Proposition de stage de M2/Thèse - 2026

Mechanics of the cytoskeleton in living cells

Although extensively studied in vitro, the mechanics of the cytoskeleton is still largely **unexplored in living cells**. We have recently developed a micromanipulation technique based on intracellular **optical tweezers** and fast confocal imaging to measure the mechanical properties and coupling between two components of the cytoskeleton, **microtubules** (MTs) and **intermediate filaments** (IFs) (see Figure). We have shown for instance that IFs but not MTs, can stiffen more than three times upon repeated deflections and that destabilizing or acetylating MTs using drugs significantly reduces IF stiffening. In parallel, the cytoskeleton is known to modulate the morphology of the **nucleu**s.

In this project, we want to better understand the role of **MT acetylation** in cytoskeletal and nuclear mechanics. MT acetylation is a post-translational modification of MTs which is catalysed by the acetylase ATAT1. The deacetylase HDAC6 conversely removes acetylation from MTs. In vitro, MT acetylation has been shown to soften MTs. Our collaborators (Sandrine Etienne-Manneville, Institut Pasteur, Paris) have generated a CRISPR-Cas9 cell line **knocked-out for ATAT1**. ATAT1 KO cells thus display reduced acetylation, which is accompanied by a change in nuclear morphology. The M2/PhD candidate will measure MT and IF stiffness in control and ATAT1-KO cells using deflection experiments (see Figure). He/she will also measure the impact of MT acetylation on IF stiffening. In longer term experiments, the candidate will also 1) reconstitute **IF and MT networks *in vitro*** to identify the minimal machinery required for IF stiffening upon repeated deflections (coll. Cécile Leduc, Institut Jacques Monod, Paris); and 2) investigate the effects of **radiotherapy and chemotherapy** on cytoskeletal mechanics in the context of glioblastoma, the most aggressive brain tumours. The combination of techniques should allow us to elucidate the **mechanical links** between the MT and IF cytoskeleton and better understand intracellular mechanotransduction.

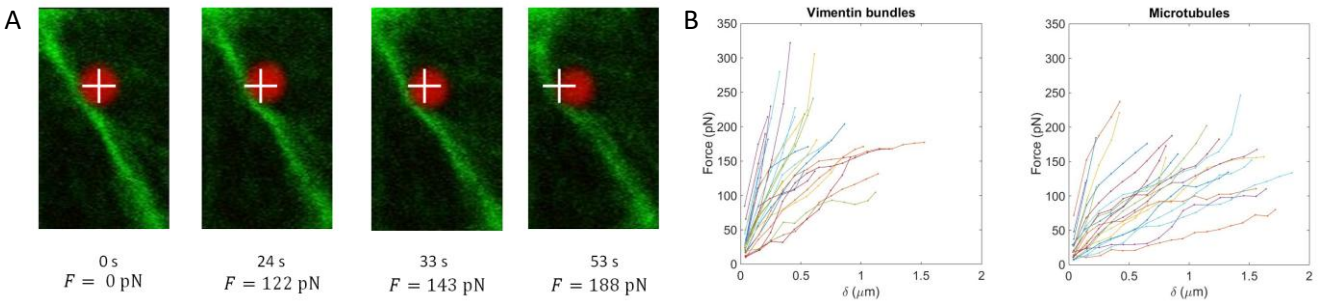

Figure: Deflection of vimentin intermediate filament (IF) bundles in living cells. A. A 2 µm diameter red fluorescent bead is internalized in the cells and trapped using optical tweezers (white cross). The cell is displaced (to the right) in order to push the IF bundle against the bead and deflect the filaments. The force F is deduced from single particle tracking of the position of the bead compared to the trap centre and the deflection of the filament δ is visualized by confocal microscopy. B. Examples of force-deflection curves $F(\delta)$ of vimentin IFs and microtubules.

Key words: cytoskeleton; microtubules; intermediate filaments; optical tweezers; microfluidics; mechanotransduction; glioblastoma

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