Medical Xpress

Stop signal for leukemia stem cells

August 23 2011

There are numerous specialized growth factors that are responsible for cells of different tissues of our body to divide and differentiate when needed. These hormone-like factors bind to matching receptors on the surface of their target cells and thus give order for the cell to divide. However, a single genetic alteration can be sufficient for the whole system to get out of control. If, for example, the gene for such a growth factor or for the matching receptor is hyperactive, then the cell permanently receives signals to divide – and this can result in cancer.

Such defective growth signals play a role in many cancers. Thus, breast cancer cells in about 20 percent of affected women form too many receptors for the Her2/neu growth factor; in bowel cancer doctors frequently find an overproduction of the EGF growth factor.

Jointly with colleagues from France, Canada and the U.S., scientists headed by Professor Dr. Andreas Trumpp of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now discovered that in T-cell acute lymphoblastic leukemia (T-ALL), too, malignant growth is driven by a particular growth factor. In this case, it is the insulin-like growth factor 1 (IGF1) which plays the key role.

The investigators found out that there is an oversupply of IGF1 receptors in T-ALL. The leukemia cells therefore become particularly sensitive to IGF1 signals. When the researchers blocked the IGF1 receptors using specific inhibitors or turned off the gene coding for the receptor, the blood cancer cells ceased to grow. This worked both in murine cancer cells and in human leukemia cells.

However, blockage of the IGF1 signal not only stopped cancer cell growth. Moreover, the dangerous cancer stem cells lost their capability of self-renewal. This was shown by the investigators in a classic experiment called serial transplantation. They transplanted T-ALL cells that formed only small amounts of IGF1 receptors on their surface into mice. Although T-ALL cells normally always cause leukemia in recipient animals, only very few mice developed leukemia after injection of the modified T-ALL. For the team this was the most important clue that leukemia stem cells were either absent or no longer active, because they are the only ones that can initiate leukemia.

"We only need to reduce the level of IGF1 receptors slightly in order to deprive cancer stem cells of their self-renewal capacity. Apparently, leukemia stem cells are particularly dependent on strong IGF1 signals," explained Dr. Hind Medyouf, first author of the article.

Acute lymphoblastic leukemias are the most frequent malignancies in children; however, elderly adults may be affected, too. The group's results open up new prospects for treatment, because substances inhibiting the IGF1 receptor are already available and are currently being tested for other types of cancers such as breast cancer in clinical trials. Andreas Trumpp, a stem cell specialist, explains: „Elderly T-ALL patients have a particularly high recurrence rate after seemingly successful chemotherapy. Inhibition of the IGF1 signaling pathway would target the leukemia stem cells in particular and might therefore prevent recurrence of the cancer."

More information: Hind Medyouf, Samuel Gusscott, Hongfang Wang, Carol Wai, Oksana Nemirovsky, Andreas Trumpp, Francoise Pflumio, Joan Carboni, Marco Gottardis, Michael Pollak, Jon C. Aster, Martin Holzenberger and Andrew P. Weng: High level IGF1R expression is required for leukemia-initiating cell activity in T-ALL and is supported by Notch signalling. *Journal of Experimental Medicine*,

2011, DOI:10.1084/jem.20110121