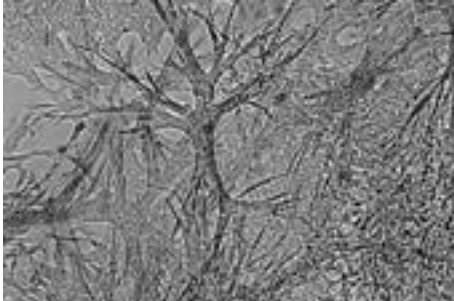


Liver Tumours – Good & Evil is Decided by Two Signalling Pathways

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The linking of two signalling pathways in the cells of liver tumours has a clear influence on their malignancy. Activation of the platelet-derived growth factor (PDGF) messenger molecule is decisive for this linking. This results related to the development of liver cancer was generated during a current project by the Austrian Science Fund FWF and has been published in the Journal Oncogene. When the signalling pathways in liver tumour cells have been linked together, these cells develop the characteristics of cancer stem cells, which are in principal resistant to chemotherapy. This new understanding of the signalling pathways involved unlocks potential for the future development of modified therapies.

The transformation of epithelial cells into mesenchymal cells can be either good or bad. It is good for embryonic development, inflammations and tissue regeneration. It is bad when this transformation, known as epithelial to mesenchymal transition (EMT), occurs in cancer cells, as the cancerous cells are then able to migrate into other tissues and form metastases.

SUPPRESSOR OR AGGRESSOR?

It was already understood that a signalling pathway of TGF-beta (transforming growth factor beta) was involved in EMT. However, as this messenger substance tends to hinder cell proliferation and also makes cells sensitive to the body's own defences, it was previously regarded as a tumour suppressor. But recent findings have shown that, when it occurs in cells that are already transformed, TGF-beta actually contributes to their aggressiveness. Until recently, it was not known how this happens.

A team headed by Prof. Wolfgang Mikulits from the Institute of Cancer Research at the Medical University of Vienna has now moved a great deal closer to better understanding these processes. The team discovered that, by activating the platelet-derived growth factor (PDGF), the signalling pathway of TGF-beta causes the accumulation of another messenger substance that had not previously been associated with the signalling pathway of TGF-beta: beta-catenin.

Prof. Mikulits explains: "PDGF forms a kind of bridge that links together two signalling pathways that were previously regarded as entirely independent. This discovery in itself was exciting. However, when we investigated the effect of beta-catenin further, we were astounded."

SLOW & RESISTANT

Beta-catenin was previously associated with an increased rate of cell division, or in other words, accelerated tumour growth. However, Prof. Mikulits' team observed entirely different cell behaviour in reaction to beta-catenin in cell cultures. "We found that beta-catenin actually slowed down the rate of cell division, which – in a tumour – is not a bad thing. However, it makes the cells unsuitable targets for chemotherapy. Cells containing beta-catenin also exhibited another characteristic. They were less susceptible to the natural defences in the body which eliminate cells that migrate from organs." In tumour cells, both these features – a lower division rate and resistance to defence mechanisms – are known to be typical properties of cancer stem cells. In other words, cells that migrate through the bloodstream and can create new tumours elsewhere in the body – metastases.

The linking of the signalling pathways of TGF-beta and beta-catenin by PGDF increases the aggressiveness of liver tumours and therefore offers a new point of attack for future liver cancer treatments. However, the results of this FWF project are already revealing ways in which the current treatment of liver cancer can be optimised. The accumulation of beta-catenin in cancer cells can be diagnosed before treatment is begun, which means that therapy could then be tailored to the aggressiveness of the tumour.

Image and text will be available online from Monday, 30th July 2007, 09.00 a.m. CET onwards:

www.fwf.ac.at/en/public_relations/press/pv200707-3en.html

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Alexandra N. Fischer, Eva Fuchs, Mario Mikula, Heidemarie Huber, Hartmut Beug and Wolfgang Mikulits. 2007. PDGF essentially links TGF-beta signaling to nuclear beta-catenin accumulation in hepatocellular carcinoma progression. *Oncogene* 26:3395.

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