Researchers identify new molecular mechanism key to planarian regeneration

February 14 2023

These flatworms are capable of regenerating any part of their bodies, even their heads. Credit: Teresa Adell

Planaria are freshwater flatworms that have become a key model for studying regeneration and stem cells, as they can regenerate any part of the body, even the head. But how does the animal know what part of its body is missing and what kind of tissue it needs to regenerate?

Researchers from the Department of Genetics, Microbiology and Statistics of the University of Barcelona and the Institute of Biomedicine of the UB (IBUB) have studied the regeneration process of these animals and have identified how the modulation of the intercellular signaling pathway Wnt modifies chromatin, the set of genetic material that cells own in the cell nucleus. A few hours after an amputation, this mechanism lets the wound stem cells know the fate of the new tissue.

The study, published in the journal *Nature Communications*, involves researchers from the Andalusian Centre for Developmental Biology (CABD), the Pablo de Olavide University in Seville and the University of East Anglia (Norwich, England).

Genomic study

The incredible plasticity of planarians occurs due to the presence of a population of pluripotent adult stem cells, the neoblasts, which are capable of reproducing any type of cell in the organism. Right after an amputation, when new tissue has to be regenerated, there is a window of time in which everything is possible for these pluripotent cells, and depending on the signal the cells receive where the cut has taken place, the destination of destination of these cells is decided.

One of the first steps in this process is to specify the body axis, such as the anteroposterior axis, which defines the position of the head and tail.

To understand how this phenomenon occurs, researchers have carried out a genomic study of the cells located near the wound that takes place after the amputation of the head and tail. Using ATAC-seq and Chip-seq techniques, the researchers were able to analyze the regions of the genome that are accessible or inaccessible in these tissues at a given time, in this case, twelve hours after amputation.

"Only open regions are accessible to transcription factors, which are responsible for the expression of genes. Therefore, these studies allow us to know which set of genes is activated in wound cells twelve hours after the cut, and if they are different between the anterior and posterior part of the planaria," says Teresa Adell, lecturer at the Faculty of Biology and coordinator of the research study.

Inhibition or activation of the Wnt pathway to regenerate the head or the tail

The results reveal that twelve hours after the amputation, chromatin —the collection of genetic material that cells have within the nucleus—changes the conformation depending on whether cells near the wound detect that they need to regenerate a head or a tail. Moreover, they show that the change in chromatin composition, which regulates the cell's gene expression, depends on whether a cell signaling pathway—the Wnt pathway—is activated.

"If the head is needed, the Wnt pathway is inhibited; if the tail is needed, it is activated. Moreover, this change in chromatin composition occurs twelve hours after cutting; new tissue has not yet been made, but the cells already know what course to follow," the researcher points out.

Similarities and differences to other organisms

Understanding this regeneration in planarians is important for understanding this process in other organisms, since the molecular mechanisms that allow the correct regeneration of organs and tissues are evolutionarily conserved, i.e. they are very similar in all animals. In this sense, previous studies had already shown that the regulation of the Wnt pathway is responsible for specifying the anteroposterior axis in many organisms—including mammals—during the embryonic development

and also in adult animals' regeneration.

"Our study reveals the mechanism by which this is so in planarians, but also in other animals: the Wnt pathway specifies which genes are expressed and, therefore, the cell destination, since they regulate chromatin conformation from the first moment of regeneration," notes Teresa Adell.

Moreover, the findings of the study also highlight the differences with other animals. "Our study validates the idea that organisms as plastic as planarians have highly active intercellular signaling pathways, as if they were embryos, which means that any change of context can change the fate of the cells. This is unlike in mammals, for example, where cell plasticity is much more restricted," says the researcher.

Risks of cell reprogramming

In the case of humans and the possible future biomedical impact of this basic research, the researcher stresses that the implications "are not direct, but of concept": "In this study, we show that regenerative capacity is linked to the ability of cells to reprogram themselves to change their destiny. Therefore, one strategy to improve the regenerative capacity of humans could be to provoke cell reprogramming," says Teresa Adell.

In any case, the researcher is cautious about this strategy and warns that it could have undesirable effects, such as tumor transformation. "In animal models that do regenerate, it has been shown that the signals that must be activated to regenerate, such as the Wnt pathway, are also those that promote tumor processes when they are activated incorrectly. As it is often the case, nothing is absolutely good or bad, it depends on the context in which we find ourselves," she concludes.

All the results of the genomic analyses carried out during the study have

been integrated into the PlanExp open-access platform, with the aim of sharing the information and facilitating the analysis of the data for the scientific community.

More information: Eudald Pascual-Carreras et al, Wnt/β-catenin signalling is required for pole-specific chromatin remodeling during planarian regeneration, *Nature Communications* (2023). DOI: 10.1038/s41467-023-35937-y

Provided by University of Barcelona