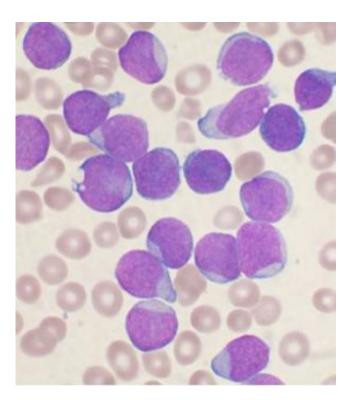


MicroRNA pathway could lead to new avenues for leukemia treatment

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

Cancer researchers at the University of Cincinnati (UC) have found a particular signaling route in microRNA (miR-22) that could lead to targets for acute myeloid leukemia, the most common type of fast-growing cancer of the blood and bone marrow.



These findings are being published in the April 26 issue of the online journal *Nature Communications*.

Acute myeloid leukemia (AML) is the most common type of acute leukemia and occurs when the bone marrow begins to make blasts, cells that have not yet completely matured. These blasts normally develop into <u>white blood cells</u>. However, in AML, these cells do not develop and are unable to ward off infections.

Jianjun Chen, PhD, associate professor in the Department of Cancer Biology at the UC College of Medicine, member of the UC Cancer Institute and lead author on the study, says that microRNAs are sophistically controlled and play key roles in the development of cancer.

"MicroRNAs make up a class of small, non-coding internal RNAs that control a gene's job, or expression, by directing their target messaging RNAs, or mRNAs, to inhibit or stop. Cellular organisms use mRNA to convey genetic information," he says. "Previous research has shown that microRNA miR-22 is linked to breast cancer and other blood disorders which sometimes turn into AML, but we found in this study that it could be an essential anti-tumor gate keeper in AML when it is downregulated, meaning its function is minimized.

"When we forced miR-22 expression, we saw difficulty in leukemia cells developing, growing and thriving. miR-22 targets multiple cancer causing genes (CRTC1, FLT3 and MYCBP) and blocks certain pathways (CREB and MYC). The down-regulation, or decreased output, of miR-22 in AML is caused by the loss of the number of DNA being copied and/or stopping their expression through a pathway called TET1/GFI1/EZH2/SIN3A. Also, nanoparticles carrying miR-22 DNA oligonucleotides (short nucleic acid molecules) prevented leukemia advancement."



Chen, who conducted the study using <u>bone marrow</u> transplant samples and animal models, says that the ten-eleven translocation proteins (TET1/2/3) in mammals help to control genetic expression in normal developmental processes in contrast to mutations that cause function loss and tumor-slowing with TET2, which is observed in blood and stem cell cancers.

"We recently reported that TET1 plays an essential cancer generating role in certain AML where it activates expression of homeobox genes, which are a large family of similar genes that direct the formation of many body structures during early embryonic development," he says. "However, it is unknown whether TET1 can also function as a repressor for cellular function in cancer, and its role in microRNA expression has rarely been studied."

Chen says these findings are important in targeting a <u>cancer</u> that is both common and fatal.

"The majority of patients with ALM usually don't survive longer than five years, even with chemotherapy, which is why the development of new effective therapies based on the underlying mechanisms of the disease is so important," he says, adding that this pathogenesis as well as drug response to AML is unclear. "Our study uncovers a previously unappreciated signaling pathway

(TET1/GFI1/EZH2/SIN3A?miR-22?CREB-MYC) and provides new insights into genetic mechanisms causing and progressing AML and also highlights the clinical potential of miR-22-based AML therapy. More research on this pathway and ways to target it are necessary."

More information: *Nature Communications*, <u>DOI:</u> <u>10.1038/NCOMMS11452</u>



Provided by University of Cincinnati Academic Health Center

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