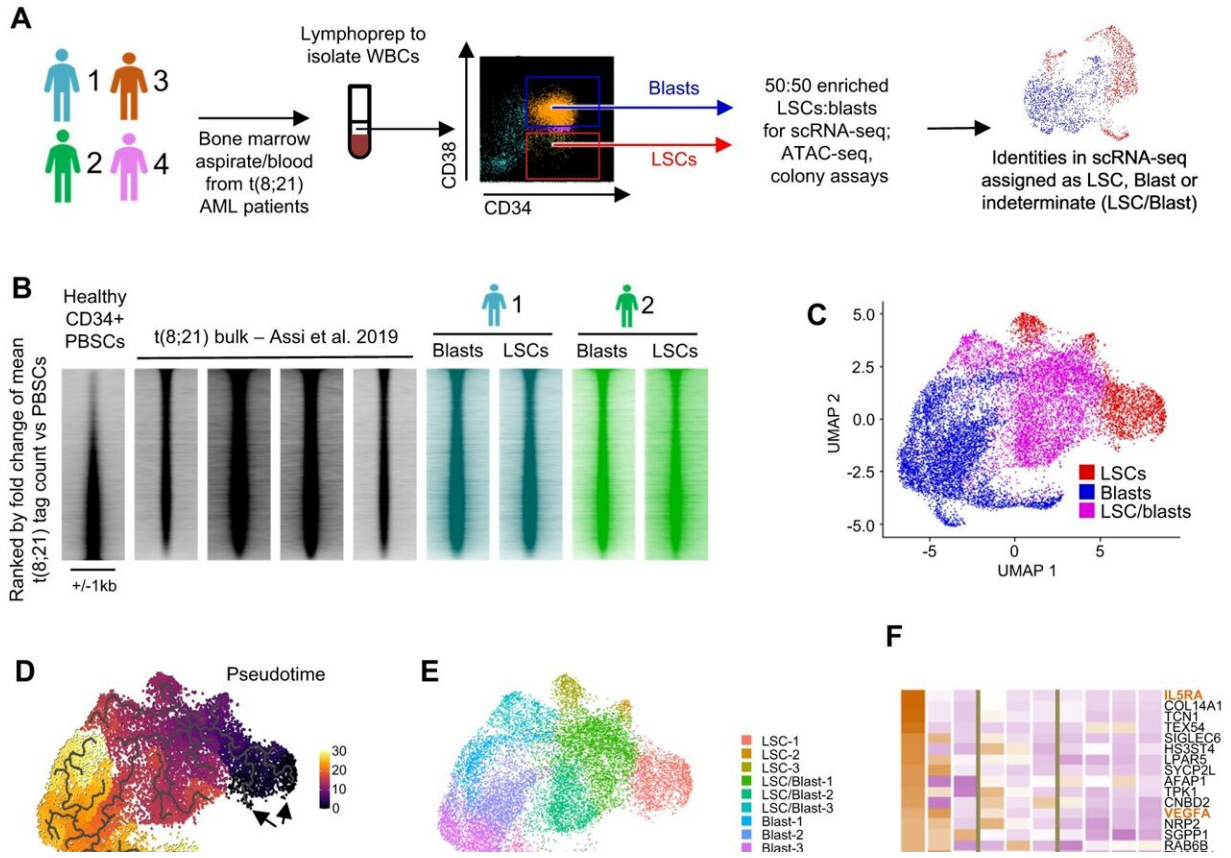

AML-subtype specific gene expression and chromatin accessibility is established in LSCs. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-45691-4

The mystery of why myeloid leukemia starts to grow again after chemotherapy has killed the bulk of malignant cells, and how growth may be blocked by repurposed drugs, has potentially been solved through new research.

The bone marrow of AML patients contains a rare population of leukemic stem cells (LSCs) that do not grow and therefore are not killed by chemotherapy. However, after treatment, these cells start to grow and produce AML cells, but it was unclear what kick-started this process.

In a new study published in *Nature Communications*, researchers from the University of Birmingham, Newcastle University and the Princess Maxima Center of Pediatric oncology studied single cells from patients with t(8;21) acute myeloid leukemia, a specific type of blood cancer, to investigate what made the rare LSCs grow.

Professor Constanze Bonifer from the Institute of Cancer and Genomic Sciences at the University of Birmingham who led the study said, "Leukemic stem cells normally seem asleep which is why they are not killed by chemotherapy, but we reasoned that something must trigger them to start growing in order for the leukemia to come back.

"These cells are very rare and difficult to study but by examining gene expression in single LSCs we found genes being expressed that encode for growth regulators normally not present in myeloid cells. Both cell types are found in the bone marrow alongside the AML cells, but healthy stem cells do not respond to their signals. By aberrantly upregulating these growth regulators, leukemic stem cells now can respond to growth factors that are present in the body and tell them to grow."

Blocking unwanted stem cell growth

The growth regulators, identified in this study were KDR, the receptor

for VEGF signaling which is normally only expressed in blood vessels and the IL-5 receptor which is normally only expressed on eosinophils. Moreover, VEGFA, the growth factor binding to KDR, was also expressed by the leukemia meaning it could trigger its own growth.

Following identification of these receptors, the researchers confirmed that by activating them in the laboratory they were able to trigger stem cell growth. Importantly, they also showed that growth could be blocked in a dish and in mice by repurposing drugs against VEGF (Avastin, approved for various solid tumors including colorectal cancer) and IL-5 signaling (Fasenra, approved for eosinophilic asthma).

Professor Olaf Heidenreich from Newcastle University and the Princess Maxima Center of Pediatric Oncology says, "An exciting result from these studies is the fact that the expression of these receptors is specific to this particular type of leukemia. They are expressed as a result of the presence of a specific disease-causing mutation giving rise to the onco-fusion protein RUNX1::ETO which reprograms the gene regulatory network that defines how a cell responds to outside growth signals.

"This work highlights the power of single cell analysis for digging deep into what regulates the growth of AML cells. It also highlights the fact that AML sub-types may have to be treated as separate entities."

The first author of the study, Dr. Sophie Kellaway who is now continuing this research at the University of Nottingham says,

"We were very excited to find not one but two new, and potentially druggable targets to prevent relapse in these patients. Being told your cancer has come back is devastating news and we want to prevent this happening. Unfortunately, as these receptors were so specific this would only work for t(8;21) acute myeloid leukemia and is not a magic bullet.

"However, inspection of other single cell data from different leukemia sub-types shows that other growth regulatory pathways are upregulated in their stem cell population as well. We are now hoping to find those that can be hit in other types of AML."

Dr. Suzanne Rix, from Blood Cancer UK, said, "Blood cancer is the UK's third biggest cancer killer and acute myeloid leukemia is a particularly aggressive form of blood cancer that can come back even after initial treatments have been successful.

"This research uncovers why one specific type of acute myeloid leukemia can return, and could lead to the development of new treatments with the potential to stop the cancer coming back, giving new hope to people affected by this specific form of leukemia. However, further work is needed to see whether a similar approach could be taken for other forms of acute myeloid leukemia and more broadly much more research is desperately needed to develop effective, kinder treatments for all blood cancers."

More information: Sophie G. Kellaway et al, Leukemic stem cells activate lineage inappropriate signalling pathways to promote their growth, *Nature Communications* (2024). DOI: 10.1038/s41467-024-45691-4

Provided by University of Birmingham