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Scientists show how hematopoietic stem cell development is regulated

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During cell division, whether hematopoietic stem cells (HSCs) will develop into new stem cells (self-renewal) or differentiate into other blood cells depends on a chemical process called DNA methylation. These were the findings of researchers at the laboratory of Dr. Frank Rosenbauer of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch in cooperation with the laboratory of Professor Sten Eirik W. Jacobsen (Lund University, Sweden and the University of Oxford, England). Furthermore, the researchers showed that DNA methylation also plays a crucial role for cancer stem cells.

A group of three enzymes, the DNA methyltransferases (Dnmt) regulates the addition of methyl groups to the DNA (DNA methylation). One of these enzymes - Dnmt1 - is responsible for the maintenance of the marks with the methyl groups, the DNA methylation pattern, because the distribution of the methyl groups on the DNA decides which genes are transcribed and which are blocked. Researchers speak in this context of epigenetic information, in contrast to genetic information.

However, it was unclear until now whether DNA methylation plays a special role in the control of hematopoietic stem cell characteristics. From the HSCs all of the blood cells of the body are formed. Since blood cells have only a limited lifetime, the body must form new blood cells over and over again. The pool for this is generated by the HSCs.

In order to discover what function DNA methylation has for HSCs, the two doctoral students Ann-Marie Bröske and Lena Vockentanz of the

MDC research laboratory of Dr. Rosenbauer switched off the enzyme Dnmt1 in the mice. As a result, the animals were not viable because the hematopoietic stem cell function was completely disturbed.

By contrast, when the two researchers arranged that the HSCs formed just a little Dnmt1, the animals survived, but the HSCs lost their potential for self-renewal. Moreover, the HSCs were restricted in their formation of B cells and T cells (blood cells of the lymphatic system and important cells of the immune system).

However, the HSCs were able to form red blood cells, which are important for oxygen transport and belong to the blood cells of the myeloerythroid system. In other words, the DNA methylation level regulates which blood cell lineages develop or not from a hematopoietic stem cell.

Cancer stem cells

Methylation processes also play a role in numerous cancer diseases. As the MDC researchers were able to show, the DNA methylation by the enzyme Dnmt1 also controls the development of leukemic stem cells.

If the DNA methylation level is low, cancer stem cell renewal is restricted. Moreover, the formation of leukemic cells of B-cell lineage (acute B-cell leukemia - ALL) is blocked.

The question is whether diseased stem cells can be switched off, possibly through a blockade of the enzyme Dnmt1. Dr. Rosenbauer and his research team want to make a more detailed investigation of this question in a further project.

More information: DNA methylation protects hematopoietic stem cell multipotency from myeloerythroid restriction, *Nature Genetics*, online,

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