Excessive numbers of ageing stem cells accumulate without a guardian

Adult stem cells grow older too. A group of researchers focusing on the ageing of stem cells at the Max Planck Institute in Ulm under the leadership of Leibniz prizewinner Lenhard Rudolph, has now made a surprising discovery in their research into telomer-associated ageing, which further substantiates this hypothesis.

According to a paper published by Yvonne Begus-Nahrmann and Lenhard Rudolph's group in Nature Genetics (30.09.2009, doi: 10.1038/ng.426), the protein p53 delays the ageing of tissues and organs because it eliminates damaged stem cells.

Potential new approach

Prof. Dr. Karl Lenhard Rudolph
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Further research will have to show whether this molecular protection mechanism can also be used to delay human ageing. Researchers still have to clarify how this "waste collection system" works on the molecular level. Nevertheless, Lenhard Rudolph and Yvonne Begus-Nahrmann, who carried out the initial experiments, are quite optimistic.

They are optimistic for two reasons. First, because recently published papers on skin cells and induced pluripotent mouse stem cells confirm the results obtained by the Ulm researchers. Second, because their findings seem to have given rise to an approach which, according to Rudolph, can be implemented more quickly than the methods normally used to transplant induced pluripotent stem cells (ipS cells). In addition, the potential new approach is very specific and only concerns chromosomally instable stem cells, said Begus-Nahrmann.

"The function of the p53 tumour suppressor protein, often termed guardian of the genome, decreases with age. But when we finally succeed in developing substances that can increase the activity of p53 and reduce the number of instable stem cells, then we might be able to delay the ageing of tissues," said Rudolph, who is the head of the team of Ulm researchers. He is not seeking to prolong life, but "to improve the quality of life in older age".

The guardian of the genome grows older too

The starting point of the Ulm researchers' investigations was the fact that the telomers of chromosomes shorten with age and the number of genetic defects increases. Unprotected chromosome ends, i.e. shortened telomers, activate the protein p53. Current knowledge suggests that this triggers the same signalling cascade in cells as occurs as a result of chromosomal double-strand breaks, explains Begus-Nahrmann.

The biologist added that recent findings show that p53 activation decreases with age. Final evidence is still lacking, but there is growing evidence that the reduced activation of p53 might also be related to the development of cancer when the "guardian of the genome" is no longer able to eliminate harmful cells.

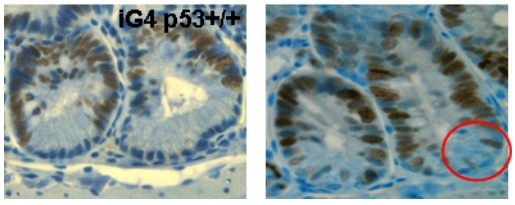
The researchers used mice for their experiments in which p53 was only deleted in the intestinal tract. Had the protein been absent in the entire model organism, the mice would have died prematurely of cancer, and the ageing processes could not have been investigated. This is why the researchers limited their investigations to the intestinal tract, an organ characterised by highly active cell division.

The experimental data led to a surprise

The Ulm researchers had to use some tricks to genetically modify the mice and carry out time-consuming crosses. Since human beings have telomers that are five times shorter than those of mice, the telomers had to be shortened to a similar length. The researchers used telomerase knock-out mice (editor's note: the enzyme telomerase can prevent the shortening of telomers by adding DNA constituents to the chromosome ends after cell division, thus making the telomers longer again).
The third and fourth generations of mice finally showed typical signs of ageing such as bent back, intestinal atrophy or hair loss.

The protein p53 is not just any protein - it is one of the most important controls of cell growth. It plays a key role in the expression of genes that are involved in the regulation of apoptosis and DNA repair. However, the Ulm researchers were surprised to see that p53 removed chromosomally instable stem cells, because preliminary data suggested that the mice lived longer when p53 was switched off.

Indeed, the survival curves in the experiments showed that telomerase knock-out mice died earlier when they did not have p53 in the intestinal tract. These results correlated with weight loss, reduced tissue homoeostasis and were not caused by tumours.

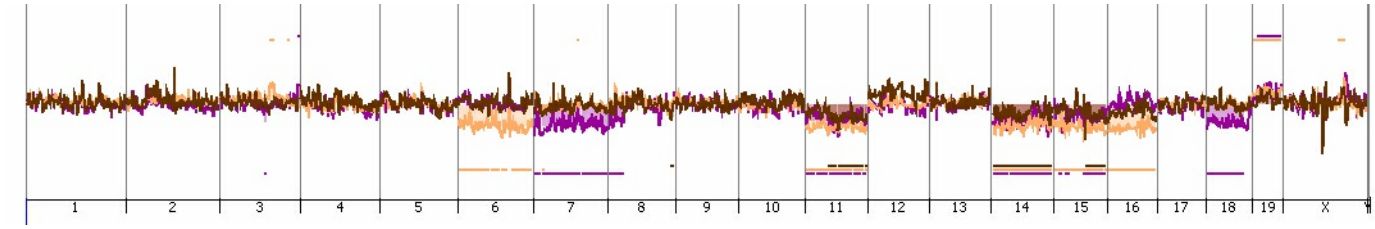


The instable stem cells of the intestine are not removed in ageing tissue and contribute to enhanced tissue ageing. The photo shows the immunohistochemical staining used to identify the intestinal stem cells. The stem cells are eliminated in ageing tissue with intact p53 (left), while they remain present in tissue where the p53 protein was deleted (right, red circle).

What is the cause of chromosomal instability?

Looking for potential explanations, the Ulm researchers used exclusion methods downstream and upstream of the molecular signalling cascade triggered by p53. The preliminary results showed that p53 knock-out mice had more DNA damage and anaphase bridges (which suggest a high number of shortened telomers), the cells proliferated in the intestinal tract, but the mice died nevertheless earlier, said Begus-Nahrmann in response to a question about the level where this chromosomal instability occurs.

The researchers started to look at stem cells whose activity was being investigated by colleagues from Utrecht using special markers and Paneth cells in the mice cohorts. The results revealed that telomerase knock-out mice only had a few stem cells. When p53 was deleted, the mice suddenly had a larger number of stem cells, achieving a population density (five to six stem cells per crypt) that was almost as high as that of the wild-type. For Begus-Nahrmann this is clear evidence for the ability of p53 to prevent cell proliferation.



The diagram shows a typical DNA profile in ageing tissue, lacking p53. The bars above and below the base line represent the loss or gain of entire chromosomes or parts thereof.

Begus-Nahrmann provided evidence for her assumption that p53 eliminated instable stem cells by excising individual crypts consisting of between 20 and thirty cells (dome-like bulges where stem cells are located) and investigating their chromosomal losses and gains using CGH (comparative genomic hybridisation). She provided clear evidence for stem cells being the carriers of chromosomal instability.

The stem cell researchers from Ulm will certainly spend lots of time thinking about the question as to how to modulate this key protein, because p53 is part of a huge signalling network and possibly has further surprises in store. Begus-Nahrmann's observations on the mouse model suggest that it might be difficult to activate the guardian of the genome so as to enable it to eliminate the damaged stem cells: if p53 is active all the time, it leads to the clearance of too many cells.

Literature:

Yvonne Begus-Nahrmann et al.: p53 deletion impairs clearance of chromosomal-instable stem cells in aging telemere-dysfunctional mice. In: Nature genetics, online 30.08.09 (doi: 10.1038/ng.426)
PM MPG, 30.08.09