Website address:
https://www.gesundheitsindustrie-bw.de/en/article/press-release/guardian-epi-genome

The guardian of the (epi-)genome

Toxicologists from the University of Konstanz have found that the protein p53 continuously protects our cells from tumorigenesis by coordinating important metabolic processes that stabilize their genomes.

The gene coding for the protein p53 is probably the most important factor in protecting human cells from cancer caused by DNA-damaging agents. The protein allows cells to repair damage to their DNA and thereby prevents the development of cancers, which is why it has been nicknamed "the guardian of the genome". An inactivation of p53 can be found in about one in two tumours. Cells lacking p53 function become genomically instable, which implies that they are prone to acquire mutations in their DNA, helping the tumours to grow in uncontrolled ways, form metastases, and resist therapy. Hence, the cancer cell becomes more aggressive.

But even when there are no DNA-damaging agents around, it is an extremely difficult task for cells to maintain their genomic (DNA) stability. Researchers have suspected that p53's protective function also covers healthy cells. The mechanism by which the protein would gain such capabilities, however, has remained unclear. A research team led by Ivano Amelio, Professor of Systems Toxicology at the University of Konstanz, and involving his Konstanz colleague Marcel Leist, Professor of In-Vitro Toxicology and Biomedicine, has now shed new light on this mystery.

Cell division is a vulnerable process

Cells – and their DNA integrity – are particularly at risk when they divide, as they duplicate their DNA in the process. "Like in any other replication process, such as photocopying a document or copying a digital file, it is disastrous if the template moves or is changed while the copy is being made. For this reason, genes cannot be transcribed – i.e. used as templates for proteins – while the DNA is being copied," Amelio explains. If they are transcribed anyway, serious disruptions occur, which can lead to cancer-promoting mutations. The results from Amelio and his team, now appearing as the cover story in Cell Reports, show that p53 inactivation favours such copy-related damage. They found that p53 normally acts by changing cell metabolism in a way that prevents activation of genome regions that should remain inactive.

The scientists painstakingly dissected the underlying mechanism down to the last detail. They made use of the knowledge that some parts of the genome, called heterochromatin, are packed densely to prevent transcription of genes in these regions. For this reason, such regions are called "silent", and they are controlled by what is known as epigenetic mechanisms, i.e. processes that do not affect the genes as such, but their overall packaging and accessibility in the genome. One of the most interesting findings of the recent study was that in the absence of p53 these usually inaccessible or "silent" regions of our DNA were transcribed, leading to catastrophic consequences.

Crosstalk between p53-driven metabolism and epigenetic integrity

"Normally, transcription of these areas of the genome should be kept under tight control, and p53 is the key to keeping their information locked-away by controlling metabolism in a way that renders the heterochromatin inaccessible," Amelio says. When p53 is absent, as in p53-inactivated tumours, the cell loses its metabolic homeostasis, and the information hidden in the heterochromatin becomes aberrantly accessible and is transcribed. This causes so much damage that it will drive cells into a state of genomic instability that favours and worsens cancer progression. "By unravelling this mechanism, we could demonstrate that there is a link between metabolism, epigenetic integrity and genomic stability. In addition, we provided evidence that p53 represents the switch controlling the on/off status of this protection system in the response to environmental stress," Amelio summarizes the finding.

The question of how p53-inactivated tumours develop genomic instability has plagued the scientific community for quite some time. "Now we have certainty that, in these tumours, there is a problem at the metabolic level that is reflected in the integrity of the epigenome. Hence, p53 should actually be called guardian of the (epi-)genome. This essential insight can direct research to identify potential new therapeutic strategies for the very frequent forms of cancers that carry p53 inactivation," Amelio concludes.

Publication:

Emanuele Panatta et al. (2022) Metabolic regulation by p53 prevents R-loop-associated genomic instability. Cell Reports. DOI: 10.1016/j.celrep.2022.111568

Press release

02-Nov-2022
Source: University of Konstanz

Further information

University of Konstanz
Communications and Marketing
Tel.: +49 (0) 7531 88 3603

- University of Konstanz