'Survival' protein a target in drug-resistant non-Hodgkin lymphomas

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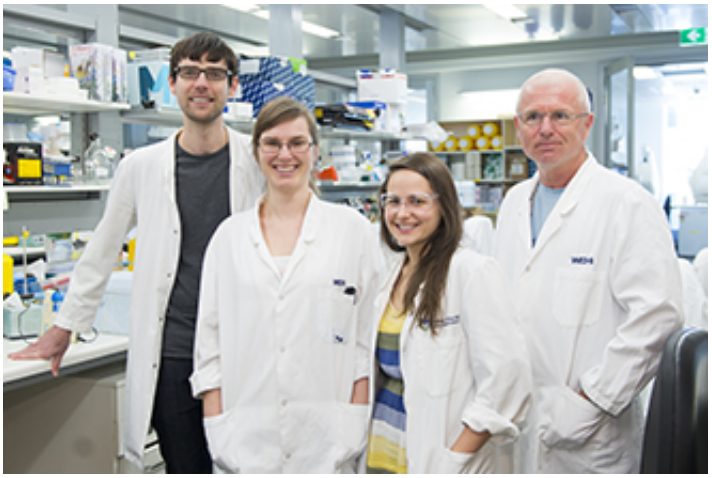

Dr Alex Delbridge, Dr Stephanie Grabow, Dr Liz Valente and Professor Andreas Strasser (L-R) found MCL-1 is an essential survival protein in T-cell lymphomas. Credit: Walter and Eliza Hall Institute

Melbourne researchers have discovered that targeting a cell 'survival' protein could help treat some lymphomas, including those cancers with genetic defects that make them resistant to many existing therapies.

Dr Stephanie Grabow, Dr Alex Delbridge, Dr Liz Valente and Professor Andreas Strasser from the Walter and Eliza Hall Institute found that removing the pro-survival protein MCL-1 caused the death and elimination of lymphoma cells that had become resistant to conventional cancer treatments.

T-cell and B-cell lymphomas are types of white blood cell cancers known as non-Hodgkin lymphomas. Non-Hodgkin lymphomas are the most common blood cancers in Australia, with about 3500 people diagnosed each year. T-cell lymphomas account for approximately 20 per cent of non-Hodgkin lymphomas.

MCL-1 is a key regulator of programmed cell death (apoptosis), a process that - when disrupted - can cause cancer to develop and can also enable malignant cancer cells to survive abnormally well when exposed to anti-cancer treatments.

Half of all cancers become resistant to chemotherapy and radiotherapy by acquiring mutations in the tumour-suppressing p53 protein. Dr Grabow said the research team discovered that MCL-1 'helped' these cancer cells to survive by subverting the normal process of apoptosis.

"There are several pro-survival proteins that promote the sustained survival of cancer cells; the challenge is to identify which one is the most important in keeping each type of cancer cell alive," Dr Grabow said.

"When we removed MCL-1 in models of T-cell lymphoma that had 'lost' the tumour suppressing protein p53, cancers could not develop, demonstrating that MCL-1 is critical for the development of T-cell lymphomas. Previous work from our colleagues at the institute has shown that MCL-1 is also critical for the survival and therapy-resistance of other blood cancers, including B-cell lymphoma and acute myeloid leukaemia, indicating that is a very important target for potential new anti-cancer treatments."

Professor Strasser said the finding reinforced the need to develop drug-like compounds that specifically targeted MCL-1. "When cancers acquire mutations in p53, they become resistant to many conventional therapies," he said. "Investigating the role of MCL-1 and other proteins

involved in controlling apoptosis has shown that MCL-1 is a critical protein in the survival of many types of cancer cells. Targeting MCL-1 could therefore allow us to develop new, urgently needed therapies to treat cancers that have stopped responding to other anti-cancer drugs."

Dr Grabow said the research team would continue to investigate the role of MCL-1 in the development and progression of other cancers, including other blood cell cancers and brain cancers. "Finding new treatment targets is crucial if we are to reduce the impact of these diseases," she said.

More information: 'MCL-1 but not BCL-XL is critical for the development and sustained expansion of thymic lymphoma in p53-deficient mice': www.bloodjournal.org/content/e … blood-2014-09-601567

Provided by Walter and Eliza Hall Institute