New promising targeted drug for a rare leukemia

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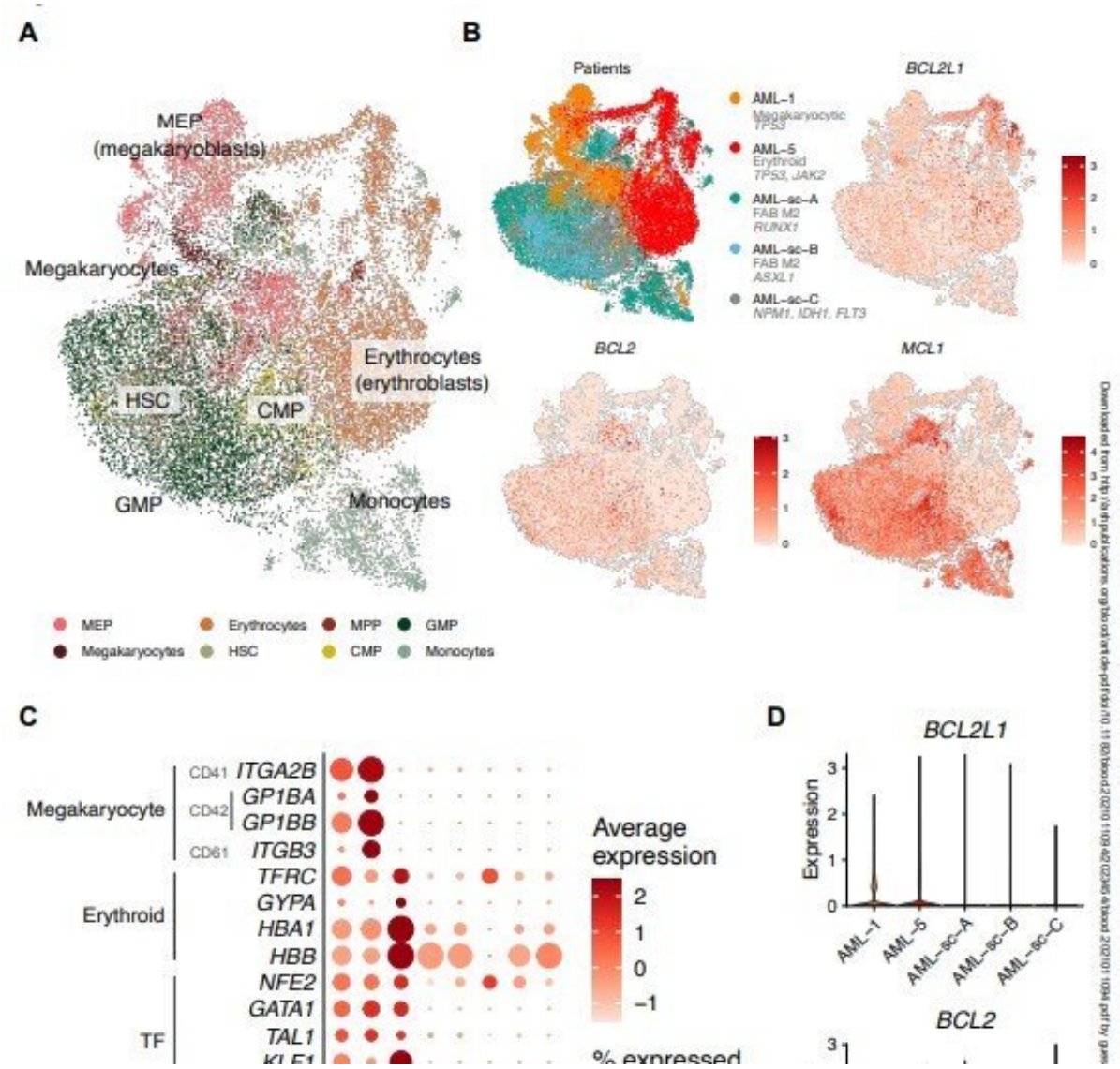

BCL-2 family gene expression in blasts across AML types at single cell resolution. (A) UMAP plot of scRNA-seq data of blasts from AML with

megakaryoblastic differentiation (AML-1), AML with erythroid differentiation (AML-5), and three AMLs representing other subtypes. Cell types identified using the reference-based method SingleR are colored. (B) UMAP plot as in A with patients and expression of BCL2L1, BCL2, and MCL1 colored as normalized and scaled log-transformed counts. (C) Dot plot of RNA expression of selected megakaryocyte and erythroid markers, TFs regulating erythroid/megakaryocytic differentiation, progenitor markers, and BCL-2 family genes in the indicated cell types based on reference-based method SingleR annotations. (D) Violin plot demonstrating BCL-2 family gene expression of the blasts in different patients. Credit: *Blood* (2022). DOI: 10.1182/blood.2021011094

Targeted drugs have been developed to supplement chemotherapy in the treatment of cancer. These drugs only affect cancer cells, leaving healthy cells alone. Venetoclax is a new targeted therapy option for the treatment of acute myeloid leukemia (AML). Venetoclax was recently granted marketing authorization in Finland.

Venetoclax works by sensitizing cancer cells to programmed cell death. However, a new study now shows that venetoclax does not appear to be effective against erythroid and megakaryoblastic leukemias, two rare subtypes of the disease that are difficult to treat. In these leukemia types, malignant cells resemble blood stem cells that produce red blood cells or platelets. Currently, few treatment options are available to these patients.

The study—carried out by the University of Helsinki, HUS Comprehensive Cancer Center and the University of Copenhagen—identified a new targeted drug, which may in the future offer a therapeutic option to patients with these subtypes of the disease. The study was published in the journal *Blood* in December.

Further research needed

In the laboratory, the researchers screened a wide selection of pharmaceutical agents that could be effective specifically against erythroid or megakaryoblastic leukemia cells.

Among the more than 500 agents analyzed, BCL-XL protein inhibitors in particular were effective in killing cancer cells isolated from these types of leukemia. The BCL-XL protein has a similar function of preventing cells from being driven to programmed cell death as BCL-2, the target of venetoclax. At the moment, BCL-XL inhibitors are not used to treat patients, but their efficacy and safety are currently being investigated in clinical trials.

"The introduction of venetoclax has significantly improved the prognosis of AML patients. However, our research indicates that venetoclax is unlikely to function optimally against the subtypes of AML in our focus. Nevertheless, the finding should be verified in larger patient datasets," says physician-scientist Olli Dufva.

Potential to improve prognosis

AML is the most common type of acute leukemia in adults. It can be divided into subtypes based on mutations and the degree of differentiation of leukemia cells. One challenge associated with the use of targeted drugs is identifying patients who benefit from the new drug options. This study contributes to making the selection of targeted drugs more precise.

"The laboratory findings provide evidence that patients with erythroid or megakaryoblastic acute leukemia would be a promising group for investigating the efficacy of BCL-XL inhibitors in clinical use," says postdoctoral researcher Heikki Kuusanmäki.

The researchers believe that BCL-XL inhibitors will be trialed in the treatment of these leukemia types in the near future.

"This finding may in the future improve the prognosis of these very rare and difficult-to-treat leukemias," says Professor of Translational Hematology Satu Mustjoki from the University of Helsinki and HUS Comprehensive Cancer Center.

More information: Heikki Kuusanmäki et al, Erythroid/megakaryocytic differentiation confers BCL-XL dependency and venetoclax resistance in acute myeloid leukemia, *Blood* (2022). DOI: 10.1182/blood.2021011094

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