



Internship proposal – 2026-2027

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Thesis possibility after internship: YES

Funding: ED 564 competition

Nuclear mechanics and cancer cell invasion

Context

In order to form metastases, cancer cells must migrate through a confined environment consisting of other cells and the extracellular matrix (ECM). The nucleus, which is the cell's largest and most rigid organelle, likely plays a limiting role in migration through such confined environments (1). A less rigid nucleus should therefore confer an advantage on a cancer cell seeking to invade surrounding tissues. Nuclear rigidity is determined by both chromatin and the lamina, intermediate filament proteins present in the nuclear envelope (2). Within the nucleus, chromatin adopts specific positions relative to the nuclear periphery, with a dense layer of rigid heterochromatin located beneath the nuclear lamina (3). These lamina-associated heterochromatin domains (LADs) are characterised by low gene density, a high content of repetitive DNA sequences and an enrichment of repressive histone modifications, notably trimethylated histone H3 at lysine 9 (H3K9me3), induced by the lysine methyltransferases (KMTs) SETDB1 and SUV39H, forming a dense layer of rigid heterochromatin associated with the lamina, which strongly influences nuclear rigidity (4). Our collaborators have shown that, in the A549 lung cancer epithelial cell model, altering the balance between SETDB1 and SUV39H1 leads to modulation of H3K9me3 levels at LADs, and we have measured that this affects both cell migration ability and nuclear mechanics (5).

Objectives

The objective of the project is to understand the role of the cytoskeleton, and more precisely of the coupling between the cytoskeleton and the nucleus, in the motility of cancer cells in confined environments and on the rigidity of their nuclei.

We characterize on the one hand the *in vitro* migration capacity of cells by using the lens-free Cytonote device (Iprasense), which enables fast and efficient reconstruction of the phase images of migrating cells over a large field of view (7) and on the other hand the mechanical properties of their nucleus, by using an experimental set-up based on optical tweezers (see Figure, A) (8)

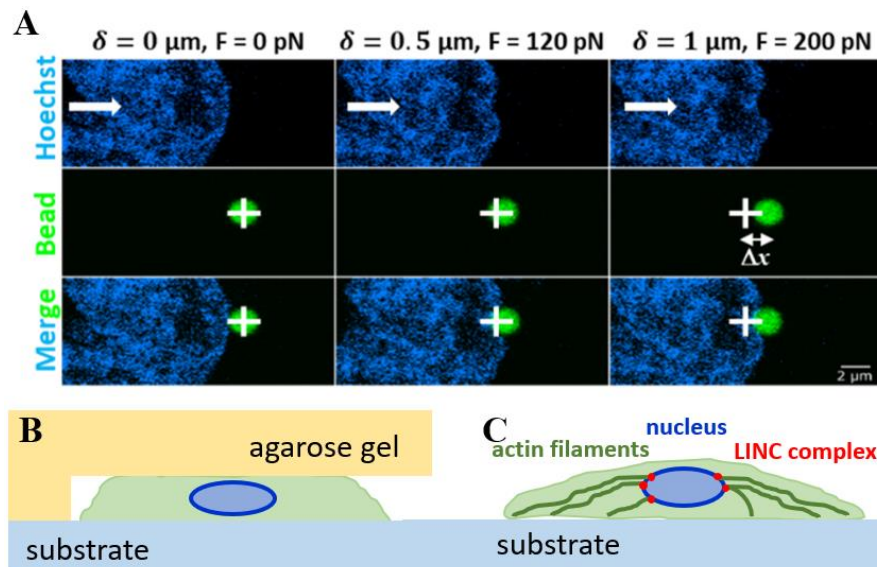


Figure: A. Measurement of the stiffness of a living cell's nucleus by indentation. The white cross represents the centre of the optical tweezers, within which a 2 μm diameter bead (green) is trapped. The nucleus (blue) undergoes indentation when the cell is moved to the right (white arrow), which displaces the bead from the centre of the trap by a distance Δx , from which the applied force is deduced. **B.** A cell confined by a gel. **C.** The LINC complex links the nucleus to the cell's cytoskeleton.

We have already characterised the migration abilities on flat surfaces of the various cell lines developed by our collaborators, which express different levels of H3K9me3, as well as the rigidity of their nuclei. We have shown that a low level of H3K9me3 is indeed correlated with greater mobility and a more flexible nucleus.

The aim now is to characterise cell motility in confined environments, which more closely resemble physiological conditions. To do this, we will use microfabricated substrates in which the volume available for cell movement is controlled (see Figure B).

We will then investigate the role of the connection between the cytoskeleton and the nucleus in cell motility and in the mechanical properties of their nuclei. This mechanical link is mediated by the LINC complex (linker of nucleoskeleton and cytoskeleton) (see Figure C) and can be disrupted, for example, by depleting certain proteins within the LINC complex. This is what our collaborators have achieved, and we will use their cellular models to address these questions.

References

1. McGregor, A. L., Hsia, C.-R. & Lammerding, J. Squish and squeeze-the nucleus as a physical barrier during migration in confined environments. *Curr Opin Cell Biol* 40, 32–40 (2016)
2. Stephens, A. D., Banigan, E. J. & Marko, J. F. Separate roles for chromatin and lamins in nuclear mechanics. *Nucleus* 9, 119–124 (2018).
3. van Steensel, B. & Belmont, A. S. Lamina-Associated Domains: Links with Chromosome Architecture, Heterochromatin, and Gene Repression. *Cell* 169, 780–791 (2017)
4. Stephens, A. D. et al. Chromatin histone modifications and rigidity affect nuclear morphology independent of lamins. *Mol Biol Cell* 29, 220–233 (2018)
5. Zakharova, V. V. et al. SETDB1 fuels the lung cancer phenotype by modulating epigenome, 3D genome organization and chromatin mechanical properties. *Nucleic Acids Res* 50, 4389–4413 (2022)
6. Comunian, S, et al. Epigenetic control of nuclear mechanics and cellular migration via histone H3 lysine 9 methylation at Lamina-Associated Domains. [bioRxiv](https://doi.org/10.1101/2025.01.15.634111) (2025)
7. Allier, C. et al. Imaging of dense cell cultures by multiwavelength lens-free video microscopy. *Cytometry Part A* 91, 433–442 (2017).
8. Alibert, C. et al. Multiscale rheology of glioma cells. *Biomaterials* 275, 120903 (2021)