Cell death researchers identify new Achilles heel in acute myeloid leukemia

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Professor Andreas Strasser was one of the lead researchers in a study that identifies a new Achilles heel in acute myeloid leukemia. Credit: The Walter and Eliza Hall Institute of Medical Research

Melbourne researchers have discovered that acute myeloid leukaemia (AML), an aggressive blood cancer with poor prognosis, may be susceptible to medications that target a protein called Mcl-1.

The research team at the institute was led by Dr Stefan Glaser, from the institute's Cancer and Haematology division, and Professor Andreas Strasser, joint head of the institute's Molecular Genetics of Cancer Division, working in collaboration with scientists from the Australian Centre for Blood Diseases and St. Vincent's Institute of Medical Research in Melbourne, as well as Austrian and American researchers. The research is published in this week's edition of the journal Genes *& Development*.

AML is the most common type of acute leukaemia (rapidly-developing cancers of immature blood cells) in Australia. Some forms of AML occur in children, while other forms are more prevalent in adults over the age of 60. Patients are normally treated with chemotherapy, but even for the least severe forms of AML, the disease returns after chemotherapy in around one-third of cases. Of patients with the most severe forms of AML, fewer than one in six will survive for five years after diagnosis.

The research team determined that treatments that remove the protein Mcl-1 from AML cells can rapidly kill these aggressive cancer cells. Mcl-1 is a so-called 'pro-survival' protein, because it can make cells long-lived. Mcl-1 is part of the 'Bcl-2 family' of pro-survival proteins, many of which are known to be important controllers of cancer development and can render cancer cells resistant to anti-cancer treatments.

The gene for Mcl-1 was first discovered in AML cells, but until now it had not been realised that the Mcl-1 protein was critical for AML cells to live, Dr Glaser said. "Other research has already shown that high levels of Mcl-1 are associated with resistance to chemotherapy," said Dr Glaser. "What we have shown is that without Mcl-1, AML cells rapidly die. This is exciting because it identifies Mcl-1 as a potential target for new anti-cancer medications."

Because of the important role pro-survival Bcl-2 family proteins, including Mcl-1, play in cancer development and in the response of cancer cells to treatment, new classes of medications are being developed to block these proteins, making cancer cells die. One class of these medications, called BH3 mimetics, which inhibit certain pro-survival Bcl-2 family proteins, are currently in clinical trials for the treatment of some forms of leukaemia.

Dr Glaser is hopeful that in the future, new treatments for AML will be developed that work by specifically blocking Mcl-1. "We found that many types of AML cells were very dependent on Mcl-1 to survive", he said. "When Mcl-1 was depleted from the AML cells, they rapidly died. Importantly, non-cancerous blood cells were much less susceptible to dying when Mcl-1 was depleted. This means that, if Mcl-1 inhibitors are developed, there

may be a 'treatment window' in which AML cells are killed, while normal blood cells that are essential for health can be spared, helping patients recover from the treatment much better. We are optimistic that in the future, Mcl-1 inhibitors may improve the outlook for AML patients, who currently have a very poor prognosis."

Provided by Walter and Eliza Hall Institute