New regulator in aggressive breast cancer cells discovered

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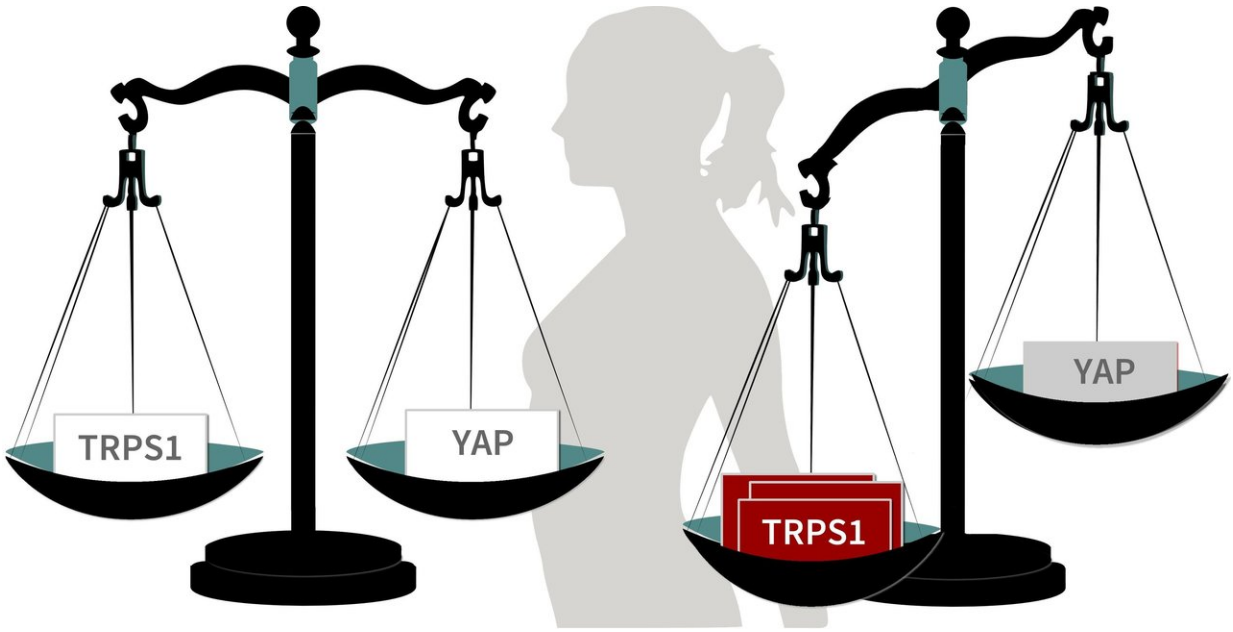

The protein TRPS1 controls the activity of the YAP protein in breast cancer. If YAP activity is downregulated, the survival prognosis for patients is reduced. If TRPS1 is missing, less or no tumors are occurring. Credit: Kerstin Wagner / FLI; Figure: i.a. www.pixabay.com

Triple-negative breast cancer is a particularly aggressive form of breast cancer. Here, important receptors are missing, which often serve as targets for treatments. Thus, these tumors are unlikely to respond to current therapies. Researchers from the Leibniz Institute on Aging –

Fritz Lipmann Institute (FLI) in Jena now identified the protein TRPS1, which is commonly over-expressed in these tumors. When TRPS1 is down-regulated, tumor growth decreases whereas survival rates increase. This is a possible therapeutic approach for the treatment of this aggressive form of breast cancer. The results have now been published in the journal *Nature Communications*.

Every day, billions of "old" cells get replaced by "new" cells in our body. Maintaining this balance between cell division and cell death is of great importance, as even small irregularities in tissue homeostasis can sooner or later lead to cancer or premature aging. The Hippo pathway plays an important role in the regeneration of tissues but also in the development of cancer. The protein YAP (Yes-associated protein) controls tissue growth and organ size. YAP acts as co-activator and it is responsible for controlling the transcription of specific genes from DNA to mRNA.

Previous studies have shown the cancer-promoting role of YAP, which results in uncontrolled cell division. However, there are certain tumor types, such as breast or colorectal cancer, where an increased activity of the YAP protein surprisingly increases the survival prognosis of cancer patients. Until now, it remained unclear, why the YAP activity differs, it is decreased in certain tissues and tumor types and what mechanisms underlie this phenomenon.

Researchers around Dr. Björn von Eyss, junior group leader at the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) in Jena, now investigated in collaboration with colleagues of the Francis Crick Institute in London, UK and the University Würzburg, how YAP activity is regulated in breast cancer. The results are now published in the journal *Nature Communications*.

TRPS1 regulates YAP activity

Many signal pathways are important regulators of YAP activity, sometimes even independently of the Hippo pathway. "This is why we conducted a genome-wide CRISPR screening, to identify new regulators of YAP in an unbiased fashion," says Dana Elster, Ph.D. student in the von Eyss Lab. With this method, the researchers were able to identify the protein TRPS1 (Trichorhinophalangeal Syndrome 1). For YAP-dependent transcription it acts as repressor, inhibiting the expression of many YAP target genes in breast cancer cells. "TRPS1 occupies a large number of genomic sites that are actually regulated by the YAP protein and impedes the transcriptional program," explains Dr. Björn von Eyss. This suppresses YAP-dependent functions such as the transcription of YAP target genes.

If TRPS1 is increased in tumors, such as triple-negative breast cancer, a particularly aggressive form of breast cancer, the patients' survival probability decreases. This implies an oncogenic effect of the protein. The results also show a relationship between the two proteins TRPS1 and YAP: If the activity of TRPS1 is increased in the tumor cells, YAP activity is down-regulated. This favors tumor growth and results in a worse survival prognosis of the breast cancer patients.

TRPS1 tricks the immune system

Furthermore, the researchers found out that this mechanism reduces the number of immune cells within tumors. Such cells are important, because they can fight tumors from "the inside." TRPS1 tricks the immune system and evades the immune defense. If TRSP1 is down-regulated, the immune system regains activity and it recognizes the tumor to fight it.

The researchers hypothesize that breast cancer cells need to maintain a certain level of YAP activity that is high enough to maintain the oncogenic functions of YAP, but low enough to evade

immunosurveillance. "The role of TRPS1 could therefore be important to maintain a specific level of YAP-activity," says Dr. Björn von Eyss. This underlines the important role of this protein for therapeutic treatments against cancer.

"We will now investigate if our results can lead to new therapeutic treatments for breast cancer patients, whose prognoses are rather poor," explains von Eyss. The development of a new mouse model already was an important step in order to further investigate the discovered mechanism. This approach is also promising for other fields: The research group of Dr. Björn von Eyss has first indications that TRPS1 is playing a role in the aging process. In future research, they thus want to investigate more in detail which age-associated changes are influenced by this factor. Perhaps this will soon make our tissues fitter in old age.

More information: Dana Elster et al. TRPS1 shapes YAP/TEAD-dependent transcription in breast cancer cells, *Nature Communications* (2018). DOI: 10.1038/s41467-018-05370-7

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