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PhD THESIS DEFENSE: Mechanisms and functions of the nucleus as a mechano-controller of cell contractility and migration plasticity

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Living tissues are crowded and dynamic environments, in which signalling molecules and physical forces constantly act on single cells. To ensure correct tissue development and homeostasis, cells function like small processors: they measure and integrate the various mechano-chemical inputs they receive from their surrounding. As an output, cells translate this information into specific signalling pathways controlling their behavior, cell specification or their physical properties, among others. %Cells can detect changes in chemicals and signalling molecules thanks to specific receptors on their surface, and the associated signalling cascades have been well characterized. In particular, as tissues are built, when

external stresses are applied, or when cells rearrange and move, single cells can undergo dynamic shape deformations. Previous studies showed that large cell deformations in confined environments control cellular contractility by tuning myosin II motor protein activity and can transform various cell types into a novel amoeboid phenotype, termed stable-bleb. Still, how single cells can sense shape changes and, as a consequence, tune myosin II activity and cell behaviour remained unknown.

Here, by combining planar micro-confinement assays with live cell fluorescence microscopy and quantitative image analysis, we performed a systematic study to characterize the response of progenitor stem cells derived from zebrafish embryos to mechanical shape deformations. By quantifying cellular contractility levels in various conditions and by interfering with specific signalling pathway, we then aimed to identify the mechano-sensitive mechanism that allows cells to sense and respond to shape changes. We found that cells can measure different degrees of confinement, which accordingly defines their contractility set-point. We discovered that the nucleus, the largest cellular organelle, acts as an intracellular mechano-sensor for large cell shape changes. Nucleus deformation induced an unfolding of the inner nuclear membrane, which controls the activity of cytosolic phospholipase A2 (cPLA2) in the nucleus. When active, cPLA2 triggers the release of arachidonic acid that activates myosin II through the Rho/ROCK pathway. As a result, the nucleus allows single cells to accurately and dynamically sense shape deformations and controls cellular contractility and migration plasticity under external force load. This process, further equips cells with an "escape reflex mechanism" that allows migration away from confined environments. Moreover, the combination of inner nuclear membrane unfolding and intracellular nucleus positioning, allows cells to sense and distinguish different shape deformations, as anisotropic cell compression versus isotropic swelling, through the same mechano-sensitive pathway. Our data support that the nucleus establishes a functional module for cellular mechano-transduction, enabling cells to sense and interpret different types of shape changes and to dynamically adapt their behavior to mechanical forces in the 3D microenvironment.

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