Master Biologie Moléculaire et Cellulaire 'BMC',
Université de Paris - *UFR Sciences du Vivant*

Parcours : **Biologie et Développement Cellulaires 'BDC'**
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Fiche de Projet de Stage M2, Année 2020-2021

Unité INSERM ou CNRS ou Université : Sorbonne-université -Institut de Biologie Paris Seine - Laboratoire de Biologie du développement – UMR7622 **Intitulé Equipe :** Cycle et Détermination Celluaires **ED d'appartenance :** CDV **Responsable de l'Equipe :** Michel Gho	**Responsable du Stage :** Agnes Audibert **Adresse** : SU – IBPS -UMR7622 9 quai Saint Bernard 75005 Paris **Email** : agnes.audibert@sorbonne-universite.fr **Tel** : 0144272249

Titre du projet : Is nucleus submitted to cell polarity?

Cell polarity is defined by the asymmetry of the cells, either in their shape, or organization of cellular components. As such in epithelial cells, polarity along the apico/basal axis and relative to the epithelium plane handles the cells organization in the tissue[1,2]. Cell polarization depends on extracellular biochemical and mechanical cues received by cells. These signals trigger polarization of the plasma membrane, drive cytoskeleton and cytoplasm reorganization[3]. A related question still unresolved is: is the nucleus also polarized and if so, whether this polarity is driven by the cytoplasmic polarity?

In the laboratory, we have made an original observation suggesting a polarization of the nucleus. Indeed, analyzing the spatio-temporal dynamics of the HP1 protein in epithelial cells, we observed that it is located preferentially on the anterior pole of nuclei. HP1 protein recognizes the histone mark H3K9me2/3 associated with constitutive heterochromatin that it is gene poor and enriched in repeated sequences (satellites) and transposable elements. Constitutive heterochromatin participates to spatial chromatin arrangement and is regulated during development[4,5]. Moreover, a change in heterochromatin organization is associated with a nuclear reorganization of HP1 in cancer cells[6]. That HP1 compacted in a patch oriented on the anterior pole of the nucleus of epithelial cells of the *drosophila* dorsal epithelium (notum) is an original, very interesting and promising observation. As such, this localization probably reveals a new mode of heterochromatin organization in link with the cell type and their fate.

In this context, we ask several questions: how is heterochromatin localized? Whether the planar cell polarity, which controls notum tissue polarity, is involved in this localization? and what is the physiological relevance of this localization?

In order to answer these questions, i*n vivo* approach allowing to follow heterochromatin dynamics will be carried out by tracking fluorescently labelled heterochromatin binding proteins (HP1, D1, ADD1, Prod etc.)[5] as well as by direct visualization of heterochromatic sequences (TALE-light construct[7]). Moreover, the impact of the planar cell polarity on heterochromatin orientation as well as the role of proteins linking the nucleoplasm to the cytoplasm will be analysed using mutants (heterozygote or heteroallelic combinations) or RNAi lines directed against these factors (such as Fz and Dsh for planar cell polarity analysis[8] and klarsicht and klaroid, two proteins of the LINC complex[9] involved in the relationship between nucleoskeleton and cytoskeleton). In parallel, we propose to study how the cytoskeleton is implied to the nuclear heterochromatin organization. To this aim, heterochromatin organization will be studied under mutants or drugs conditions affecting specifically either microtubules or actin filaments. Drugs will be injected directly into the organism or added to tissue culture using protocols currently used in the laboratory. To carry out his project, the student will use approaches from genetics and cell biology. He/she will thus participate in the more general project concerning the impact of the dynamics of constitutive heterochromatin on development.

1. Goodrich, L. V & Strutt, D. Principles of planar polarity in animal development. *Development* **1892**, 1877–1892 (2011).
2. Simons, M. & Mlodzik, M. Planar Cell Polarity Signaling: From Fly Development to Human Disease. *Annu. Rev. Genet.* **42**, 517–540 (2008).
3. Assémat, E., et al. Polarity complex proteins. *Biochimica et Biophysica Acta* **1778**, 614–630 (2008).

4. Janssen, A., Colmenares, S. U. & Karpen, G. H. Heterochromatin: Guardian of the Genome. *Annual Review of Cell and Developmental Biology* **34**, 265–288 (2018).
5. Swenson, J. M., et al. The composition and organization of Drosophila heterochromatin are heterogeneous and dynamic. *eLife*-1–37 (2016).
6. Gurrion, C., Uriostegui, M. & Zurita, M. Heterochromatin Reduction Correlates with the Increase of the KDM4B and KDM6A Demethylases and the Expression of Pericentromeric DNA during the Acquisition of a Transformed Phenotype. *J. Cancer* **8**, 2866–2875 (2017).
7. Yuan, K. & Farrell, P. TALE-light imaging reveals maternally emergence of functional heterochromatin in Drosophila embryos. 579–593 (2016).

Publications de l'équipe relatives au projet de stage (max 5)

- Cortical Cyclin A controls spindle orientation during asymmetric cell divisions in Drosophila. (2022) Darnat P, Burg A, Sallé J, Lacoste J, Louvet-Vallée S, Gho M, Audibert A. Nat Commun. 2022 May 17;13(1):2723. doi: 10.1038/s41467-022-30182-1.

- A neural progenitor mitotic wave is required for asynchronous axon outgrowth and morphology. Lacoste J, Soula H, Burg A, Audibert A, Darnat P, Gho M, Louvet-Vallée S. Elife. 2022 Mar 7;11:e75746. doi: 10.7554/eLife.75746.

- Simon F, Ramat A, Louvet-Vallée S, Lacoste J, Burg A, Audibert A*, Gho M*. (2019) Shaping of Drosophila Neural Cell Lineages Through Coordination of Cell Proliferation and Cell Fate by the BTB-ZF Transcription Factor Tramtrack-69. Genetics. Jul; 212(3):773-788. * These authors contributed equally to this work

- Ramat A, Audibert A, Louvet-Vallée S, Simon F, Fichelson P, Gho M. (2016). Escargot and Scratch regulate neural commitment by antagonizing Notch activity in Drosophila sensory organs. Development. 143(16):3024-34.

- Ayeni JO*, Audibert A*, Fichelson P, Srayko M, Gho M, Campbell SD. (2016) G2 phase arrest prevents bristle progenitor self-renewal and synchronizes cell division with cell fate differentiation. Development. 143(7):1160-9. These authors contributed equally to this work