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 artificial intelligence – 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.

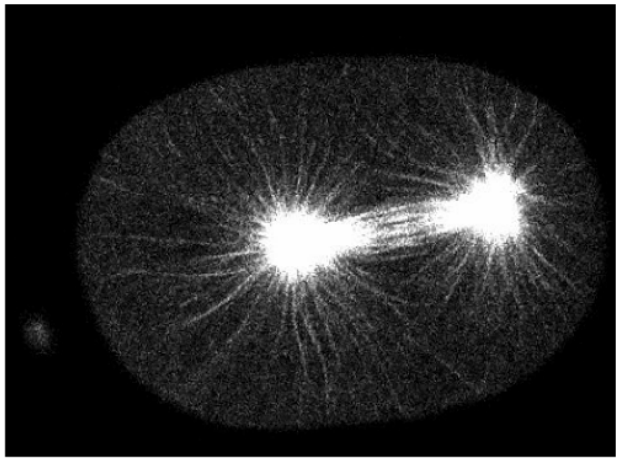

Figure 1: C. elegans embryo with fluorescent labelling of the microtubules.

Context of the study:

The protein DCLK1 (doublecortin-like kinase 1) of the doublecortin family (DCX) **appears to be overexpressed in many solid tumours** (e.g. 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 and could, among other roles, regulate microtubule dynamics and stiffen the microtubules**. Indeed, DCX bind at the interface of 4 tubulin dimers, likely preventing the sliding of the microtubule protofilaments. 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.
While the role of microtubule dynamics in cell division, especially via end-binding proteins, has been intensively studied, we lack knowledge about the role of microtubule mechanics and its regulation in the cell division context.

We hypothesize that the deregulation of DCLK1, observed in solid tumours, 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.

Recent work realised by our team using the *C. elegans* embryo revealed that the mitotic spindle length during metaphase and the centrosome-oscillation frequency during anaphase are disturbed upon the

partial depletion of ZYG-8. These observations complement the defects in mitotic spindle positioning observed in *zyg-8* mutants [1].

Aim:

The objective of the internship is to understand how ZYG-8^{DCLK1} participates to a faithful cell division, by studying its implication in the regulation of microtubule dynamics and rigidity.

For that, we will use the **nematode *C. elegans* as an *in vivo* laboratory to study the role of ZYG-8^{DCLK1}**, by performing *zyg-8(RNAi)* treatments, or by using *zyg-8* mutants to target the different ZYG-8 functional domains, or using a *C. elegans* strain overexpressing ZYG-8.

We will quantify the possible changes in the mitosis mechanics and the cortical forces thanks to two biophysical tools developed by the team [2,3]. We will also study microtubule dynamics using existing approaches [4], and the microtubule rigidity using a tool based on artificial intelligence currently under development in the team.

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,

(4) **Experimental validations** of the approaches and the tools used in the present study.

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 and molecular biology, in image and data analysis. Besides, he/she will improve his/her English and teamwork skills.

Contact:

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Bibliographic references:

1- Gonczy P. et al. (2001). Developmental Cell, 1 (3) : 363- 376.
2- Bouvrais H., et al. (2021). EMBO reports, *22 (5)* : e50770.
3- Mercat B., Thèse à l'université de Rennes 1 (2016). Analyse temps-fréquence en mécanique cellulaire et adaptabilité du fuseau mitotique.
4- Srayko M. et al. (2005). Developmental Cell, 9 (2) : 223-226.