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Defective tumor suppressor leads to leukemia – by an indirect route

Cancer often arises as a result of defects in genes known as tumor suppressors that inhibit cell growth. Scientists at the German Cancer Research Center (DKFZ) have studied how the loss of a tumor suppressor called PTEN leads to the development of leukemia. They were surprised to discover that the absence of PTEN does not cause blood stem cells themselves to divide excessively. Instead, leukemia develops as a result of the overproduction of a chemical messenger (G-CSF) in granulocytes that causes blood stem cells to leave the bone marrow and migrate into the spleen, where this causes an out-of-control multiplication of white blood cells.

Genetic defects that lead to cancer can basically be classified in two groups: defects that turn growth-promoting genes into permanently activated “cancer genes” (oncogenes), and defects that cause a growth-inhibiting gene, or tumor suppressor, to lose its functions.

Every cell contains multiple tumor suppressors; some have been found to undergo mutations in numerous types of cancers. One of these is the phosphatase PTEN, an enzyme which is often defective in cancers such as glioblastoma, prostate cancer and leukemia. In these cases it loses its capacity to repress growth and promotes the development of cancer.

“We always believed that a PTEN defect causes blood stem cells in the bone marrow to divide infinitely, and that this leads to leukemia,” says Prof. Andreas Trumpp, a stem cell expert. Trumpp is head of DKFZ’s Division of Stem Cells and Cancer and director of the Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM), which is supported by the Dietmar Hopp Foundation and DKFZ.

To verify this hypothesis, Melania Tesio, a coworker in Trumpp’s laboratory, bred mice in whose cells the scientists could “switch off” the production of PTEN in blood stem cells and their descendants. Animals whose PTEN production had been turned off developed enlarged spleens and showed signs of a precancerous phase of leukemia known as myeloproliferative syndrome. Ultimately they developed various types of blood cancer.

The researchers were surprised, however, to find that cell division in the blood stem cells was not increased, as they had expected. Instead, they discovered that levels of a cellular messenger called G-CSF (granulocyte colony-stimulating factor) were much higher than normal. This messenger, which is also produced in small amounts in the granulocytes of normal animals, is known to “mobilize” blood stem cells; they leave the bone marrow and migrate through the body. This is exactly what happened in PTEN-negative animals: Blood stem cells leave the bone marrow and settle in the spleen.

Is the excessive production of G-CSF really responsible for the migration of blood stem cells into the spleen? The DKFZ researchers examined this in experiments with mice whose cells are unable to produce both PTEN and G-CSF. In these animals, blood stem cells remained in the bone marrow, and the animals did not develop myeloproliferative syndrome.

“This proves that the overproduction of G-CSF in PTEN-mutated granulocyte cells is what causes blood stem cells to migrate,” says Andreas Trumpp. “G-CSF not only mobilizes stem cells, but also has an effect on the granulocyte cells themselves by inducing them to divide. This double effect on stem cells and granulocytes sets off the progression toward leukemia. The disease therefore develops along an indirect path, rather than by a defect in the PTEN tumor suppressor that drives stem cells to multiply, as previously assumed.”

Melania Tesio, Gabriela M. Oser, Irène Baccelli, William Blanco-Bose, Hong Wu, Joachim R. Göthert, Scott C. Kogan, and Andreas Trumpp: Pten loss in the bone marrow leads to G-CSF–mediated HSC mobilization. Journal of Experimental Medicine 2013, DOI: doi:10.1084/jem.20122768

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 2,500 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

Founded in 2008, the Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM) bundles activities in the areas of stem cell biology and stem cell therapy. In this public-private partnership of the Dietmar Hopp Foundation and the DKFZ, young scientists from around the world focus on application-oriented, clinical studies of tumor and metastasis stem cells. HI-STEM scientists are closely collaborating with partners to carry out tests of novel methods in order to advance the development of new drugs and effective therapies against various types of cancer, and to promote their transfer into medical applications. The Dietmar Hopp Foundation, as a shareholder, contributes €1.5 million per year to HI-STEM.

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