UNIVERSITÉ DE GENÈVE

PRESS RELEASE

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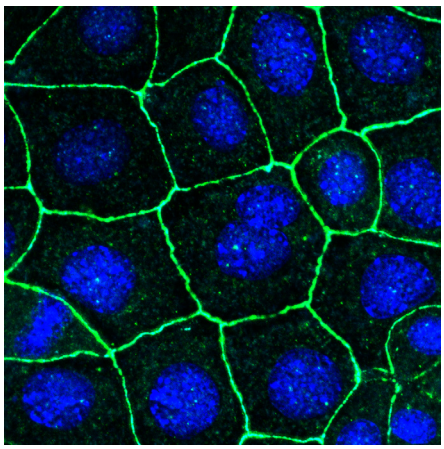
To proliferate or not to proliferate? A cellular spring replies

The cell protein ZO-1 promotes or not epithelial cell proliferation depending on the tensions to which it is subjected.

The epithelium, a tissue made up of closely juxtaposed cells, forms the glands and covers the outer surface of the human body as well as its internal cavities, such as the lungs or intestines. There are different types of epithelia, depending on the surfaces they cover and the functions they carry out. These tissues are subjected to multiple types of mechanical stretch, such as those caused by passing food or filling a bladder. The mechanical input strongly influences the proliferation and differentiation of epithelial cells, whether healthy or cancerous, but the underlying processes remain poorly understood. Researchers at the University of Geneva (UNIGE), Switzerland, have discovered that the proteins *Zonula Occludens-1* and *-2* (ZO-1 and ZO-2), which contribute to the tightness of the epithelium, perceive these physical signals and activate different cellular responses accordingly. Published in the journal *Current Biology*, these results reveal a novel process by which mechanical forces can regulate the structure of epithelia, their dynamic equilibrium and the establishment of tissue barriers. Targeted inhibition of ZO-1 in tumors could therefore be a pathway to explore, given its likely role in the proliferation of cancer cells.



Cells forming an epithelium. The nucleuses are marked in blue and ZO-1 in green.

High definition pictures

Epithelial cells, which are connected to each other through intercellular junctions, a network of more or less densely assembled proteins, make up the glands and coat the cavities and the surface of the body. These cells can for example absorb water and solutes in the kidneys, secrete milk in mammary glands or resist mechanical stress during the filling and emptying of the bladder. Understanding how epithelial cells function is a major challenge, both in healthy and cancerous conditions, as the majority of tumors develop from epithelial cells.

A flexible cell skeleton

"The mechanical forces exerted on these cells influence their behavior, by inducing them for example to proliferate in order to repair an injury, or to form a three-dimensional structure such as a gland", explains Sandra Citi, professor at the Department of Cell Biology of the UNIGE Faculty of Science.

The proteins ZO-1 and ZO-2, which are part of the intercellular junctions, are also in contact with the cytoskeleton, the network of contractile filaments that give shape to the cell. The biologists from UNIGE, in collaboration with researchers from the Swiss Federal Institute of Technology in Lausanne (EPFL) and the National University of Singapore, wondered whether these proteins played a role in the transmission of mechanical signals, leading for example to a change in cell proliferation.

Sequester a key factor on demand

Domenica Spadaro, researcher at UNIGE and first author of the study, details the results: "ZO-1 assumes different conformations depending on the tension exerted by the cytoskeleton, like a flexible spring. When the cytoskeleton is taut, this traction stretches ZO-1, which will sequester a factor essential for cell multiplication. Conversely, following an injury for example, ZO-1 loosens and releases this factor so that the cells proliferate again to repair the lesion."

Depending on the organization of the cytoskeleton and the tension it exerts, ZO-1 and ZO-2 work together to stabilize factors that regulate gene expression, cell proliferation and epithelial tightness, as well as the epithelium's ability to organize itself into three-dimensional structures. ZO-1 and ZO-2 are also likely to play a role in the proliferation of cancer cells, which are sensitive to mechanical forces in their environment. The development of molecules capable of inhibiting them within tumors could therefore be an asset in combating malignancies.

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