How do our organs know when to stop growing?

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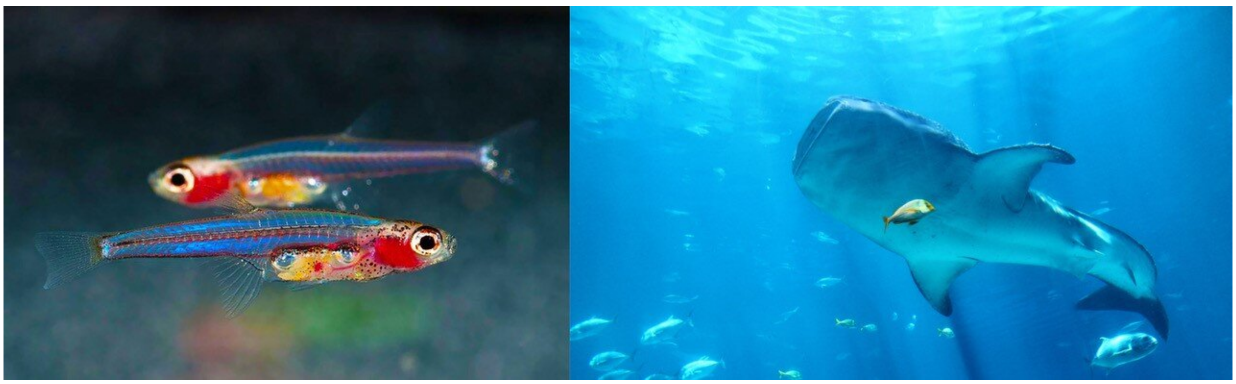

How do the fins of a 7 millimeter fish, similar to those of a whale shark, know when to stop growing? Credit: Lukas Rüber/Shamila Chaudhary

The smallest fish in the world, the Paedocypris, measures only 7 millimeters. This is nothing compared to the 9 meters of the whale shark. The small fish shares many of the same genes and the same anatomy with the shark, but the dorsal and caudal fins, gills, stomach and heart, are thousands of times smaller! How do organs and tissues of this miniature fish stop growing very quickly, unlike those of their giant cousin? A multidisciplinary team led by scientists from the University of Geneva (UNIGE), Switzerland, and the Max Planck Institute for the Physics of Complex Systems (MPIPKS), Germany, was able to answer this fundamental question by studying its physics and using mathematical equations, as revealed by their work published in the journal *Nature*.

Cells of a developing tissue proliferate and organize themselves under the action of signaling molecules, the morphogens. But how do they know what size is appropriate for the living organism to which they belong? The research groups of Marcos Gonzalez-Gaitan, Professor at the Department of Biochemistry of the Faculty of Science of the UNIGE and Frank Jülicher Director at the MPIPKS in Dresden, have solved this mystery by following a specific morphogen in the cells of tissues of different sizes in the fruit fly Drosophila.

In Drosophila, the morphogen Decapentaplegic (DPP), a molecule required for the formation of the fifteen (deca-penta) appendages (wings, antennae, mandibles...) diffuses from a localized source within the developing tissue and then forms decreasing concentration gradients (or gradual variations) as it moves away from the source. In previous studies, Marcos Gonzalez-Gaitan's group, in collaboration with the German team, has shown that these concentration gradients of DPP extend over a larger or smaller area depending on the size of the developing tissue. Thus, the smaller a tissue, the smaller the spread of the DPP gradient from its diffusion source. On the other hand, the larger a tissue, the larger the spread of the DPP morphogen gradient. However, the question remained as to how this concentration gradient scales to the growing size of the future tissue/organ.

A multidisciplinary approach to solve a biological question

"The original approach of my team, composed of biologists, biochemists, mathematicians, and physicists, is to analyze what happens at the level of each cell, rather than placing our observations at the scale of the tissue," comments Marcos Gonzalez-Gaitan. "The central point is to deal with living matter as if it was just matter, that is to say, studying biology with the principles of physics," says Frank Jülicher. The two teams have developed a battery of sophisticated tools to follow the fate of the DPP molecule in and between cells of a tissue with great precision using quantitative microscopy techniques. "These tools have allowed us to define a multitude of parameters, linked to cellular processes, for this morphogen. For example, we measured the efficiency with which it binds to cells, penetrates inside cells, is degraded or is recycled by the cell before diffusing back to other cells. In summary, we measured all the important transport steps of DPP," explains Maria Romanova Michailidi, senior researcher in the Department of Biochemistry and first author of this study.

The mechanism of scaling explained by a mathematical equation

The scientists collected all this data on DPP in cells belonging to tissues of different sizes in normal flies and in mutants that failed to scale. They found that it is these different individual transport steps that define the extent of the gradient. Thus, in a small tissue, the DPP molecule is mainly spread by diffusion in between cells. Its concentration therefore falls quite rapidly around its source because of degradation, yielding a narrow gradient. On the other hand, in larger tissues, DPP molecules that went inside cells are also highly recycled, making it possible to extend the gradient over a larger area. "We were finally able to propose an unbiased, unified theory of morphogen transport, going down to the key equations of the system and to unravel the mechanism of scaling!" Maria Romanova enthuses.

The combination of theoretical physics and experimental approaches, established from the study of the DPP molecule in Drosophila, can be generalized to other molecules involved in the formation of various developing tissues. "Our singular and multidisciplinary approach allows us to provide a universal answer to a fundamental biological question that Aristotle was already asking himself nearly 2,500 years ago: how does an egg know when to stop growing to make a chicken?" concludes Marcos Gonzalez-Gaitan.

More information: Morphogen gradient scaling by recycling of intracellular Dpp, *Nature* (2021). DOI: 10.1038/s41586-021-04346-w

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