Internship offer for Master Biology students

Role of ZYG-8 and microtubule stiffness in a faithful cell division.

This internship offer is for Master students (or equivalent), who have trainings in cellular and molecular biology and ideally some basic knowledge in microscopy.
The project aims to understand the **role of ZYG-8 and microtubule stiffness in a faithful cell division**, using the nematode *Caenorhabditis elegans* as a model organism.
The internship will be carried out within the Rennes Institute of Genetics and Development (IGDR, Univ. Rennes 1, UMR-CNRS 6290), and more specifically in the CeDRE team "Reverse Engineering of the Cell Division".

Host team research project:

Our team – which has the peculiarity of being an **interdisciplinary team** made up of specialists in biology, physics, image analysis and statistics – studies cell division using a biophysical approach. For this, we use the first division of the *C. elegans* one-cell embryo, which is an asymmetric, very dynamic and reproducible division. We aim to **understand the robustness of cell division** by studying and modeling the biophysical and mechanical interactions between the molecular actors of mitosis, which are microtubules and their regulators, as well as the molecular motors.

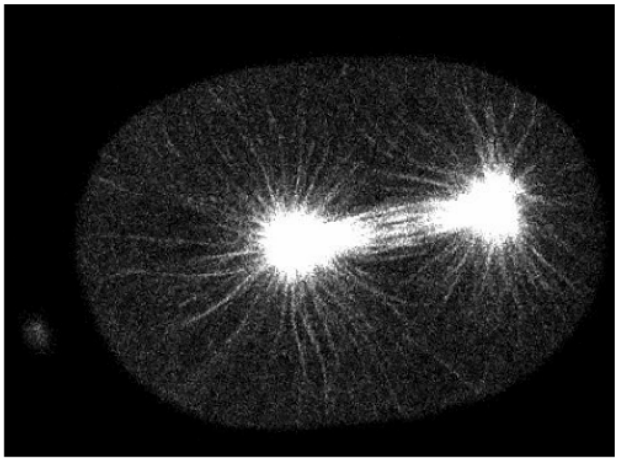

Figure 1: C. elegans embryo with fluorescent labelling of the microtubules.

Context of the study:

The proteins of the **double-cortin (DCX) family**, including DCLK1 (doublecortin-like kinase 1) that contains two DCX domains, **appear to be overexpressed in many solid tumors** (eg colorectal, pancreatic, renal and breast cancers). The high expression of this protein correlates with a poor prognosis in patients with these cancers.

The **mechanisms by which the DCLK1 protein is involved are still unclear**. **This protein associates with microtubules** through its DCX domain. DCLK1 could, among other roles, stiffen microtubules. In the nematode *Caenorhabditis elegans*, an established model of cell division, ZYG-8 is the only ortholog for DCLK1 and DCLK2. In particular, it allows the grouping of microtubules into bundles in neuronal cells, thus regulating their rigidity. In addition, during the first embryonic division, the positioning and orientation of the mitotic spindle are disturbed in *zyg-8* mutants.

We hypothesize that the deregulation of DCLK1, observed in solid tumors, affects the rigidity of microtubules, disrupting the proper course of cell division. Indeed, microtubules are key players there, both for the positioning of the mitotic spindle and for the segregation of the chromosomes. Defects in any of these stages of division can lead to aneuploidy, a major mechanism of carcinogenesis.

Using the nematode *C. elegans* as an *in vivo* laboratory to study the role of ZYG-8^{DCLK1}, we will ask how the suppression or overexpression of ZYG-8 disrupts cell division. The study of the positioning of the spindle will inform us in particular about an impact of the proliferation/differentiation balance and will serve as a basis for understanding the effects on the mitotic spindle. The unicellular *C. elegans* embryo appears as a good model organism with its asymmetric division, which is very stereotypical and lasts only 15 minutes.

Aim:

The objective of the internship is to reveal the consequences of the suppression or overexpression of ZYG-8^{DCLK1} during the first division of the *C. elegans* embryo. To do this, we will study the positioning of the mitotic spindle, its mechanics and chromosome segregation (i) in the context of *zyg-8(RNAi)* of the *C. elegans* nematode and (ii) in a *C. elegans* strain overexpressing ZYG-8. We will use biophysical tools developed by the team, which will allow us to reveal new phenotypes linked to the suppression or overexpression of ZYG-8^{DCLK1}.

Tasks to be carried out:

During his/her internship, the student will perform four major tasks:

(1) **Acquisition of movies** of embryos during the first cell division **by fluorescence microscopy** (realised at the periphery of the cells to visualize the contacts of the microtubules, at the median plane to visualize the poles of the spindle, or with double fluorescent labelling for visualizing the chromosomes and the microtubules/centrosomes),

(2) **Depletion of ZYG-8 by a targeted approach** (interfering RNA),

(3) **Analysis of microscopy images and data** obtained using tools developed within the host team to characterize the mitotic spindle positioning (DiLiPop tool, Bouvrais et al., 2021), its mechanical behaviour (tool S3, Mercat et al., 2016), and chromosome segregation.

This internship will allow the student to acquire skills in breeding, dissection and taking images on living samples (*C. elegans* nematode), in fluorescence microscopy (spinning disc microscopy, wide-field microscopy), in cell biology, in image and data analysis, and to improve English and teamwork skills.

Contact:

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