First signalling pathway of the digestive lineage in planarians is described

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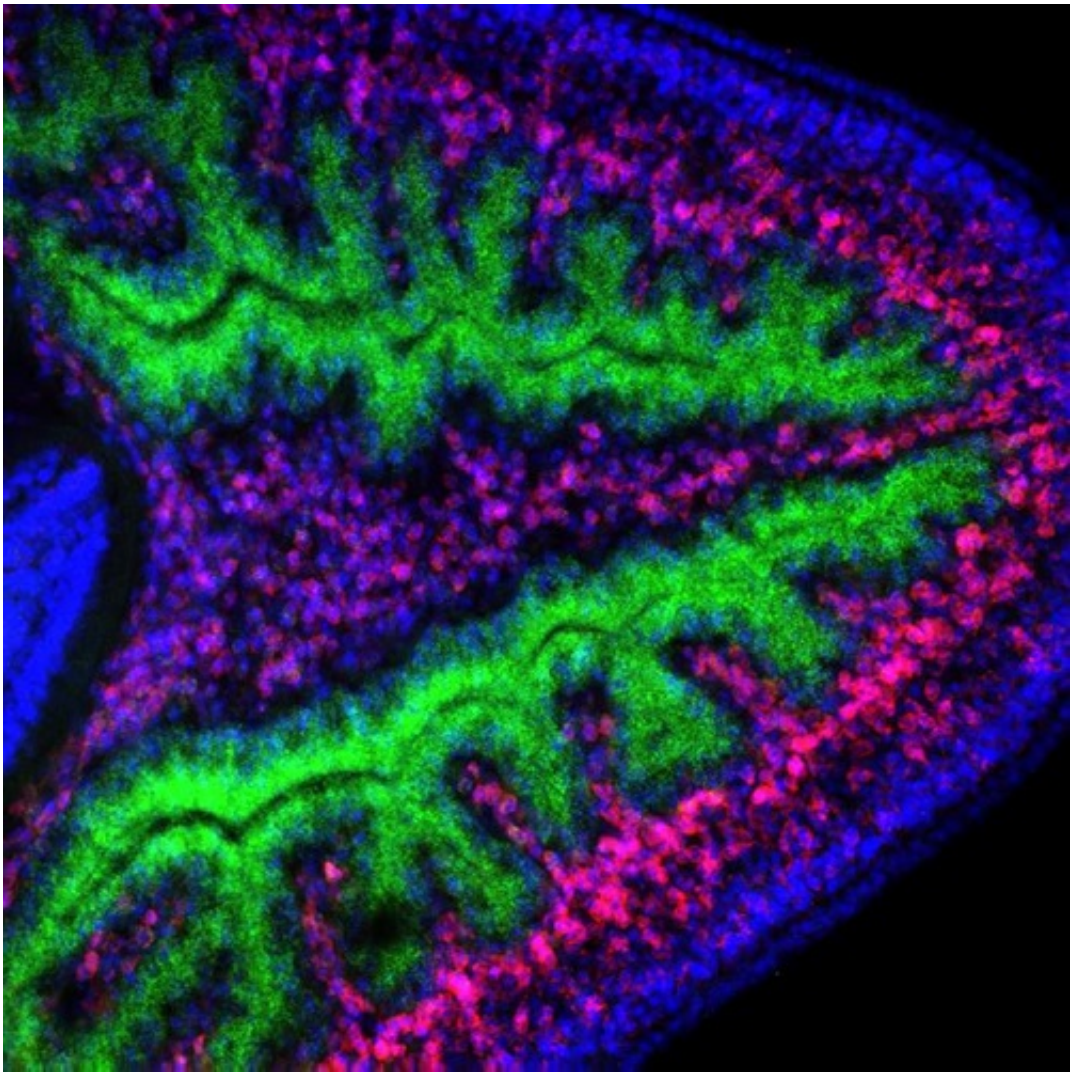

Labeling image of the planarian gut (green), neoblasts (pink), and cell nuclei (blue) digestive system.

A scientific study describes for the first time the function of a signalling pathway –particularly, the pathway of epidermal growth factor receptors (EGFR) - in the differentiation of the planarian digestive lineage. EGFR pathway, evolutionarily preserved, has a fundamental role when regulating the cell differentiation and proliferation in lots of organisms (such as mammals' neural stem cells) and it is over-activated in most of human cancers.

The article, published in an article of the distinguished magazine Development, is made by the researchers Francesc Cebrià, Sara Barberán and Susanna Fraguas, from the Department of Genetics, Microbiology and Statistics of the Institute of Biomedicine of the University of Barcelona (IBUB).

Studying the destiny of planarian adult stem cells

The planarian Schmidtea mediterranea is an invertebrate used as a model in studies for genetics of development and biomedical research. It shows a great regenerative ability, based on pluripotent adult stem cells –neoblasts- which are maintained over all the life cycle of the organism, and is an exceptional model to study the behaviour of these stem cells in vivo in regenerative processes of an animal using a small part of it. In regenerative medicine, research with planarians could promote the design of future therapies based on stem cell transplant or differentiated cells taken from stem cells in patients affected by neurodegenerative illnesses (Parkinson, Alzheimer, etc.), diabetes or cardiac pathologies.

According to Professor Francesc Cebrià, who directed this scientific project, "the neoblasts, which are the only cells with ability to be divided, are necessary for the renewal of cells that die in the physiologic usual renewal or tissue homeostasis. When we cut a planaria, neoblasts are equally needed to regenerate tissues and amputated organs".

"We still do not know how these progenitors end up differentiating from the several cell types" says Cebrià. "In most of the cases, we do not know the signalling pathways or genetic programs regulating this final differentiation of the different cell types coming from their progenitors. It is known from long ago that neoblasts are not a homogeneous cell population: some show specific transcription factors which derive to particular lineages. That means they are no longer pluripotent neoblasts but specialized progenitors: for example, progenitors shown by the transcription factors sim or coe, give place to particular neural types, and it has been postulated that progenitors expressing hnf4 or gata4/5/6 would give place to digestive cells".

EGFR pathway: revealing enigmas about cell differentiation

Since the discovery of the epidermal growth factors (EGF) in 1962, isolated by Stanley Cohen (Nobel Prize in Medicine 1986), the route of epidermal growth factor receptors (EGFR) has been linked to cell proliferation processes, cancer and designs for new oncology therapies. Previous planaria studies suggest that the EGFR pathway could regulate the differentiation of different cell types (pigment cells in eyes, pharynx, excretory cells or different neural types, etc.). However, there is still no definite evidence and there are lots of unanswered enigmas about the mechanisms of differentiation of different progenitor cells on specific cell types.

This is the first scientific study that shows the fundamental role of the EGFRs pathway in the final differentiation of a particular cell type: in this case, the digestive system cells. In order to have the results, the experts have combined RNA interference experiments to silence the function of genes and markers with ethinil-deoxyuridine (EdU) to know the final destiny of the cells coming from the neoblasts.

Until now the other projects had identified some genes which were important for the digestive system's regeneration. But according to Sara Barberán, main author of the study, "In those cases there was no determination of the level these genes were at". "In our case –she continues- it is shown for the first time that EGFR pathway is important to regenerate and keep the digestive system and it is absolutely necessary for the digestive system progenitor cells to differentiate from old digestive cells".

The University of Barcelona team has characterized the function of the Smed-egfr-1 gene in the planarian EGFRs pathway, which is made of 9 EGF type ligands and 6 receptors (EGFR). "What we have first verified –says Barberán- is that when the Smed-egfr-1 gene is silenced, the digestive system cells which die due to natural tissue renewal cannot be replaced by new cells, therefore, in a few weeks, the digestive system degenerates". This happens because progenitors of this lineage cannot be differentiated and are accumulated out of the digestive system. "The same happens during this tissue's regeneration" says the researcher.

Studying receptors and ligands in the EGFR pathway

Apart from characterizing the function of the Smed-egfr-1 gene, the experts could also determine that Smed-nrg-1 could be the ligand that eases the differentiation of the digestive system progenitors. According Barberán, "it is known that Smed-nrg-1 shows the homology with other organisms' EGF ligands. Prominently, when we make RNAi experiments to silence the Smed-nrg-1 gene, we see that planaria have the same defects than when we silence the Smed-egfr-1 gene. That means, planaria cannot regenerate nor maintain the digestive system and that happens because the progenitors cannot completely differentiate and they amass in the parenchyma out of the digestive system" say the authors.

The new study by the UB and IBUB experts is important to verify the role of the Smed-egfr-1 receptor and the probable Smed-nrg-1 ligand in the differentiation of the digestive system progenitors. "But in planaria, the EGFR pathway consists of 9 ligands and 6 receptors. Therefore we now have to see if the other receptors and ligands have a role too in differentiation of other progenitor cell populations" researchers say. That is why they are studying the Smed-egfr-3 receptor, which is expressed in the central nervous system, to see if it has a role in the progenitor cells differentiation of the different neural populations of these animals. If it was so, they could conclude that EGFR pathway can have a general function as an intermediary of the planarian cell differentiation.

More information: Sara Barberán et al. The EGFR signaling pathway controls gut progenitor differentiation during planarian regeneration and homeostasis, *Development* (2016). DOI: 10.1242/dev.131995

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