

Systems Biology Helps to Understand Hematopoiesis

After blood loss, large amounts of the hormone Epo flood the hematopoietic system in the bone marrow. Scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg and the University of Freiburg have now published an article in *Science* uncovering how a rapid turnover of Epo receptor molecules on hematopoietic cells ensures that these remain ready to react. Thus, our body can respond even to extreme increases of Epo levels with an adequate supply of red blood cells.

Our body reacts to blood loss by stimulating the production of red blood cells (erythrocytes). The cells of the hematopoietic (blood-forming) system in the bone marrow do so upon receipt of a signal by a hormone called erythropoietin, or Epo for short. This hormone is produced mainly by the kidney that increases the Epo level by up to a thousand-fold as a response to falling oxygen saturation of the blood.

The hematopoietic cells receive the Epo signal through Epo receptors on their surface. How do the blood progenitor cells that carry only few receptor molecules manage to react adequately to a high rise in the Epo level and to always provide the required amount of red blood cells? "If too much of the hormone floods too few receptor molecules, we would expect the saturation point to be reached soon. This would mean that the hematopoietic cell can no longer respond to a further increase in the hormone level," says Dr. Ursula Klingmüller of DKFZ.

Researchers in her department, who participate in the Helmholtz Alliance for Systems Biology and the MedSys Network LungSys funded by the Federal Ministry of Education and Research (BMBF), collaborated with colleagues of a working group headed by Professor Jens Timmer at Freiburg University to find out how hematopoietic cells can react in a linear way if Epo levels increase by several orders of magnitude. To do so, the researchers combined experimental data with mathematical models in a systems biology approach.

The research team was able to show that after binding of Epo to its receptor both molecules are rapidly taken up into the interior of the hematopoietic cells where they are broken down. During the process, the cell surface is continuously equipped with newly synthesized receptor molecules that are supplied from intracellular storage places. "This turnover of receptor molecules is a very rapid process," Jens Timmer explains who is a member of the Freiburg Institute for Advances Studies (FRIAS) as well as the excellence cluster BIOS. "Thus, the cell keeps being able to recognize further hormone molecules in its environment and to react accordingly."

Genetically engineered Epo is an important medication for treating anemia, for example in dialysis patients who often suffer from low counts of red blood cells because these are destroyed during dialysis and, in addition, the failure of renal function leads to a lack of natural Epo. The results of the Heidelberg and Freiburg scientists may contribute to developing Epo variants with enhanced binding properties and thus increase the effectiveness of anemia treatment.

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%).

Dr. Stefanie Seltmann
Leiterin Presse- und Öffentlichkeitsarbeit
Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2854
F: +49 6221 42 2968
presse@dkfz.de