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Stem Cells: Deadly Awakening by Interferon

Interferon-alpha, a messenger substance of the immune system, awakens dormant hematopoietic stem cells in the bone marrow to become active, thus making them vulnerable for the effect of many drugs. This finding was published in *Nature* by researchers from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) jointly with colleagues from Lausanne. The researchers suppose that this might also be a way to stimulate tumor stem cells to divide and, thus, sensitize them to anticancer drugs.

After injuries with blood loss, the body quickly needs to restore the vital blood volume. This is accomplished by a special group of stem cells in the bone marrow. These hematopoietic stem cells remain dormant throughout their lives and are only awakened to activity in case of injury and loss of blood. Then they immediately start dividing to make up for the loss of blood cells. This has recently been shown by a group of scientists headed by Professor Andreas Trumpp of DKFZ.

Dormancy is an important protection mechanism of stem cells. First, it protects their genetic material from genetic alterations, which happen primarily during cell division. In addition, dormancy helps them escape attacks of many cytotoxins, which act only on dividing cells.

Scientists were still puzzling over which signaling molecules actually wake up stem cells from their dormancy. Andreas Trumpp and Marieke Essers from his team have now reported in *Nature* that interferon-alpha, a messenger substance of the immune system, acts like an alarm clock for hematopoietic stem cells. The scientists have thus shown for the first time that interferon-alpha can have a direct influence on the function of stem cells.

Interferon-alpha is released by immune cells when the organism is threatened by bacteria or viruses. The scientists triggered interferon production in mice by administering a substance that simulates a viral infection to the animals. Subsequently, there was a great increase in the division rate of hematopoietic stem cells. In control animals that were unable to process the interferon signals, the substance did not lead to an awakening of the stem cells.

The investigators obtained further proof of the effect of interferon-alpha using a drug called 5-fluorouracil, a cytotoxic substance frequently used for treating breast or bowel cancer. Dormant stem cells are resistant to the drug, which unfolds its effect only during division. However, if animals are given interferon-alpha prior to treatment with 5-fluorouracil, they die of anemia after a short time. This is because prior treatment with interferon forces quiescent stem cells into cell division, which sensitizes them for the effect of 5-FU and kills them. Thus, there are soon no more stem cells to keep up the supply of short-lived mature blood cells such as erythrocytes and blood platelets.

What researchers find particularly exciting about this finding is the prospect that the newly found working mechanism might help improve cancer treatment: “Using interferon-alpha, we might be able to wake up from dormancy not only hematopoietic stem cells but also tumor stem cells and, thus, break their frequently observed resistance to many anticancer drugs,“ Andreas Trumpp speculates.

A clinical observation already suggests that this assumption is more than just wishful thinking: Patients suffering from a type of blood cancer called chronic myelogenous leukemia who are treated with a drug called Gleevec almost always relapse after drug treatment has

ended. Several patients were given interferon-alpha prior to the Gleevec treatment. Surprisingly, these patients experienced long relapse-free phases without any medication. “We believe that the leukemia stem cells were awakened by the interferon administration and, thus, were sensitized to elimination by Gleevec,” Andreas Trumpp explains.

Marieke A.G. Essers, Sandra Offner, William E. Blanco-Bose, Zoe Waibler, Ulrich Kalinke, Michel A. Duchosal and Andreas Trumpp: IFNα activates quiescent HSCs *in vivo.* Nature 2009, online published on 11 February 2009; DOI:10.1038/nature07815

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) is the largest biomedical research institute in Germany and is a member of the Helmholtz Association of National Research Centers. More than 2,000 staff members, including 850 scientists, are investigating the mechanisms of cancer and are working to identify cancer risk factors. They provide the foundations for developing novel approaches in the prevention, diagnosis, and treatment of cancer. In addition, the staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. The Center is funded by the German Federal Ministry of Education and Research (90%) and the State of Baden-Württemberg (10%).

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