Research puts a 'Fas' to the cause of programmed cell death

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Professor Andreas Strasser's team at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, has put an end to a 10-year debate over which form of a molecular messenger called Fas ligand is responsible for killing cells during programmed cell death. Credit: Cameron Wells, Walter and Eliza Hall Institute

Walter and Eliza Hall Institute researchers have put an end to a 10-year debate over which form of a molecular messenger called Fas ligand is responsible for killing cells during programmed cell death (also called apoptosis).

Apoptosis is an important process in human biology as it removes unwanted and dangerous cells from our bodies, protecting us against cancer development and diseases where the immune system attacks the body's own tissues, such as in lupus or insulin-dependent diabetes.

This cell death process can be activated by proteins on the surface of cells. The most prominent of these cell surface proteins is Fas ligand, which exists in two forms - membrane-bound or secreted - and binds to a surface receptor called Fas. Professor Andreas Strasser, co-head of the institute's Molecular Genetics of Cancer division (with Professor Jerry Adams), has been looking to settle a decade-long scientific debate by investigating whether membrane-bound Fas ligand, secreted Fas ligand, or both, cause cell death.

"There has been a lot of debate among the scientific community over which of the forms causes cell death but also which of the forms may induce an inflammatory response," Professor Strasser said. "What we have shown is that it is the membrane-bound Fas ligand that is essential for cell death and is therefore the body's guardian against lymphadenopathy (the swelling of lymph nodes), autoimmunity and cancer."

Professor Strasser's research, done in collaboration with Dr Lorraine O'Reilly and Ms Lin Tai from the Molecular Genetics of Cancer division and Dr Lorraine Robb from the Cancer and Haematology division, has been published in today's issue of the international journal *Nature*.

The research also demonstrated that although secreted Fas ligand does not have a role in cell killing, too much secreted Fas can promote tumour development and autoimmunity.

"In certain autoimmune conditions and types of lymphoma/leukaemia there is massive over-production of secreted Fas ligand. Since our research shows that secreted Fas is pro-inflammatory, and therefore detrimental, and since the aforementioned disease states are characterised by inflammatory tissue destruction, it may be possible to alleviate some of the manifestations of these diseases by neutralising the secreted Fas ligand with antibodies or soluble receptors," Professor

Strasser said.

Now the roles of membrane-bound and secreted Fas ligand have been clearly defined, Professor Strasser's team is investigating the molecular pathways that are activated by a surplus of secreted Fas ligand and their role in autoimmune conditions and lymphomas/leukaemias.

Source: Walter and Eliza Hall Institute