Researchers suppress cell division in prostate tumour tissue through enzyme inhibition

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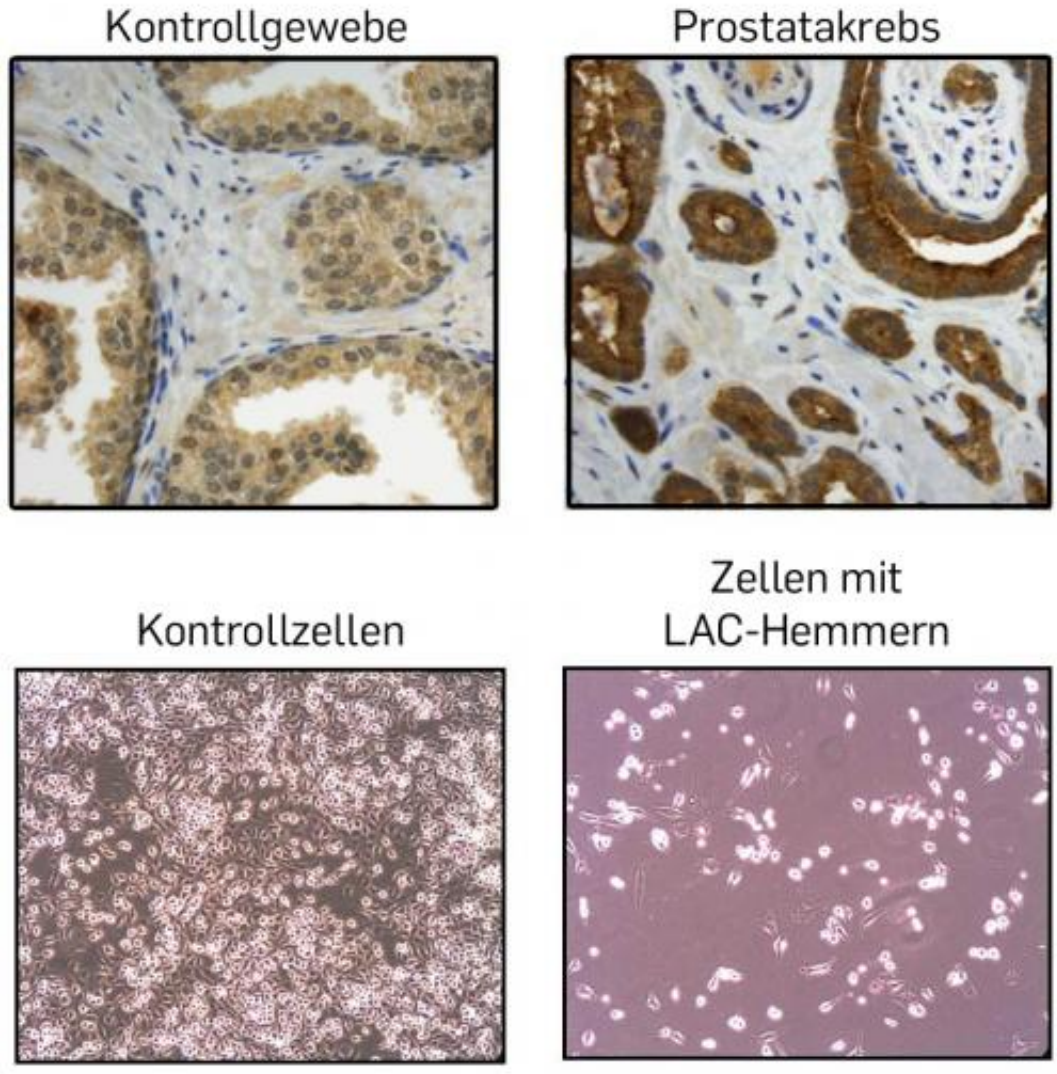

Top: Cells from a benign enlargement of the prostate contain less LAC enzyme (brown coloured) than prostate tumour cells. Bottom: If prostate cancer cells are cultivated for three days with an inhibitor of the enzyme LAC, they proliferate

much less (right) than without the inhibitor (left). All images were recorded using the light microscope. Credit: adapted from Journal of Biological Chemistry

A previously poorly investigated signalling pathway is crucial for the growth and proliferation of prostate cancer cells. An international research team discovered this when studying the enzyme "soluble adenylyl cyclase" that produces the second messenger molecule cAMP. When the scientists inhibited the enzyme, the cancer cell proliferation was suppressed. The team led by Dr. Yury Ladilov from the Department of Clinical Pharmacology at the Ruhr-Universität Bochum reported together with colleagues from the Department of Urology at the RUB and the Cornell University in New York in the *Journal of Biological Chemistry*.

cAMP is generated at several locations in the cell

Cyclic AMP (cAMP) is a second messenger molecule that controls many processes ranging from cell growth to cell death. An enzyme located in the cell membrane, called adenylyl cyclase, produces the molecule. Generated at the cell membrane, cAMP affects, for example, ion channels or other enzymes which are anchored in the membrane. However, the messenger also influences intracellular processes in the nucleus or in the mitochondria, the powerhouses of the cell. The common view was that cAMP diffuses from the membrane through the cell liquid – the cytosol – to its destination. Recent studies, however, suggest that cAMP is not only produced at the cell membrane, but also in the cytosol – by the enzyme soluble adenylyl cyclase (LAC). The function of LAC has so far barely been studied.

The enzyme LAC plays a role in cell division

In a previous study, the RUB-team from the Department of Clinical Pharmacology showed that LAC plays a role in programmed cell death. The scientists and their colleagues are now elucidating the function of the enzyme in proliferation of tumour cells. First, they examined tissue samples from patients. They compared the amount of LAC in cells of a malignant prostate tumour with the amount of LAC in cells taken from benign enlargement of the prostate. The "malignant" cells contained more cAMP-forming enzyme than the "benign" cells. In cell culture experiments, the researchers then genetically altered the cancer cells so that they hardly produced LAC. The modified cells almost completely stopped proliferating. The same effect was achieved when the scientists inhibited the enzyme LAC by administering drugs. The team also identified the signal paths involved. cAMP formed by LAC activates two proteins, which in turn control the MAP kinase pathway. This signalling cascade is known to control cell growth and division. "The results of this study shed new light on the regulation of cell division and tumour formation", says Yury Ladilov.

Potentially interesting for therapy

One way to treat prostate cancer is radiation therapy. Dr. Ladilov's team is currently testing on cell cultures how a combination of radiation and LAC inhibitors effects the growth of cancer cells. "Of course, we hope that one day it will be possible to use this knowledge for the treatment of patients", says Bochum's biologist. "But there's still a long way to go." It is conceivable that the use of LAC inhibitors could reduce the amount of radiation required. The LAC inhibitors previously used in cell culture cannot, however, be used on humans.

More information: Flacke, J. et al. (2013): Type 10 soluble Adenylyl Cyclase is overexpressed in prostate carcinoma and controls proliferation of prostate cancer cells, *Journal of Biological Chemistry*, doi: 10.1074/jbc.M112.403279