Mechanism for more efficient cancer treatment decoded

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(Medical Xpress) -- A research team from the Institute for Cancer Research at the MedUni Vienna has decoded a previously unknown mechanism of the active ingredient imiquimod in tumour defence. They have been able to prove that imiquimod transforms plasmacytoid dendritic cells (pDCs) into "tumour-killers" which can fight the tumour independently from other immune cells. This discovery could be an important step on the way to a more efficient treatment for cancer.

The scientist, Barbara Drobits, one of the doctorate students of the "Inflammation and Immunity" doctorate lecture course promoted by the FWF (Austrian Science Fund) and the MedUni Vienna, and her colleagues, have researched, under the leadership of Maria Sibilia, Head of the Institute, which mechanisms are set into operation when skin cancer is treated with imiquimod. In doing so mast cells in the skin are stimulated which produce the signal protein CCL2. This causes immune cells, in particular plasmacytoid dendritic cells (pDCs) to be recruited to the skin being treated. Imiquimod activates these pDCs through a specific receptor of the congenital immune system, the so-called toll-like receptor (TLR) 7, whereupon the pDCs produce and discharge interferon alpha (IFNa). IFNa also affects the pDCs themselves and stimulates them to emit cytolytic molecules which "shoot holes" into the tumour's wall, perforating it and thereby attacking the tumour cells.

"With imiquimod we can therefore make the pDCs enter the tumour on the one hand and attack the tumour cells on the other. The medication therefore acts as an activating signal for the congenital immune system", explains Drobits.

Only little had previously been known about the working mechanism of imiquimod and the positive effect of the pDCs in tumour defence. Says Sibilia: "We have shown for the first time that the pDCs are good and helpful and attack the tumour cells, without requiring the adaptive immune system (note: B and T cells) for this." The MedUni Vienna researchers have furthermore been able to prove in process of elimination and in vivo that the mechanism does not function even if only one of the factors is missing, meaning, if for example no TLR7 or no interferon alpha is involved.

In this model with imiquimod, however, it is not possible to eliminate the tumour entirely. "However, if we administer the active ingredient in addition to conventional cancer treatment, that could increase the efficiency and thereby reduce the duration of treatment. Furthermore our discovery is an impetus for further studies at the MedUni Vienna", says Sibilia. „As it is still not known, whether the effect, which we have been able to prove in melanomas, also occurs in other tumours." A study which looks into this question has already been started at the Institute for Cancer Research.

Imiquimod is a medication from the antiviral group, which is used for the treatment of small, superficial basal cell skin cancer, melanomas or actinic keratosis (damage of the epidermis through many years of intensive exposure to UV radiation). Imiquimod is an immunomodulator which activates the skin's immune system, so that it fights viruses

or tumours. In Europe, the active ingredient is known as a medication under the "Aldara" trade name.

More information: "Imiquimod clears tumors in mice independent of adaptive immunity by converting pDCs into tumor-killing effector cells." Barbara Drobits, Martin Holcmann, Nicole Amberg, Melissa Swiecki, Roland Grundtner, Martina Hammer, Marco Colonna, Maria Sibilia.. *J Clin Invest.* doi:10.1172/JCI61034

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