Cancer drug target also essential for blood cell recovery

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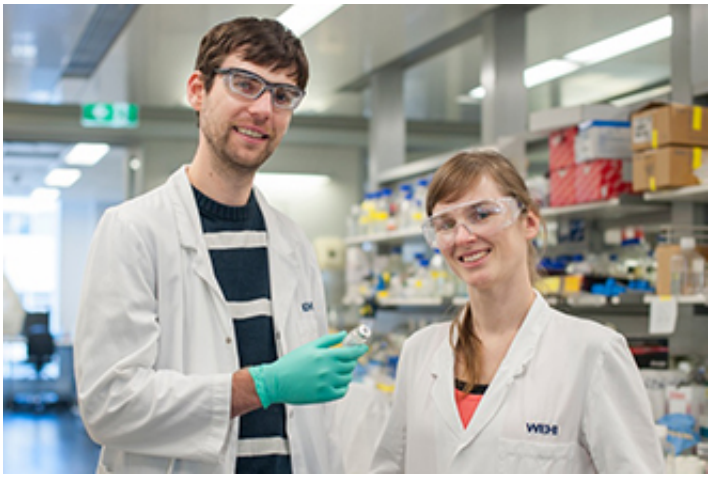

Dr. Alex Delbridge (left), Dr. Stephanie Grabow, and colleagues found a survival protein being targeted in new anti-cancer drugs is critical for emergency blood cell production. Credit: Walter and Eliza Hall Institute

Blocking key 'survival' proteins is a promising tactic for treating cancer, however new research suggests care should be taken as these proteins are also vital for emergency blood cell production.

Dr Alex Delbridge, Dr Stephanie Grabow and Professor Andreas Strasser from the Walter and Eliza Hall Institute discovered that blood cell production following massive blood cell depletion was fatally compromised when the cell survival protein MCL-1 was depleted.

The research team found that reducing MCL-1 levels hindered recovery of the blood cell system after extensive destruction of mature blood cells, which is a common side-effect of chemotherapy and radiotherapy. Reducing MCL-1 also impaired reconstitution of the bone marrow after blood stem cell transplants, a vital curative treatment for some cancers.

Dr Delbridge said MCL-1 was critical for the survival of many cancer cells, including a number of leukaemias and lymphomas, but also played an important role in normal blood cell production. "Our previous research has shown that targeting MCL-1 could be used with great success for treating certain blood cancers," he said. "However we have now shown that MCL-1 is also critical for emergency recovery of the blood cell system after cancer therapy-induced blood cell loss."

Overproduction of cell survival proteins, such as MCL-1, allows emerging cancer cells to escape from death-inducing signals, enabling the accumulation of further genetic mutations that promote cancer development. Drugs that reduce the activity of 'pro-survival' proteins can kill cancer cells and are a promising therapeutic strategy that is currently being explored.

The research team used a genetic trick to mimic the effect of reducing MCL-1 activity to examine the impact it had on the blood cell system after conventional cancer treatments such as chemotherapy, Dr Delbridge said. "Removing one copy of the gene encoding MCL-1 reduced its concentration, replicating the effects of a partial inhibition by a drug," he said. "We found that reducing MCL-1 protein levels severely impaired recovery of the blood cell system following chemotherapy. This exquisite dependency on MCL-1 for emergency blood cell production has important implications for potential cancer treatments involving MCL-1 inhibitors."

Dr Grabow said many current treatments for blood cancers involved

patients being treated with chemotherapy or radiotherapy, sometimes followed by stem cell transplantation to repopulate the bone marrow.

"What we have shown is that, if MCL-1 activity is compromised, a patient would face a significant hurdle in producing new blood cells," she said. "If MCL-1 inhibitors are to be used in combination with other cancer therapies, careful monitoring of the blood cell system will be needed. "The research findings would aid the design of future clinical studies trialling MCL-1 inhibitors, Dr Grabow said. "Our institute colleagues are working to evaluate a potential new drug to treat blood cancers by targeting MCL-1," she said. "Our findings suggest that MCL-1 inhibitors and chemotherapeutic drugs should not be used simultaneously."

Dr Delbridge said the discovery also offered insights for improving stem cell transplantation. "Stem cell transplants can be dangerous because, until the blood cell system is functionally restored, patients are vulnerable to infection," he said. "Our research suggests that increasing levels of MCL-1 or decreasing the activity of opposing proteins could be a viable strategy for speeding up the regeneration process and reducing the risk of infection after stem cell transplantation."

The research was published today in the journal *Blood*. The study was funded by Cancer Council Victoria, the Lady Tata Memorial Trust (UK), the Leukemia and Lymphoma Society (US), Cancer Therapeutics CRC, National Health and Medical Research Council, The Redstone Foundation and the Victorian Government.

Provided by Walter and Eliza Hall Institute