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Silenced Genes as a Warning Sign of Blood Cancer

In the genetic material of cancer cells, important growth inhibitors are often switched off by chemical labels in the DNA. How this happens has been investigated by scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in collaboration with colleagues from the Ohio State University in the United States. They discovered in mice that cancer-typical DNA labeling occurs long before the first symptoms of leukemia appear. A test for the genetic label might therefore help to detect a developing cancer at an early point.

In many types of cancer, parts of the genetic material of tumor cells are switched off by chemical labels called methyl groups. This kind of methyl labeling ranges among the epigenetic changes that do not change the sequence of DNA building blocks. Such labels are found particularly often in genes which act as important inhibitors of pathogenic cell growth.

Cancer researchers do not know why healthy cells and cancer cells differ in their methylation patterns and why it is particularly the cancer inhibitors that are frequently switched off. The study of these questions is a very promising area of research, because there are drugs available that can prevent the attachment of methyl groups or other epigenetic changes and, thus, at least delay the onset of cancer.

Professor Dr. Christoph Plass at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) has investigated, jointly with colleagues from the Ohio State University in Columbus, U.S.A., the processes leading to the different methyl labels in cancer cells. A key question is when the first labels occur in the development of cancer. In their recently published study the investigators used mice affected by chronic lymphocytic leukemia as a model for studying the disease.

The researchers investigated the genetic material of these mice at regular intervals from birth. They discovered first cancer-typical methylation patterns in mice that were only three months old. This means that deviations in methylation occur long before the first signs of disease appear. These were not observed before the animals were thirteen months old. Moreover, the researchers were able to show that methylation patterns in murine DNA are largely corresponding to those found in humans suffering from leukemia. This confirms that the mouse model is suitable for studying the disease.

“Since first deviations in methylation occur so early in mice, we should find out whether this is also true for humans. If so, an early methylation test in high-risk individuals could provide clues about a developing cancer,” Christoph Plass says. In this case, preventive medical intervention might be possible. Drugs preventing methyl group attachment might delay the onset of cancer. First clinical studies have already been started to check this. “This is probably most effective in a very early phase of methylation,” Plass explains. The researchers believe that the first chemically deactivated genes trigger whole cascades of changes in the genetic material which can hardly be controlled at a later stage.

Keyword: Epigenetics

The cells of the roughly 200 different tissues of the human body can fulfill their special tasks only by regulating the activity of their respective genes very specifically. Although every

single gene is equipped with its own control elements, this is not enough for complex coordination. There is a second code that serves as an additional control level. In addition to the genetic switches that are directly integrated in the genetic material, the DNA, genes can also be switched on or off by chemical labeling of the DNA or the DNA packaging proteins. The most common of such epigenetic mutations is the attachment of methyl groups. The effect of these small chemical compounds is that a gene can no longer be read and translated into proteins.

Unlike genetic mutations, which permanently change the sequence of the DNA building blocks, all epigenetic mutations are reversible and, therefore, potential target structures of appropriate drugs.

Shih-Shih Chen, Aparna Raval, Amy J. Johnson, Erin Hertlein, Te-Hui Liu, Victor X. Jin, Mara Sherman, Shu-Jun Liu, David W. Dawson, Katie E. Williams, Mark Lanasa, Sandya Liyanarachchi, Thomas S. Lin, Guido Marcucci, Yuri Pekarsky, Ramana Davuluri, Carlo M. Croce, Denis C. Guttridge, Michael A. Teitell, John C. Byrd,' and Christoph Plass: Epigenetic changes during disease progression in a murine model of human chronic lymphocytic leukemia. Proceedings of the National Academy of Science, USA, 2009, DOI: 10.1073/pnas.0906455106

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