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Researchers identify way to overcome chemotherapy-resistant leukaemia

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AML is a highly aggressive form of blood cancer in which immature white blood cells rapidly grow out of control, restricting the production of healthy blood cells. Over 2,400 people are diagnosed with AML each year in the U.K. Intensive chemotherapy, followed by a stem cell transplant, currently offers the best chance of a long term cure. But some people are unable to tolerate this treatment, or do not respond, and many more will relapse.

Researchers at the University of Glasgow found that increased activity of a gene called Trib2 is responsible for the development of particularly chemotherapy-resistant leukaemia cells in around a quarter of AML patients. Trib2 switches on the production of BCL2 proteins, which promote cell survival and regulate against cell death. The BCL2 protein has been linked to treatment resistance in other types of cancer, including lymphoma, breast cancer and prostate cancer.

Leukaemia cells with an active Trib2 gene in mice did not die when subjected to standard chemotherapy. When the researchers added a new targeted drug called venetoclax, which inhibits BCL2 protein production, the Trib2-positive leukaemia cells were sensitised to chemotherapy and treatment resistance was overcome.

The Trib2 gene affects different cells in different ways and in some cells it is known to actually protect against cancer development. By switching the Trib2 gene on and off in different types of healthy blood cells grown in the lab and in mice, the researchers were able to identify the most

likely original blood stem cells from which chemotherapy-resistant Trib2-driven AML develops.

It was only in a type of blood stem cell called a 'granulocyte macrophage progenitor' cell that Trib2 activity led to the development of fast-growing, treatment-resistant leukaemia cells in mice. Knowing that it is only these cells that lead to chemoresistance will make it easier for tests to identify chemoresistant cells in patients.

Dr. Karen Keeshan, who led the project at the University of Glasgow, said: "Combining BCL2 inhibitors such as venetoclax with standard chemotherapy appears to be extremely effective at overcoming treatment resistance in this aggressive leukaemia in the laboratory.

"An international clinical trial is currently underway using venetoclax in combination with low dose chemotherapy to treat older patients with AML who cannot tolerate intensive curative chemotherapy. Our findings suggest that testing for Trib2 at diagnosis and relapse could be put in place to identify patients who are most likely to benefit from this targeted treatment."

High levels of BCL2 are also linked to chemotherapy resistance in childhood AML, which accounts for 20% of childhood leukaemia. The Glasgow team will investigate whether their findings could be relevant to improving treatment for children with AML as well.

Dr. Alasdair Rankin, Director of Research at Bloodwise, said: "The outlook for people with AML is currently extremely poor and new treatments are desperately needed. Fewer than one in five patients will survive for longer than five years after diagnosis and many are not strong enough to undergo curative treatment.

"The more knowledge we have of what has gone wrong in leukaemia

cells, the more we will be able to understand and improve treatment strategies and designs. Venetoclax is already licensed for use in chronic lymphocytic leukaemia, for a group of patients with a specific genetic mutation that indicated they will respond to treatment. These findings suggest that this class of drug could be used in a similar way for a significant number of patients with AML too."

Cliff O'Gorman, Chief Executive of Children with Cancer U.K. said: "Aggressive forms of cancer are particularly cruel on children and improving treatment outcomes for young people with AML is very important, especially for those with chemotherapy-resistant cells. We look forward to seeing how their next study could help improve treatment for young people with AML. It's essential moving forward that we find kinder, more effective treatments for our young cancer patients. Here at Children with Cancer U.K., we are committed to building on such breakthroughs. We must continue to fund further studies and clinical trials to develop safer and more effective treatment for young cancer patients in the U.K."

AML is a form of cancer that affects blood cells called myeloid cells, which include red blood cells, platelets and certain types of white blood cells. Patients experience uncontrolled growth of immature myeloid cells and do not produce enough healthy blood cells.

Over 2,400 people are diagnosed with AML each year in the U.K. It can affect anyone of any age, but the majority of patients are over 60. Chemotherapy and stem cell transplantation offer the best chance of a permanent cure. Many patients are too elderly to undergo intensive treatment, however, and overall fewer than one in five patients will survive for longer than five years after diagnosis.

More information: Caitriona O'Connor et al. Trib2 expression in granulocyte-monocyte progenitors drives a highly drug resistant acute

myeloid leukaemia linked to elevated Bcl2, *Oncotarget* (2018). DOI: 10.18632/oncotarget.24525