Cell survival protein discovery rewrites immune system story

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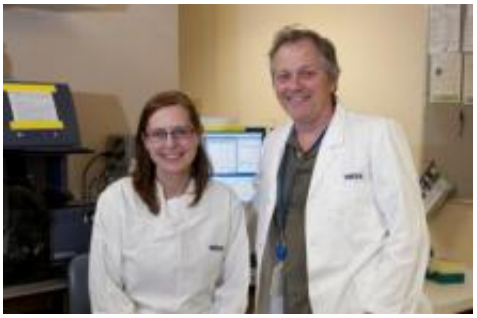

This is Dr. Ingela Vikstrom and associate professor David Tarlinton, from the institute's immunology division. Credit: The Walter and Eliza Hall Institute

A discovery by Walter and Eliza Hall Institute researchers in Melbourne, Australia, reported in today's edition of *Science*, is set to rewrite a long-held belief about how the body's immune system establishes its memory.

The findings of Dr Ingela Vikstrom and Associate Professor David Tarlinton, from the institute's Immunology division, centre on immune cells called B cells that produce the antibodies which fight infection.

"B cells and antibody production are the key to the success of all currently used vaccines for immunity in humans," said Associate Professor Tarlinton. "It is therefore critical that we continue to develop our knowledge of the molecular interactions that lead to immune function, which are still only vaguely understood."

Memory B cells are essential for the long-lived immunity that arises after immunisation. To develop into memory cells, B cells have to survive the natural process of apoptosis, or programmed cell death, that occurs following a large immune response.

Associate Professor Tarlinton and Dr Vikstrom study the so-called pro-survival proteins that regulate B cell survival and are therefore responsible for instructing these cells whether to live or die.

Dr Vikstrom said that B cell memory arises in temporary cellular structures called germinal centres that develop in response to activation of the immune system.

"We used genetic and pharmacological methods to identify which pro-survival molecules were essential for the process of 'instructing' these cells to establish germinal centres, as well as instructing activated B cells to proliferate and differentiate into memory B cells," Dr Vikstrom said.

"We studied two well-known pro-survival proteins called Bcl-xL and Mcl-1, which we knew were involved in the process. It surprised us to find that, contrary to popular belief, Mcl-1 is the essential pro-survival protein required for creation and maintenance of B cell memory."

The finding contradicts the widely accepted theory in immunology circles that Bcl-xL is the major pro-survival protein responsible for sustaining the development of memory B cells.

The findings build on a paper Associate Professor Tarlinton and Dr Vikstrom published earlier this year in Proceedings of the National Academy of the Sciences, with institute researchers Dr Andrew Lew and Dr Emma Carrington. Using a molecule that blocked the action of Bcl-xL, the study revealed that Bcl-xL was not necessary for the development of germinal centres and memory B cells, indicating that

another pro-survival protein – now shown to be Mcl-1 – was the key to survival.

Mcl-1 is known to be an important survival protein for cancers. Associate Professor Tarlinton said the discovery could have repercussions for cancer treatment, as cancerous cells often arise from unregulated cell growth caused by defects in the apoptotic pathway. It could also have implications for the treatment of autoimmune disease and inhibiting transplant rejection.

"All cells have the potential to undergo apoptosis, so developing our understanding of the major proteins responsible for this process will have applications to all cell types in the body," he said.

Provided by Walter and Eliza Hall Institute