RÉPUBLIQUE FRANÇAISE
Liberté Égalité Fraternité

INRAE

IMAGO

EXPLORATORY PROJECT

2022-2024

Exploring the function of hormone receptor signalling pathways in mammals

Coordination

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Key words

GPCR
Cell signalling
Intracellular imaging
Dynamic model
Complex system

INRAE units involved

PRC
MaIAGE

Partnerships

Inria
Imperial College London

Context and challenges

G protein-coupled receptors (GPCRs) play a key role in cellular communication in mammals. Among these, the membrane receptors for the gonadotropic hormones - luteinizing hormone (RLHCG) and follicle stimulating hormone (FSH) - are essential for reproduction.

The binding of each hormone to its receptor ultimately results in an adapted biological response through the transduction of several intracellular signalling pathways. These signalling pathways are relatively well described individually, but their organisation into networks is complex. Indeed, the biochemical reactions that make up these pathways are difficult to capture, as they are not only kinetically regulated, but also constrained in intracellular space. To date, the dynamics of signalling pathways are only described in a simplified manner: their interactions, spatial-temporal organisation and the intensity of signals remain poorly accessible simultaneously.

In order to understand how the cell decodes this complexity of intracellular signals and then produces graduated physiological regulations, it is essential to have a detailed analysis of the dynamics of the signalling networks and their organisation. That is where the IMAGO project comes in. It proposes to build models of the spatio-temporal organisation of signalling pathways associated with gonadotropin receptors.

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Métaprogramme
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Goals

The IMAGO project proposes to explore the complexity of the spatial-temporal organisation of signalling pathways and to develop dynamic models to understand their functioning at the cellular and molecular levels.

Firstly, the project plans to interrogate several distinct signalling pathways (cAMP, PKA, ERK and Ca2+) simultaneously, using fluorescence microscopy and biosensor approaches selectively addressed in various cellular compartments (e.g. nucleus, mitochondria, plasma membrane, endosomes, endoplasmic reticulum, etc.). The objective is to reveal the mechanisms of localisation of signalling pathways according to the site of activation of the receptor, the kinetics of activation and the spatial-temporal dynamics of biochemical reactions.

To do this, the IMAGO project will rely on the generation of data from biosensors of signalling pathways and fluorescence microscopy approaches.

These data will allow the following:

1. To perform a quantitative multiplexed analysis of the compartmentalisation of different signalling pathways and receptor trafficking
2. To develop a dynamic model of the signalling networks and receptor traffic

In the long term, this research into receptors of interest in reproductive physiology could lead to a review of traditional pharmacological approaches, which essentially target receptors located at the plasma membrane. This project will also provide new knowledge to the signalling network community.

Research units involved and partnerships

INRAE scientific division	INRAE research units	Expertises
Animal physiology and livestock systems	PRC	Quantitative cell imaging, real-time signalling, design and analysis of spatial-temporal models, deterministic and stochastic modelling
Mathematics, computer and data sciences, digital technologies	MaIAGE	Dynamic modelling (EDO, EDP), data analysis and estimation
External partners		**Expertises**
Inria	Équipe projet SERPICO	Microscopy image processing for intracellular transport analysis
	Équipe projet MUSCA	Dynamic modelling, endocrinology
Imperial College London		Traffic analysis and recycling of RLHCG and RFSH