Development of innovative super-resolution modalities to study the fast dynamic reorganization of adhesion sites in cells

Xuesi Zhou[1,2]
Supervisor: Brahim Lounis[1], Gregory Giannone[2]
Laboratoire Photonique, Numérique et Nanosciences (LP2N)
Institut interdisciplinaire de neurosciences (IINS)

Cells adjust their adhesive and cytoskeletal organizations according to changes in the biochemical and physical nature of their surroundings. In return, by adhering and generating forces on neighboring cells and the extracellular matrix (ECM), cells control their microenvironment, shape and movement. Integrin based focal adhesions (FAs) are strategically located at the interface of the plasma membrane, the actin cytoskeleton, and the ECM. Integrins, that constitute the functional core of FAs, mediate adhesion, F-actin connection, force transmission and signal transduction[1]. FAs are crucial cellular mechano-sensors able to process mechanical forces and strengthen under mechanical loads[2]. A molecular understanding of mechano-sensing started to emerge from in vitro mechanical manipulations of mechano-sensitive proteins[3], and from fluorescent tension-sensors[4]. Mechanical force could reinforce[5] or destabilize[6] interactions, control enzymatic activities[7], expose cryptic binding sites[3]. However, the molecular basis of force-sensing in cells are far from being understood.

Super-resolution microscopy revolutionized cell imaging. By delivering images with spatial resolutions below the diffraction limit of light, these techniques created possibilities to study the architecture and dynamics of structures at the protein level in cells[8,9,10]. Scrutinizing sub-cellular structures using super-resolution microscopy unraveled new protein organizations and showed that proteins are spatially segregated into distinct functional nano-domains.

We combined super-resolution microscopy with techniques enabling to measure and generate forces on proteins within mechano-sensitive structures in particular FAs. This will enable to decipher the molecular mechanisms driving mechano-sensing and mechano-signaling in cells. By combining these techniques, we aim to reveal how the dynamic landscape of interaction in FAs lead to mechano-sensing.

References:

1. Iskratsch. Nat. Rev. Mol. Cell Biol. 15, 825–833 (2014).
2. Kechagia. Nature Reviews Molecular Cell Biology (2019) doi:10.1038/s41580-019-0134-2.
3. del Rio. Science (80-.). 323, 638–641 (2009).
4. Grashoff. Nature 466, 263–266 (2010).
5. Giannone. J. Cell Biol. 163, 409–419 (2003).
6. Jiang. Nature 424, 334–337 (2003).
7. Wang. Nature 434, 1040–1045 (2005).
8. Liu. Mol. Cell 58, 644–659 (2015).
9. Sahl. Nat. Rev. Mol. Cell Biol. 18, 685–701 (2017).
10. Grotjohann. Elife, 2012, 1: e00248.