A two-pronged attack: Why loss of STAT1 is bad news

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Breast cancer represents about a fifth of all cancers diagnosed in women. The reasons for the rapid progression of the disease remain relatively poorly understood but recent work in the group of Veronika Sexl at the University of Veterinary Medicine, Vienna has pointed the finger strongly at loss or inactivation of the transcription factor STAT1. The results are published in the current issue of the journal *Oncotarget*.

The so-called signal transducers and activators of transcription (STATs) are involved in the regulation of cell division but details of their functions remain a matter of conjecture. In the development of breast cancer, the role of STAT1 is particularly interesting as high levels of STAT1 activity are known to be correlated with a better prognosis for breast cancer patients. There is a considerable body of evidence that STAT1 can act to suppress tumour growth in breast cancer but how does it function? Important clues are provided by the latest results of Christine Schneckenleithner and colleagues in the group of Veronika Sexl at the Vetmeduni Vienna.

By means of a series of sophisticated transplantation experiments in a mouse model, Schneckenleithner was able to show that in the absence of the STAT1 protein the mouse develops breast cancer more frequently, partly because the animal's immune system loses the ability to control developing tumours. Under normal circumstances, i.e. in the presence of STAT1, a type of white blood cells known as cytotoxic T lymphocytes or CTL recognizes and kills developing tumours as part of the body's normal tumour surveillance mechanism. In the absence of STAT1,

however, the CTL can no longer perform this essential function, allowing cancer cells to grow unchecked (the other mechanism for killing tumour cells, involving "natural killer" cells, was found to play at best a very minor part in destroying breast cancer cells, at least in this model system).

The loss of susceptibility to CTL enables tumour cells to grow unimpeded. But Schneckenleithner's work also uncovered a further way in which STAT1 helps keep breast cancer in check. When the protein is removed from breast cells, there is an increased formation of small cancerous growths within the epithelia, known as mammary intraepithelial neoplasias or MINs. MINs arise as a result of accelerated cell division within the epithelial cells and are believed to represent a stepping-stone on the way to full-blown cancer. In other words, removing STAT1 is somehow interfering with a mechanism – presumably involving the transcription factor IRF1, which is known to be under the direct control of STAT1 – for preventing unwanted cell division.

The loss of STAT1 thus causes the development of breast cancer via two mechanisms. Schneckenleithner summarizes the problem very neatly: "not only does deleting STAT1 cause the mice to develop more mini-cancers, it also prevents the main mechanism by which these are destroyed, leading to much faster tumour development." This double effect explains why the prognosis for breast cancer patients with low activities of STAT1 is so poor and also points the way towards a possible treatment for this most widespread of cancers.

More information: The scientific article in full text online: www.impactjournals.com/oncotar … ath[]=371&path[]=625

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