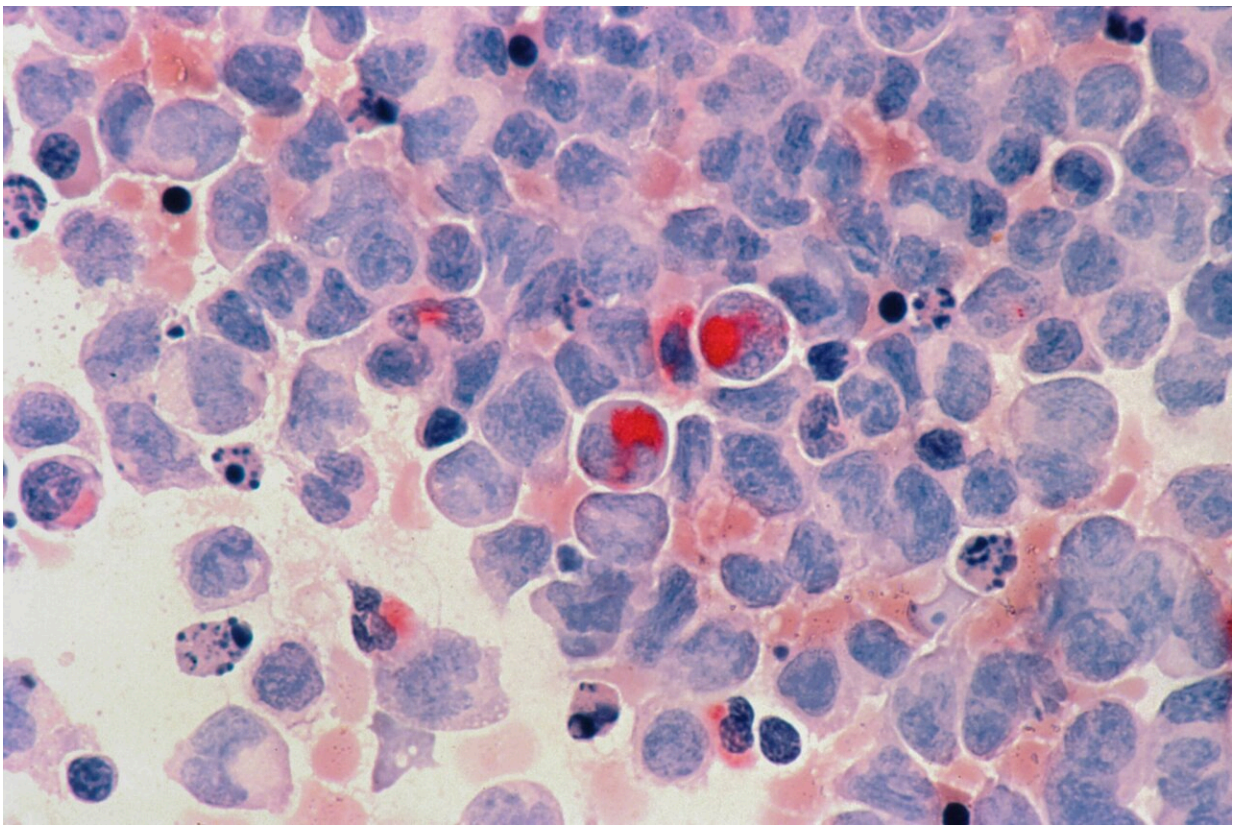
Drug combination restores ability of leading treatment to signal for death of blood cancer cells

April 24 2023



Credit: Unsplash/CC0 Public Domain

Despite the promise of new medications that promote cancer cell death in people with acute myeloid leukemia, leukemic cells often adopt

features that let them evade the drugs' effects within a year.

Now, new research using human tissue samples and mouse models has found that resistance of leukemia cells to a widely prescribed drug called venetoclax occurs because of a rapid increase in the breakdown and turnover of mitochondria, structures inside the cell that help power its functions. In addition to their role in producing energy, mitochondria also tell cells to die under certain adverse conditions.

This process of "programmed cell death" often goes wrong in cancer. Damaged mitochondria can also undergo a form of "self-eating" termed mitophagy that prevents them from sending "death signals."

Led by scientists at NYU Langone Health and its Perlmutter Cancer Center, the study showed that mitophagy helps leukemia cells to evade the killing effects of venetoclax, a drug in a class of medications known as BH3 mimetics.

Publishing in the journal *Cancer Discovery* online April 24, researchers found that the levels of several genes associated with mitophagy were increased in 20 leukemia patient samples compared with normal controls. The level of these genes was even higher in samples from leukemia patients with drug resistance than in those leukemic patients who were not. Particularly notable was the increased expression of the gene for Mitofusin-2 (MFN2), which codes for a key protein in the outer mitochondrial membrane.

Further experiments using mice into which bone marrow from acute myeloid leukemia patients was transplanted showed that the drug chloroquine, a known mitophagy inhibitor, restored the ability of venetoclax to kill the cancer cells.

"Overcoming resistance to BH3 mimetic drugs like venetoclax is of

unique clinical significance because these medications are often used for treating people with acute myeloid leukemia," said study co-lead investigator Christina Glytsou, Ph.D., a former postdoctoral researcher at NYU Grossman School of Medicine and now an assistant professor at Rutgers University.

"Acute myeloid leukemia is notoriously difficult to treat, with fewer than a third of those affected living longer than five years after their diagnosis, so it is important to maximize the impact of existing therapies," said study co-lead investigator Xufeng Chen, Ph.D., an instructor in the Department of Pathology at NYU Grossman.

"Our preclinical findings suggest that combining BH3 mimetics like venetoclax with either MFN2 or general mitophagy inhibitors could possibly serve as a future therapy for acute myeloid leukemia, as current drug treatments are stalled due to drug resistance," said study senior investigator Iannis Aifantis, Ph.D.

Aifantis, the Hermann M. Biggs Professor and chair of the Department of Pathology at NYU Grossman and Perlmutter, says the research team plans to design a clinical trial to test whether chloroquine, when used in combination with venetoclax, prevents drug resistance in people with acute myeloid leukemia.

Speaking about other study results, the researchers say they not only found that MFN2 was overly active in people with drug-resistant disease, but also that cancer cells exposed to similar cell-death-inducing compounds demonstrated a doubling in mitophagy rates.

Additional testing in cancer cells engineered to lack MFN2 showed increased sensitivity to drugs similar to venetoclax compared with cells that had functional MFN2. The new study and previous research by the team showing misshapen mitochondria in drug-resistant leukemic cells

confirmed that increased mitophagy was the source of the problem.

Acute myeloid leukemia, the most common form of adult leukemia, originates in the bone marrow cells and involves the rapid buildup of abnormal blood cells. The blood cancer results in the deaths of more than 11,500 Americans annually. Current treatments include chemotherapy and a limited number of targeted drug therapies. Bone marrow transplantation has also been used when other options fail.

More information: Christina Glytsou et al, Mitophagy promotes resistance to BH3 mimetics in acute myeloid leukemia, *Cancer Discovery* (2023). DOI: 10.1158/2159-8290.CD-22-0601

Provided by NYU Langone Health