Master 2 and PhD thesis project

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Subject 1 nucleus/cytoskeleton: **Cell motility: quantification of cytoskeleton-nucleus mechanotransduction**

The cytoskeleton is the structure that ensures cell motility and cell shape changes, and also transmits forces throughout the cell. The cytoskeleton contains actin and microtubules, two types of filaments with different mechanical and dynamical properties. Those filaments are highly involved in various aspects of cell fate such as cell division and motility. The Sykes lab has a know-how in the reconstitution, with a minimal number of purified proteins, of actin dynamics and membrane shape changes. This thesis project aims at applying this knowledge to forces transmitted by the actin cytoskeleton to the nucleus.

A limiting factor for 3-D cell migration is the stiffness of the large and rigid nucleus. Considerable force needs to be applied by the cytoskeleton to the nucleus, yet many aspects of mechanical linkage and force transmission from the cytoskeleton to the nucleus are still poorly understood. Many nuclear envelope proteins, including nesprins, which mechanically link the actin cytoskeleton to the nuclear membrane have been implicated in cancer. A thorough study of the ability of metastatic cells to migrate through narrow pores, their nuclear stiffness and their nucleo-cytosketal connections is increasingly becoming crucial. Microfluidic devices have been developed in the lab to measure the capacity of cells to translocate through narrow spaces of micrometer size. Cells that have more deformable nuclei (due to low lamin A/C levels) can pass through constrictions smaller than 3 µm more easily than wild-type cells. Using these tools, we want to assess the mechanism of nucleus deformation through forces transmitted by the cytoskeleton, and in particular through nesprins. This project will lead to a comprehensive molecular portrait of nuclear and cytoskeleton proteins that are involved in cell translocation. We will dissect the role of the stiffness of the nucleus and its cytoskeletal connections in cell migration. We will develop a high-throughput micropipette aspiration device to measure the mechanical properties of cells and their nuclei, in the presence or absence of the proteins linking the nucleus to the cytoskeleton. A CRISPR labelling of nesprins and lamins is already available in the lab.

Tools available in the lab: optical imaging, microfluidics, optical tweezers, biochemistry, cell biology.