Critical link in cell death pathway revealed

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The role of a protein called XIAP in the regulation of cell death has been identified by a team led by Professor Andreas Strasser from the Walter and Eliza Hall Institute. The finding has led the researchers to recommend caution when drugs called IAP inhibitors are used to treat cancer patients with underlying liver conditions. Credit: Walter and Eliza Hall Institute

The role of a protein called XIAP in the regulation of cell death has been identified by Walter and Eliza Hall Institute researchers and has led them to recommend caution when drugs called IAP inhibitors are used to treat cancer patients with underlying liver conditions.

A team led by Professor Andreas Strasser from the institute's Molecular Genetics of Cancer division has found that XIAP (X-chromosome-linked inhibitor of apoptosis protein) is the critical factor that determines which of two pathways will be followed to culminate in a cell's death.

Programmed cell death (also called apoptosis) 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 insulin-dependent diabetes.

This cell death process is activated by proteins on the surface of cells. The most prominent of these cell surface proteins is FAS, but curiously it does not always activate apoptosis the same way, Professor Strasser said. "One of the things that's very curious about FAS is that, depending on the cell type, the way the killing of the cell happens is substantially different," he said.

"In so-called type I cells, such as lymphocytes (white blood cells involved in the immune response), the killing is very direct. When FAS is activated a protein-destroying enzyme called caspase-8 is recruited and activated, leading to activation of other enzymes (effector caspases) and rapid cell demolition," Professor Strasser said.

"But in so-called type II cells, which include hepatocytes (liver cells) and pancreatic β-cells (the cells that produce insulin), that direct pathway is not sufficient to kill the cells; amplification of the apoptosis signalling pathway is required."

Professor Strasser, with Drs Philipp Jost and Thomas Kaufmann (a former post-doctoral researcher from the institute who is now running his own lab in Bern, Switzerland) as well as with colleagues from St Vincent's Institute of Medical Research, LaTrobe University and the Institute of Molecular Medicine and Cell Research in Germany, has found that the protein XIAP is the discriminating factor between type I and type II FAS-induced cell death signaling.

The research has been published today in the international journal *Nature*.

For death to occur in type II cells, caspase-8 must activate the death-promoting protein called BID. Without this activation of BID the cells don't die.

But the experiments of Professor Strasser's team revealed that when the gene that produces XIAP is turned off or if the XIAP protein is pharmacologically blocked, hepatocytes or pancreatic β-cells (both type II cells) will die in a type I manner; that is: independent of the presence of BID.

Professor Strasser said that the finding had implications for cancer patients with underlying liver conditions who were being treated with IAP inhibitors. These inhibitors would block the production of XIAP, thereby interfering with the normal cell death pathway for liver cells and increasing the likelihood of healthy liver cells being killed, he said.

The research would also be of interest to gastroenterologists as in several chronic liver diseases activation of FAS is thought to contribute to cell destruction, he said.

Source: Walter and Eliza Hall Institute