Scientists discover kill-switch controls immune-suppressing cells

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Scientists have uncovered the mechanism that controls whether cells that are able to suppress immune responses live or die. Dr Daniel Gray (right) and Ms Antonia Policheni from Melbourne's Walter and Eliza Hall Institute of Medical Research were part of a research team that made the discovery, which could one day lead to better treatments for immune disorders. Credit: Walter and Eliza Hall Institute of Medical Research.

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The discovery of the cell death processes that determine the number of 'regulatory T cells' an individual has could one day lead to better treatments for immune disorders.

Regulatory T cells are members of a group of immune cells called T cells. Most T cells actively respond to clear the body of infections. By contrast, regulatory T cells are considered to be immune suppressing cells because they can 'switch off' an immune response to a particular molecule. This immune suppression is important for preventing inappropriate immune attack of the body's own tissues, which is the underlying cause of autoimmune diseases such as lupus and type 1 diabetes.

A shortage of regulatory T cells is linked with the development of autoimmune and inflammatory conditions, while some people with higher than normal numbers of regulatory T cells cannot fight infections properly.

Dr Daniel Gray and Ms Antonia Policheni from the Walter and Eliza Hall Institute's Molecular Genetics of Cancer and Immunology divisions made the discovery about how regulatory T cell numbers are controlled as part of an international team of researchers jointly led by Dr Gray and Dr Adrian Liston who is head of the Flanders Institute for Biotechnology (VIB) Laboratory for Autoimmune Genetics at the University of Leuven, Belgium. They found that regulatory T cells are constantly being produced in the body, but their numbers are held steady by a process of cell death. The findings are published today in the journal *Nature Immunology*.

Cell death, or apoptosis, is important in many immune cell types for the removal of excess, defective or damaged cells. The decision of these cells on whether to live or die is controlled by a family of proteins called the 'Bcl-2 protein family'. This includes proteins that can either promote cell

survival or trigger cell death, in response to many different stimuli.

Dr Gray said the team had discovered that Bcl-2 family proteins were important determinants of regulatory T cell numbers. "Regulatory T cell death is highly dependent on the activity of two opposing Bcl-2 family proteins, called Mcl-1 and Bim," he said. "Mcl-1 is required for regulatory T cell survival, allowing them to suppress unhealthy immune responses, while Bim triggers the death of regulatory T cells. Without Mcl-1 activity, regulatory T cell numbers fall, provoking lethal autoimmune disease. Conversely, if Bim activity is lost, regulatory T cells accumulate in abnormally high numbers."

Dr Liston said the finding was exciting, because it opened up new ways to control regulatory T cell numbers in disease. "Already, there is considerable interest in a new class of agents, called 'BH-3 mimetics' that target Bcl-2-like molecules including Mcl-1," he said. "If agents that can influence regulatory T cell survival can be developed, we could see new ways to suppress autoimmune disease, by boosting regulatory T cell numbers, or to enhance beneficial immune responses, by silencing regulatory T cells."

More information: Antiapoptotic Mcl-1 is critical for the survival and niche-filling capacity of Foxp3+ regulatory T cells, DOI: 10.1038/ni.2649