UNIVERSITÉ DE GENÈVE

PRESS RELEASE

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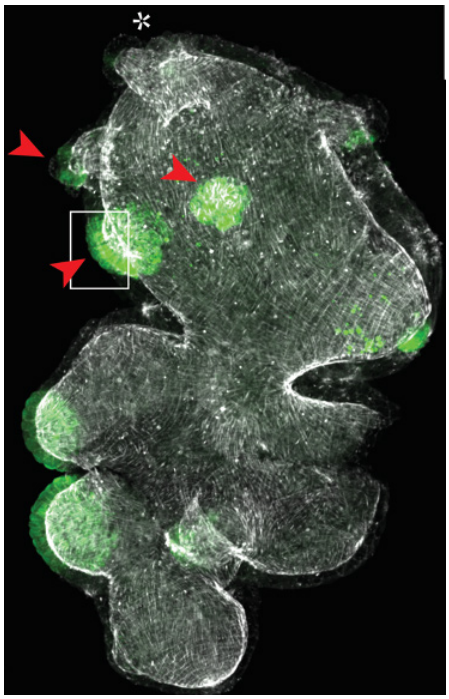
How to turn a tentacle into a foot

By identifying a key regulator of cell identity, a team from the UNIGE and the FMI has succeeded in modifying the structure and function of tentacle cells in hydra.

Humans, animals, plants: all multicellular organisms are made up of specialized cells called differentiated cells. Thus, the cells that make up the epidermis do not have the same identity - nor the same function - as those that line the digestive system, for example. However, the mechanisms by which these cells maintain their identity are still poorly understood. Working on the freshwater polyp named Hydra, a team from the University of Geneva (UNIGE), in collaboration with the Friedrich Miescher Institute for Biomedical Research (FMI) in Basel, discovered one of the key regulators: the transcription factor Zic4. After reducing Zic4 expression, the researchers found that Hydra tentacle cells changed their identity and turned into foot cells, forming functional feet in the animal's head. These results can be found in the journal *Science Advances*.



Hydra with reduced Zic4. The red arrowheads indicate the tentacles that have been transformed into feet, the asterisk indicates the animal's mouth.

High resolution pictures

As a living organism develops, its stem cells divide and gradually give rise to new cells capable of performing one or more specific functions. This process of cell specialization is called differentiation. Thus, the cells that make up the surface of the skin will be different, morphologically and physiologically, from those that make up, for example, digestive tissue or the nervous system. In very rare cases, some cells that are already differentiated can change their structure and function - and therefore their identity - during their existence. This process is called transdifferentiation.

If the mechanisms of differentiation are well known, those that allow the specialized cell to maintain its identity - and thus to prevent its dedifferentiation (loss of identity) or its transdifferentiation (change of identity) - remain mysterious. To study them, species that regenerate their organs, limbs or whole body are privileged models. In these organisms, some cells temporarily lose or change their identity before renewing themselves and performing a new function. This is particularly true of the freshwater hydra, a small invertebrate averaging 1.5 cm in length that is capable of regenerating any amputated part throughout its life.

A key regulator identified

Using this animal model, researchers from the University of Geneva (UNIGE), in collaboration with the Friedrich Miescher Institute for Biomedical Research (FMI) in Basel, have identified a key regulator of cell identity maintenance: the transcription factor Zic4, a protein located in the nuclei of hydra cells, responsible for regulating the expression of a series of target genes. "We show more precisely that Zic4 plays a crucial role in the formation and maintenance of the cells that make up the tentacles, and that by reducing Zic4 expression, it

is possible to modify the organization and function of these cells," explains Matthias Christian Vogg, senior research and teaching assistant at the Department of Genetics and Evolution of the Faculty of Science and the Institute of Genetics and Genomics (iGE3) at the UNIGE, and first author of the study.

By reducing the level of Zic4 expression by half, the scientists found that the epithelial cells on the outer layer of the tentacles were transformed into foot epithelial cells. "In the hydra, the foot is called the basal disc of the animal. The cells that compose it are very specialized: they secrete mucus that allows it to attach to the surrounding environment. After reduction of Zic4, it took only a few days for the process of transdifferentiation of the tentacle cells to take place, leading to the development of feet in place of the tentacles," says Brigitte Galliot, emeritus professor at the Department of Genetics and Evolution of the Faculty of Science and at the iGE3 of the UNIGE, who supervised the study.

A return to the cradle

The scientists also discovered that transdifferentiated cells return to the cell cycle beforehand, without dividing. They then lose their first identity. "These cells reactivate the process of DNA synthesis, and thus of chromosome duplication, at work during cell proliferation without going as far as mitotic division," explains Charisios Tsiairis, junior group leader at the FMI and co-last author of the study.

To reduce the expression of the Zic4 gene, molecules inhibiting its expression were "electroporated" into the epidermis of the animal. "Then, we detected by double labeling, both a marker specific to tentacle cells and a marker for foot cells in the same cells, proving that these cells are transdifferentiating as they go through a stage where they are still a little bit tentacle and already a little bit foot. This transitional phase is the signature of the transdifferentiation process," explains Chrystelle Perruchoud, research assistant at the Department of Genetics and Evolution of the Faculty of Science and at the iGE3 of the UNIGE.

These results provide new keys to understanding transdifferentiation. They could pave the way for new therapies to regenerate certain deficient cell types in humans. For now, many questions remain: "Does Zic4 play the same role in other animals? Would further decreasing its expression allow the generation of other cell types? And let's not forget that there are probably other important regulators of transdifferentiation yet to be discovered," concludes Brigitte Galliot.

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