Proposition de stage de M2/Thèse
2023-2024

Nuclear mechanics as a diagnostic and therapeutic target for glioblastoma

Glioblastomas (GBMs) are the most lethal primary brain tumours. The absence of effective therapies is mainly due to tumour invasion and to the resistance of invading cells to treatments such as radio- and chemo-therapies. In GBMs, lamin proteins that control **nuclear envelope stiffness**, have recently emerged as potential markers of aggressiveness and tumourigenicity. Nuclear mechanics has appeared as a key determinant of cancer cell invasion leading us to hypothesize that **genes controlling nuclear mechanics** of GBM cells may be used as **diagnostic tools** and potential **therapeutic targets** to improve the prognostic of GBMs.

The working hypotheses of this M2 internship project is that alterations in nuclear mechanics contribute to **GBM aggressiveness** and directly influence cell invasive behaviour. The intern will first use clinically annotated primary patient-derived GBM cells and **rheological techniques** (optical tweezers, microfluidics) to measure **nuclear morphology and mechanics** (Figure). Second, he/she will modulate the **expression levels** of lamins to modify both nuclear mechanics and GBM cell invasion and test whether lamins could be used as potential **molecular targets to control GBM aggressiveness.**

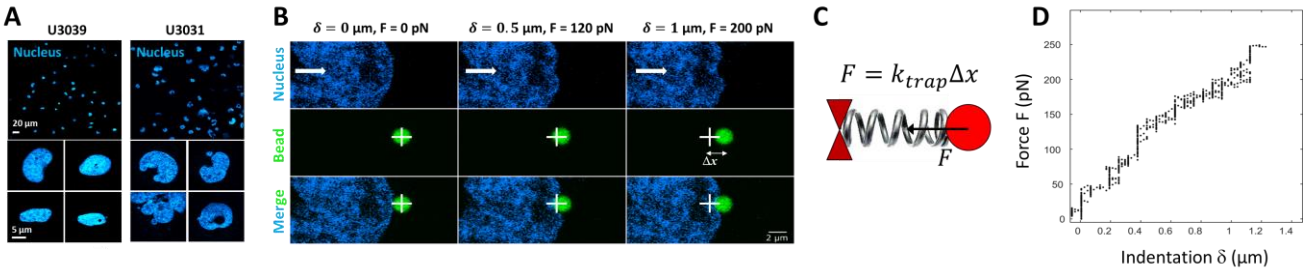

Figure: A. *Comparison of the* ***morphology of the nucleus*** *in two different GBM cell lines (U3039 and U 3031). B. Measurements of the* ***viscoelasticity of the nucleus using indentation of GBM nuclei in living cells.*** *A. Images showing a typical nuclear indentation experiment. The white cross represents the centre of the optical tweezers in which the 2 µm-diameter bead is trapped (green). The nucleus (blue) is indented by moving the cell towards the right (white arrow) which displaces the bead away from the trap centre of a distance Δx. C. Scheme of the bead in the optical trap. D. Force-indentation curve showing the force F as a function of the indentation δ in the experiment shown in B.*

Key words: nuclear envelope; lamin A/C; lamin B1; lamin B2; LINC complex; optical tweezers; microfluidic; cancer; glioblastoma; cytoskeleton; migration; invasion.

Collaborators: Sandrine Etienne-Manneville (Institut Pasteur, Paris), Catherine Villard (Institut Curie, Paris), Wang Xi (IJM, Paris), Nicolas Borghi (IJM, Paris)

Laboratory: Matière et Systèmes Complexes, UMR 7057 CNRS-Université de Paris, 10 Rue Alice Domon et Léonie Duquet, 75013 Paris

Contact: Jean-Baptiste Manneville (Jean-Baptiste.Manneville@u-paris.fr)