New treatment options for a fatal leukemia

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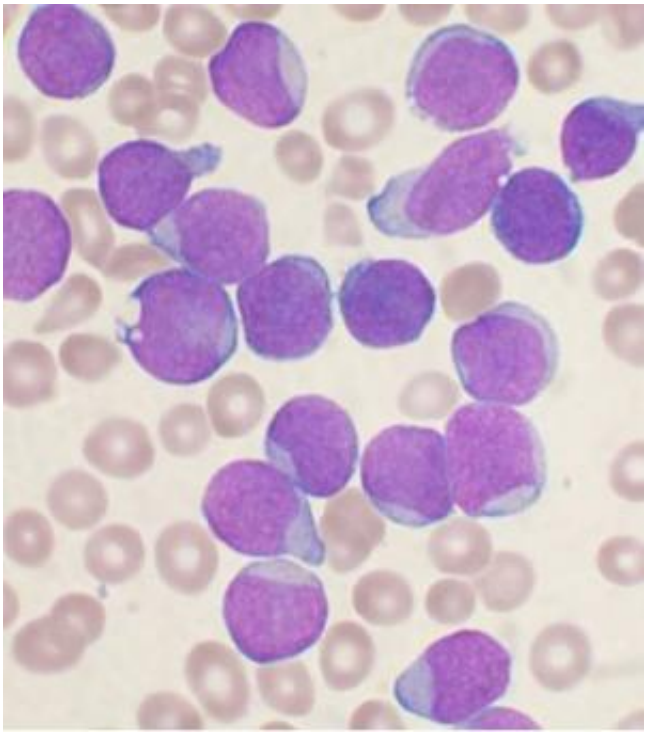

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

In industrialized countries like in Europe, acute lymphoblastic leukemia is the most common form of cancer in children. An international research consortium lead by pediatric oncologists from the Universities of Zurich and Hannover has now succeeded in decoding a specific form of this leukemia, which is regarded as incurable, and in obtaining insights for new therapeutic possibilities.

Acute lymphoblastic leukemia (ALL) frequently develops between the age of two and three. This leukemia has various forms, which differ through certain changes in the genetic material of the leukemia cells. A team of scientists involved in a joint international project headed by Jean-Pierre Bourquin, a pediatric oncologist from the University Children's Hospital Zurich, and Martin Stanulla, a professor at Hannover Medical School, has now succeeded in decoding the genome and transcriptome of an as yet incurable sub-type of acute lymphoblastic leukemia. These results were achieved in collaboration with leading experts in the field, Marie Laure Yaspo, a research group leader at the Max Plank Institute for Molecular Genetics in Berlin, Arndt Borkhardt, a professor at the University of Düsseldorf, Jan Korbel a professor at the European Molecular Biology Laboratory in Heidelberg and André Franke from the University of Kiel.

The two genes TCF3 and HLF are already known to be fused together aberrantly in this subtype of acute lymphoblastic leukemia. This change in the genetic code makes the leukemia resistant to all current treatments. The scientists have now discovered that other DNA areas are also changed in addition to the two aberrantly fused genes and that the activity of key genes was modified thus determining a novel program associated to the leukemic cells.

A wolf in sheep's clothing

Modifications of genes that control the development and promote the growth of highly specific blood defense cells, so-called B-lymphocytes, were evident in the leukemia cells studied. The interplay between the pathogenic fusion of TCF3 with HLF and newly identified alterations triggers a previously undetected reprogramming of the leukemia cells to a very early, stem-cell-like developmental stage, which is not externally visible on the cells. "This form of leukemia might be described as a kind of 'wolf in sheep's clothing'," stresses Martin Stanulla. "These key

findings could be made, in particular, by reading out the messenger molecules synthesized in the tumor cells, a powerful technique allowing not only a deeper understanding of the genetic program specifying the behavior of tumor cells, but also of therapeutic entry points" adds Marie-Laure Yaspo.

The group of Jean-Pierre Bourquin developed a humanized mouse model at the University Children's Hospital in Zurich that enables researchers to explore leukemias in conditions that are very similar to the situations encountered in humans. "In other words, we created a model to accelerate the discovery of more personalized treatment options," explains Jean-Pierre Bourquin. The human leukemia cells growing in the mouse retain the crucial genetic changes and, according to Bourquin, therefore constitute a realistic possibility to examine new courses of therapy in a patient-oriented manner.

Promising drug tests

On this basis, the Zurich researchers tested hundreds of novel drugs. Some of them, which are still undergoing further clinical development, displayed a very positive effect. One such drug is Venetoclax, which specifically targets the protein BCL2 relevant for the programmed cell death and already worked for other cancer strains.

In the mouse model, Venetoclax induced remissions of the disease, followed by prolonged phases without any signs of the disease if administered together with conventional chemotherapy for leukemia. "Further studies are now needed to test how the results of our study might be used for therapeutic possibilities," says Bourquin. "Our work just goes to show the great potential of coordinated, interdisciplinary research approaches involving cutting-edge technological possibilities for cancer research," concludes Stanulla.

The development of new courses of therapy in the humanized leukemia model was supported by the Swiss National Science Foundation and the University of Zurich's clinical research focus program "Human Hemato-Lymphatic Diseases". The genetic studies were funded by the German Federal Office for Radiation Protection via the environmental research program of the German Federal Environment Ministry and by the Max Planck Institute for Molecular Genetics.

More information: Ute Fischer et.al. Genomics and drug profiling of fatal TCF3-HLF?positive acute lymphoblastic leukemia identifies recurrent mutation patterns and therapeutic options. 27 July, 2015. *Nature Genetics*. DOI: 10.1038/ng.3362

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