Immune cell death defects linked to autoimmune diseases

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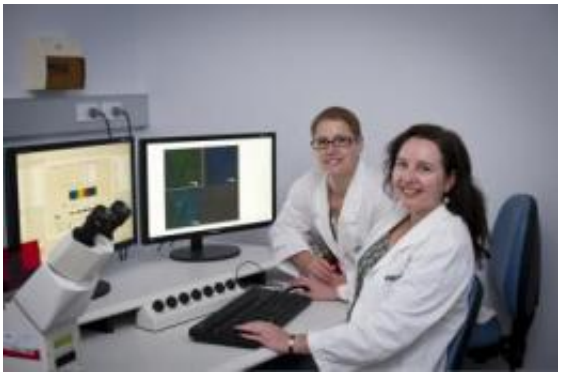

Dr. Kylie Mason (left), Dr. Lorraine O'Reilly and colleagues have discovered how a protein defect in immune cells can trigger autoimmune disease. Credit: The Walter and Eliza Hall Institute, Australia

Melbourne researchers have discovered that the death of immune system cells is an important safeguard against the development of diseases such as type 1 diabetes, rheumatoid arthritis and lupus, which occur when the immune system attacks the body's own tissues.

The finding suggests that these so-called autoimmune diseases could be treated with existing medications that force long-lived immune system cells to die.

In the development of the immune system, some cells are produced that have the potential to attack the body's own tissues, causing autoimmune

disease. The death of these 'self-reactive' immune cells through a process called apoptosis is an important safeguard against autoimmune disease.

But Dr Kylie Mason, Dr Lorraine O'Reilly, Dr Daniel Gray, Professor Andreas Strasser and Professor David Huang from the Walter and Eliza Hall Institute, and Professor Paul Waring from the University of Melbourne have discovered that when immune cells lack two related proteins, called Bax and Bak, the cells can attack many healthy tissues, causing severe autoimmune disease. The research is published online today in the journal Proceedings of the National Academy of Sciences.

Bax and Bak are members of the 'Bcl-2 protein family', a large group of proteins that control cell death. Dr O'Reilly said it was thought that Bax and Bak acted like an irreversible switch in cells, determining when cells die by apoptosis. In healthy cells, Bax and Bak are in an 'inactive' form, but when cells are under stress or receive external signals instructing them to die, Bax and Bak switch into an 'active' form that starts the destruction of the cell by apoptosis. Without Bax and Bak, cells are highly protected against apoptosis.

Dr O'Reilly said that some immune cells that lacked the proteins Bax and Bak were able to attack healthy tissues in many organs of the body. "Normally, these 'self-reactive' immune cells are deleted during development," she said. "In the absence of Bax and Bak, enough self-reactive cells survive development to persist in the body and cause autoimmune disease in organs such as the kidneys (glomerulonephritis), similar to what is seen in the most severe form of lupus.

"Our findings confirm that defective apoptosis of immune cells can cause autoimmune disease, and that Bax and Bak are important determinants of immune cell death. We were also interested to see that, in our model, loss of Bak on its own was sufficient to cause autoimmune disease, albeit to a lesser extent than losing both Bak and Bax. This

supports a recent discovery that humans with mutations in the BAK gene are predisposed to certain autoimmune diseases."

The research provides hope for people with autoimmune diseases as Bax and Bak activity can be triggered by a new class of potential anti-cancer agents, called BH3-mimetics, which are currently in clinical trials for certain types of leukaemia in Melbourne, Dr O'Reilly said. "Our findings suggest that BH3-mimetics might be an exciting new option for treatment for autoimmune conditions, by activating Bax and Bak and making the self-reactive immune cells which are causing the autoimmune disease to die," she said.

Provided by Walter and Eliza Hall Institute