Sex hormone induces elongation of stem cell telomeres

The telomere ends of chromosomes become shorter with any cell division round. This is why the lifespan of most cells is limited. One of several exceptions to this rule is the haematopoietic stem cells of the bone marrow. The enzyme telomerase enables them to compensate telomere attrition. However, defective telomerase function can cause bone marrow failure disorders such as aplastic anaemia, amongst others. Prof. Dr. Uwe Martens from the SLK Hospitals in Heilbronn found out why some aplastic anaemia patients benefit from androgen therapy. Working with colleagues from Aachen, Hamburg and Ulm, Martens was able to show that this sex hormone triggers the elongation of haematopoietic stem cell telomeres.
Haematopoietic bone marrow stem cells generate around $10^{11}$ blood cells per day. Aplastic anaemia is a condition where the bone marrow does not produce enough new stem cells to replenish the blood cells, resulting in a drastic reduction in red and white blood cell as well as of platelet (thrombocytes which clot and stop blood flow in wounds) counts. “Aplastic anaemia patients often suffer from lassitude and weakness as well as life-threatening infections and bleeding,” said Prof. Dr. Uwe Martens, director of the SLK Hospitals' Medical Hospital III and chairman of the Cancer Center Heilbronn-Franken. Patients are given blood transfusions to alleviate acute disease symptoms. Aplastic anaemia patients are also at risk of developing acute leukaemia.

The major reasons that people develop aplastic anaemia are because of a misguided response of the immune system to a viral infection or the consumption of certain drugs. In the majority of cases, immunosuppressive drugs help to improve the situation. In patients who do not respond to immunosuppressive therapy it is assumed that the disease has other causes. Around ten percent of aplastic anaemia patients have blood cells with noticeably short telomeres. Research has shown that telomere length correlates with the total cell number – the shorter the telomeres, the more distinctive the lack of cells. “It seems that there is a causal relationship between telomere length and cell number,” said Martens.

**Cellular life clocks**

Martens, who heads up a group of researchers at the Freiburg University Medical Centre in addition to his activities at the Cancer Center Heilbronn-Franken, has been studying the role of
Telomeres in the development of diseases for quite a few years. Telomeres consist of non-coding DNA repeats located at the end of the linear chromosomes of most eukaryotes. They have an important “capping” role in that they prevent the chromosomes from fusing with neighbouring chromosomes or deteriorating. In addition, telomeres also represent cellular life clocks, getting shorter as the cells divide. As telomeric sequences do not contain any genetic information, losing them does not become a problem for a long time. Only when the telomeres have reached a critical length will the cells stop dividing and die. “The shortening of the telomeres limits cells’ ability to divide and reduces their lifespan, which is an effective protection against the development of cancer,” said Martens.

Genetic defect inhibits telomerase activity

Exceptions to this rule are germ cells that produce sperm and eggs as well as the haematopoietic stem cells in the bone marrow. These cells possess the enzyme telomerase, which is able to counteract telomere shortening. In addition, this mechanism confers on the cells the life-long ability to divide, which is necessary in order to replenish cells that circulate in the blood. Moreover, the enzyme is reactivated in many cancer cells and confers immortality upon them.

“Some aplastic anaemia patients have considerably reduced stem cell telomerase activity due to a mutation in the so-called TERT (telomerase reverse transcriptase) gene,” said Martens. The TERT gene encodes the part of the telomerase complex that controls DNA synthesis. The mutation leads to a defective gene product, which is no longer able to add DNA repeats to the chromosome ends, with the result that the newly synthesised DNA strand becomes shorter with each cell division. This reduces the ability of haematopoietic stem cells to divide. People with such a TERT gene mutation have a high risk of developing aplastic anaemia.

Telomere elongation opens up new perspectives

Working with colleagues from Aachen, Hamburg and Ulm, Martens was able to show that androgen treatment not only led to the reactivation of telomerase in haematopoietic stem cells, but that it in fact resulted in the elongation of the telomeres. In a paper recently published in the Annals of Hematology, the researchers report on an aplastic anaemia patient who underwent androgen treatment and whose white blood cell telomeres grew by a mean 400 bp per year during
the three-year treatment. In contrast, healthy adults would lose between 30 and 50 bp during the same time period.

“This is the first time that medicinal therapy was shown to lead to telomere elongation,” said Martens pointing out that now, more than 25 years after Elizabeth Blackburn’s and Carol Greider’s discovery of how chromosomes are protected by telomeres and the enzyme telomerase, for which they were awarded the 2009 Nobel Prize in Physiology or Medicine, the therapeutic potential of the enzyme telomerase has reached clinical application. “Our work has provided evidence for the function and role of the enzyme telomerase and the telomeres,” said Martens, who now hopes that the discovery will lead to other therapeutic approaches for treating disorders that are the result of eroded chromosome ends. “The phenomenon of stem cell depletion is also found in Dyskeratosis congenita, a rare congenital disorder, and in certain forms of lung fibrosis,” said Martens going on to add that further studies will be carried out to elucidate the connection between disease and telomere shortening.

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