More than just a backup system: PI3K-Delta in tumour surveillance

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If something is really important, it's best not to rely on it. This basic principle is followed equally by human engineers – for example, the NASA space shuttle has three main engines – and by nature. Thus it could be expected that each of the four subtly different forms of class I phosphoinositide 3-kinase (PI3K) works in much the same manner.

Class I PI3Ks add a phosphate group to phosphatidylinositol biphosphate, a phospholipid normally located on the inside of cell membranes, and thereby activate a number of important cellular processes. All four forms of the enzyme are expressed in T cells, suggesting that these cells have an 'insurance' system in place to protect them against the inadvertent loss of one or more form. Surprisingly, though, this is not the case and recent work by Eva Maria Putz, Michaela Prchal-Murphy and colleagues at the University of Veterinary Medicine, Vienna, has revealed that the body's defence against tumour cells absolutely requires the activity of one particular form. Their results were published recently in the prestigious online journal PLoS ONE and the authors comment on them in the current issue of the journal *Oncoimmunology*.

It has long been known that the four different forms of class I phosphoinositide 3-kinase (PI3K) in mammals are expressed in different tissues, with two forms – PI3K-Gamma and PI3K-Delta – essentially confined to blood cells. There had been indications that PI3K-Delta is important in controlling the secretion of cytokines from so-called helper T cells but its role in the functions of cytotoxic T cells had not previously

been investigated. Cytotoxic T cells are cells of the immune system that respond to cancerous or virally infected cells, ultimately killing them and thus limiting the spread of the disease. The issue is not purely academic: a specific inhibitor of PI3K-Delta is being tested in clinical trials for use in the treatment of haematological malignancies, cancers that affect the blood, bone marrow and lymph nodes. It is important to investigate its effects on the human immune system to understand any potential long-term consequences of its use, thereby enabling detrimental side effects to be avoided or addressed.

In a longstanding collaboration with colleagues at the Medical University of Vienna – the scientists at the Vetmeduni acknowledge particularly the contribution of Eva Zebedin-Brandl – and with partners in Germany and Japan, Putz and Prchal-Murphy tested the ability of cytotoxic T cells from normal mice and from mice lacking PI3K-Delta to multiply when stimulated by the presence of a foreign protein. The cells lacking PI3K-Delta failed to respond, showing that although the enzyme form is not required for the normal proliferation of cytotoxic T cells, it is needed to enable the cells to proliferate in response to an attack. The scientists were able to show further that in the absence of PI3K-Delta cytotoxic T cells had far lower levels of the enzymes they normally rely on to kill diseased cells and were unable to release these enzymes when they should. They also produced lower levels of interferon-γ, a cytokine that is important in the defence against viruses.

By means of an elegant series of experiments, Putz and Prchal-Murphy were able to replicate their findings in mice, confirming that the lack of PI3K-Delta made the cytotoxic T cells far less effective at killing tumour cells. The result is that animals lacking PI3K-Delta develop larger tumours than mice in which this enzyme form is present. In other words, tumour surveillance absolutely requires the activity of PI3K-Delta.

The strict requirement for PI3K-Delta – as opposed to the other three

forms of the enzyme – in the immune response to cancer was highly surprising and has important consequences for the treatment of haematological cancers, such as leukaemia, in humans. As both Putz and Prchal-Murphy say, "We know that inhibiting PI3K-Delta should slow the growth of the leukaemic cells but it will also stop normal cancer surveillance by cytotoxic T cells from working properly. This might be disadvantageous for cancer patients. On the other hand, it would be a huge help to people suffering from autoimmune diseases or to patients who have received transplants."

The paper "PI3Kd Is Essential for Tumor Clearance Mediated by Cytotoxic T Lymphocytes" was published by the open access journal *PLoS ONE.*

The comment "Targeting PI3Kδ - One man's meat is another man's poison" appears in the current issue of *Oncoimmunology* (Vol. 2(1) 2013, pp. 1-2).

More information: www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0040852
www.landesbioscience.com/journ … ls/53/article/22272/

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