UNIVERSITÉ DE GENÈVE

Frontiers in Genetics
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CHEMICAL BIOLOGY
VISUALISATION AND CONTROL
OF BIOLOGICAL PROCESSES USING CHEMISTRY

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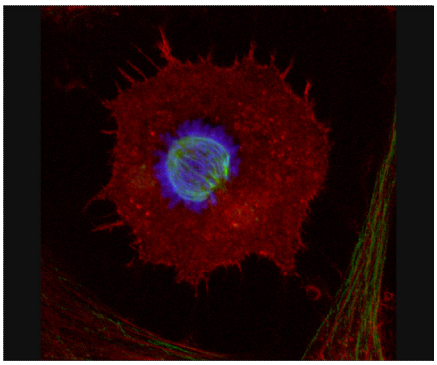
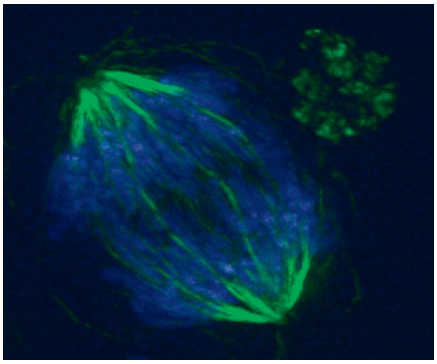
THE ROLE OF THE CELLULAR ENTRY POINT OF ANTHRAX IDENTIFIED

Researchers at the University of Geneva, Switzerland, demonstrate that the receptors that bind the toxin of this bacterium control how cell division is oriented.



Cell division: the chromosomes (blue) migrate along the mitotic spindle (yellow) to opposite poles, before separating into two daughter cells. Image: Christophe Bauer



Detail of the mitotic spindle. Image: Christophe Bauer

Anthrax uses a receptor on the surface of cells to inject its lethal toxins. However, the physiological function of this receptor, named Anthrax Toxin Receptor 2a (Antxr2a), remained unknown until now. A team led by Marcos Gonzalez-Gaitan, a professor at the University of Geneva (UNIGE), Switzerland, in collaboration with Gisou van der Goot at EPFL (École Polytechnique Fédérale de Lausanne), reveals that Antxr2a actually plays a role in embryonic development, orienting cell division along a specific plane, which is a prelude to the formation of future tissues and organs. At the cellular level, this receptor exerts traction on the system that allows chromosomes to separate to opposite poles, the mitotic spindle, to position it along the plane of division. These results are presented in the journal *Nature Cell Biology*.

Anthrax is a particularly virulent germ once a person is infected by inhaling its spores. The severity of symptoms, which affect various organs, is mainly due to bacterial toxins which are lethal to cells. It is by attempting to understand how the bacillus' toxins enter cells that the Antxr2a receptor was discovered. Otherwise, its physiological role would not have been identified at present.

A cap of proteins indicates the plane of division

During animal development, the orientation of cell division along a specific plane is important for the organization of the different tissues and the generation of cellular diversity. This orientation is provided by the position of the mitotic spindle in the cell that is about to divide. This temporary assembly of microtubules forms an actual spindle between opposite poles of the cell in order to guide the migration of each set of chromosomes.

"When the cell receives an external signal to initiate its division, a cascade of biochemical events is launched to transmit the message to the interior of the cell and have it carried out. We knew that an external signal, a protein called Wnt, was necessary to properly position the mitotic spindle, but knew nothing of the intracellular messengers involved," explains Marcos Gonzalez-Gaitan, Professor in the Departments of Biochemistry and Molecular Biology at the University of Geneva.

This has now been accomplished. The scientist and his group have established the complete sequence of intracellular events allowing the mitotic spindle to align itself along the general plane of division. They conducted their experiments on zebrafish embryos, a model system in developmental studies. "Once Wnt binds to the cell membrane, different molecular agents prompt the formation of a layer of filamen-

tous proteins along the cell membrane, at the site of the future plane of division," explains Irinka Castanon, first author of the article.

The anthrax receptor used as a control lever

This internal 'cap' associates itself in turn with the Antxr2a receptors, known to bind the anthrax toxin. The accumulation of these receptors will thus form a second layer, superimposed on the first. Everything is now in place for the final phase: "The Antxr2a receptors recruit in turn 'motor' proteins capable of attaching themselves to the mitotic spindle and pulling it towards the internal cap," states Marcos Gonzalez-Gaitan. Motor proteins probably act by travelling back up along the cap's filaments, allowing the alignment of the spindle with the plane of cell division.

In mammals, the Antxr2a receptor is also involved in the formation and proliferation of blood vessels. "It is therefore possible that the role of this receptor in the orientation of cell division is not restricted solely to embryonic development," states the professor, who is a member of two Swiss National Research Programs: *Frontiers in Genetics*, and *Chemical Biology*.

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