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PRESS RELEASE

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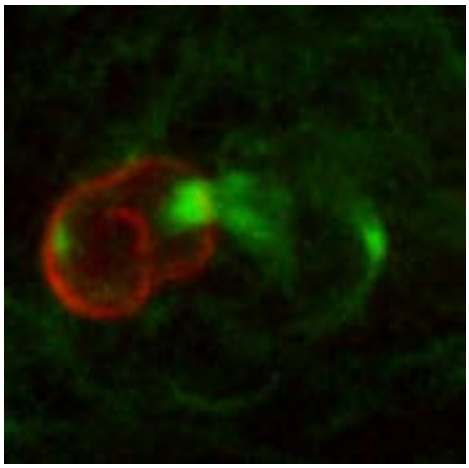
It's all about polarity

Researchers discover a mechanism behind asymmetric cell division

The concept of sharing is a basic social principle that most of us are taught from an early age on. In general, we are told to share equally with each other. Sharing is also a concept that applies to cells; they need to share information during cell division to function properly. But in the case of cells, the exchange of information does not always have to be equal. During asymmetric cell division, so-called endosomes, vesicles that store signalling molecules, only go to one daughter cell. Researchers from the University of Geneva (UNIGE) had discovered this already a few years ago, but they did not know the mechanism behind this unequal sharing. But now the team of Professor Marcos Gonzalez-Gaitan was able to shed light on how endosomes know to which cell to go to and how they physically do it. The results, which can further aid to understand the development of tumors, now appear in the journal Nature.

In living cells, information is encoded in signalling molecules that determine their fate. This "software" instructs cells what to do. During cell division, this information is handled in two different ways: symmetrically or asymmetrically. During symmetric division, the information inside the mother cell is passed on equally to the two daughter cells. During asymmetric division, the two daughter cells are different from each other. For instance, in the case of stem cells, one of the daughter cells is a carbon copy of the mother cell and becomes another stem cell, while the other daughter has a different fate and becomes specialised to perform a function in the organ.

The group of Marcos Gonzalez-Gaitan from the Department of Biochemistry at the Faculty of Science at UNIGE has now reported a mechanism that explains how asymmetric division could work. Their study, which was supported by an ERC grant and the NCCR Chemical Biology, showed that no matter what kind of division, a scaffold structure inside the cell, the so-called central spindle, plays an important role for the dispatch of this signalling information. This scaffold is made up of so-called microtubules, tiny rigid rods that converge in the middle of the cell. Microtubules possess a plus and a minus pole, with the plus pole pointing towards the centre. Endosomes, the small vesicles that store the signalling information, use these microtubules as transportation routes, they move along them like on a one-way street. The "motor" for this molecular vehicle is a protein called Klp98A. Since the plus poles act as a direction marker, the endosomes move towards the centre of the cell.



Light microscopy image of an asymmetric central spindle. Microtubules (labelled in green) are more enriched on the left side of the central spindle (cell cortex labelled in red).
© Emmanuel Derivery

Asymmetric spindle means asymmetric distribution

Two more proteins are at work on the microtubules, and those two are causing an asymmetry of the central spindle. The depolymerising protein Klp10A chops the microtubules from their minus ends. Patronin, on the other hand, covers the minus ends and stops Klp10A from chopping microtubules. Patronin is more abundant in one side of the asymmetrically dividing cell and, therefore, minus-end chopping of microtubules is counteracted in that side of the cell. As a consequence, this side will have more microtubules. This layout can be compared to a two-way highway with more lanes going

in one direction than the opposite. If a driver enters the highway randomly, he will more likely end up at the destination where more lanes are going to.

For the cell, this asymmetry means that more microtubules point towards one daughter cell rather than towards the other, and in turn, this polarizes endosome motility because the "car engine" Klp98A moves the endosomes towards this cell. The researchers wondered if it was possible to invert this process. And they did indeed achieve this with the help of so-called nanobodies. With these tiny, very simple antibodies, they trapped away Patronin from the side of the cell where it was normally in abundance and suddenly more microtubules pointed towards the other cell. This inverted spindle sent the endosomes in the opposite, wrong direction. Like this, the scientists were like roadmen who changed the number of lanes in one of the directions of the highway. «This gave us the proof that endosomes can be indeed fooled as we were able to sent them in the wrong direction», says Emmanuel Derivery, first author of the study. "It means that it's really the polarity of the spindle that orchestrates the polarity of the endosomes."

In order to be able to analyse a multitude of different cells, the researchers developed their own software. This lets the computer measure by itself things like spindle size and velocity of the endosome movement on the microtubules, all based on movies of the process made with a spinning-disc confocal microscope. «By doing so, we can analyse thousands of tracks at once", explains Marcos Gonzalez-Gaitan. Furthermore, the researchers could show that this mechanism of asymmetric distribution works exactly the same in different cells including neural stem cells and intestinal stem cells in flies, as well as neural precursors of the spinal cord in zebrafish. "This gives us a pretty good concept of what goes on in an archetypical average cell during asymmetric cell division, and we obtain this information in a totally unbiased way because the computer does it», he adds.

Marcos Gonzalez-Gaitan is certain that these findings can also have an impact for cancer research. "If asymmetric cell division of stem cells does not work properly, proliferation in organs such as the intestine or the skin does not proceed to gradually replenish dead cells, but exponentially. And this uncontrolled growth may ultimately cause a tumor", explains the cell biologist. It is therefore vital to understand the molecular mechanisms and the physics of asymmetric cell division.

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