Scientists uncover how hormones achieve their effects

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New insights into the cellular signal chain through which pheromones stimulate mating in yeast have been gained by scientists at the European Molecular Biology Laboratory (EMBL).

Similar signal chains are found in humans, where they are involved in many important processes such as the differentiation of nerve cells and the development of cancer. A sophisticated microscopy technique allowed the researchers to observe for the first time the interplay of signalling molecules in living yeast cells, and to work out how they pass on a signal through the cell. The results are published in the current issue of *Nature Cell Biology*.

Upon release of a pheromone – a chemical signal stimulating mating behaviour - by a nearby cell, yeast cells form a projection that serves as a mating organ and brings about the fusion of two cells. The pheromone binds to a receptor on the cell's exterior – in the same way as many growth hormones in humans do – which then sets off a signalling chain inside the cell. This chain consists of a series of proteins called MAP kinases, which pass on the signal by interacting with each other and activating the next downstream member of the chain by adding on phosphate residues. At the end of the chain are those molecules that bring about the changes that underpin the formation of the mating organ and the fusion of the cells.

Scientists in the groups of Michael Knop and Philippe Bastiaens at EMBL labelled members of the MAP kinase signalling chain with

fluorescent molecules and observed their diffusion and interaction in living yeast cells stimulated with pheromones using a novel microscopic approach that does not disturb the natural state of the cell.

“Our method is so precise that we could virtually count the molecules and the interactions between chain components,” says Knop. “To our surprise, the observed proteins in the cell’s interior did not interact more after stimulation by the pheromone. This means changes in interaction are not the way by which the signal is transmitted through the interior of the cell.”

Knop and his team revealed that the actual signal is not produced uniformly throughout the cell but only by the few chain components found in the mating projection. They activate a protein called Fus3, which diffuses into the centre of the cell to spread the signal. While travelling, however, Fus3 is constantly inactivated by proteins found in the interior of the cell.

“We found that the concentration of Fus3 activity is very high at the tip of the developing mating organ and then gradually gets less towards the centre of the cell,” says Celine Maeder, who carried out the research in Knop’s lab. “This sets up a gradient of Fus3 activity, which might allow the signal to have different effects in different parts of the cell.”

“This result is exciting,” concludes former EMBL group leader Philippe Bastiaens, who now is a director at the Max Planck Institute of Molecular Physiology. “It revolutionizes our understanding of signalling processes and the way we need to study them.” The MAP kinase signalling chain is conserved across species, and the insights gained in yeast contribute to a better understanding of a pathway also relevant to human biology and disease.

Source: European Molecular Biology Laboratory