New functions of integrin and talin discovered by an international research network

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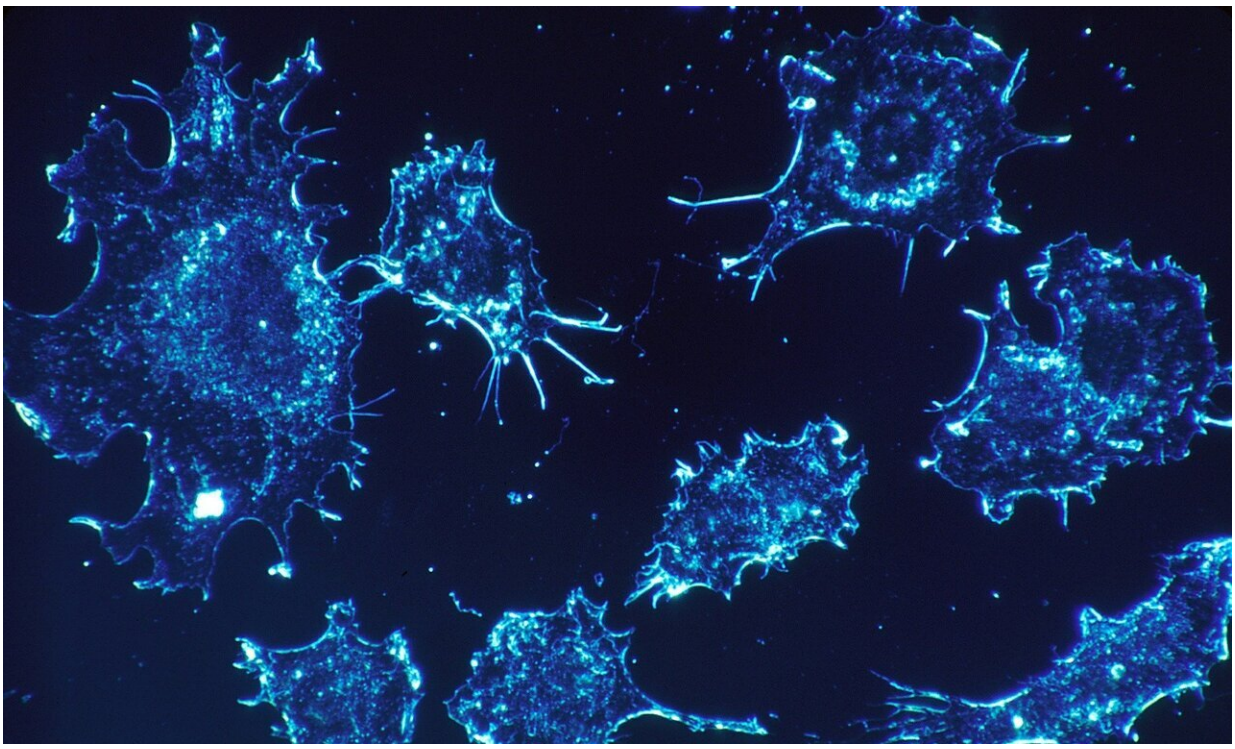

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Researchers at Tampere University, Finland, have published new results in collaboration with an international research network that help to understand the biological phenomena mediated by cell membrane

integrin receptors and contribute to the development of methods for the treatment of cancer.

In the cell membrane, integrins form the connection between the cytoskeleton and the extracellular matrix. The regulation of integrin activity is essential for the function of tissues and individual cells.

The studies investigated the structure and function of talin, a cytoskeletal protein, which is important in the regulation of the integrin receptor activity. Talin binds to integrin via its 'head' and connects it to the cytoskeleton, thereby acting as a part of the cellular mechano-signaling network, which affects cell adhesion, migration, but also gene expression among other things.

One of the studies now published used X-ray crystallography to reveal the atomic structure of talin head, giving unprecedented insights how talin binds to integrins.

"The activation of integrins mediated by talin is essential in various cancers, for example, and knowing the detailed structure of talin opens up new possibilities to combat cancer by developing inhibitors that prevent the interaction of talin and integrin," says Professor Vesa Hytönen from Tampere University.

The structure of talin was discovered in a group led by Professor Jinhua Wu (Fox Chase Cancer Center, PA, USA), and a research group at Tampere University led by Professor Vesa Hytönen was responsible for the biophysical characterizations in the study, while the cell-biological consequences were studied at the University of Geneva, Switzerland in a research group headed by Professor Bernhard Wehrle-Haller. The results were published in the *Proceedings of National Academy of Sciences (PNAS)*.

The significance of the structure of talin for integrin activation gained new perspectives in Sampo Kukkurainen's doctoral dissertation, which used molecular dynamics simulations to study the interaction of the talin-integrin pair.

The multidisciplinary research project related to Kukkurainen's dissertation project was also carried out in close collaboration with the research group of Professor Bernhard Wehrle-Haller (University of Geneva, Switzerland) and involved several research groups from Europe and the United States, including Professor Janne Jänis's research group at the University of Eastern Finland and Research Director Markku Varjosalo's and Professor Ilpo Vattulainen's research groups at the University of Helsinki. The results were published in the *Journal of Cell Science*.

The study provided new detailed information on the mechanism of protein interaction.

"The study showed that the loop of the F1 subunit of talin is essential for the activation of integrins," says Dr. Kukkurainen.

At Tampere University, doctoral researcher Latifeh Azizi is currently investigating how the mutation of talin affects protein function.

An article related to Azizi's study published in *Scientific Reports* showed how mutations observed in cancer patients affect the structure, interactions, and biological activity of talin in cells. The study was conducted in collaboration with a research group led by Dr. Ben Goult (University of Kent, UK). The mutations selected for the study were screened from sequence databases using structural data and bioinformatics methods.

"It was interesting to find that a single mutation in a large protein can

affect cell function so much," says Azizi.

The study showed that talin mutations affect cell motility and cell communication. The research result is a step towards personalized medical treatments in which information from a cancer patient's tumor can be used to select an appropriate treatment.

More information: Pingfeng Zhang et al. Crystal structure of the FERM-folded talin head reveals the determinants for integrin binding, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.2014583117

First person – Sampo Kukkurainen. *Journal of Cell Science* Published 12 October 2020 doi: 10.1242/jcs.254615

Sampo Kukkurainen et al. The F1 loop of the talin head domain acts as a gatekeeper in integrin activation and clustering, *Journal of Cell Science* (2020). DOI: 10.1242/jcs.239202

Latifeh Azizi et al. Cancer associated talin point mutations disorganise cell adhesion and migration, *Scientific Reports* (2021). DOI: 10.1038/s41598-020-77911-4

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