The Force is Within You: Fluorescent probes to map molecular forces in cells

(*Emory University*) ○Khalid Salaita
Keywords: Fluorescent Force Probe; Mechanobiology; DNA technology; Hydrogel

Cells are highly dynamic structures that are constantly pulling and pushing on one another and on their surroundings. These pulls and pushes are mediated by molecular complexes that experience forces at the scale of piconewtons (pN). For context, 7 pN applied a distance of 1 nm is ~1 kcal/mol and most biological forces are in the range of 1-50 pN. Despite the small magnitudes of these forces, they can have profound biochemical consequences. For example, the rapidly fluctuating forces between immune cells and their targets can drastically tune immune response and function. Unfortunately, there are limited methods to study forces at the molecular scale and particularly within the context of living cells. In this talk, I will discuss my group's efforts at addressing this gap in knowledge by developing fluorescence tools to map the molecular forces applied by cells. The talk will focus on nucleic acid probes that respond to specific magnitudes of molecular forces by undergoing conformational changes. These conformational changes are then designed to trigger biochemical and catalytic reactions that can enhance the sensitivity of the probe. One specific example is the hybridization chain reaction which enhances the mechanical signal by multiple fold and allows one to readout cell forces using a standard benchtop plate reader. The work represents an important step towards democratizing the field of mechanobiology by creating probes that can be used without the need for sophisticated instrumentation.

[Recent Publications]

1) "Mechanically-triggered Hybridization Chain Reaction" *Angew. Chem. Int. Ed.*, **2021**, *60*, 19974.
2) "Turn-key super-resolution mapping of cell receptor force orientation and magnitude using a commercial structured illumination microscope" *Nature Commun.*, **2021**, *12*, 4693.
3) "DNA-based microparticle tension sensors (μTS) for measuring cell mechanics in non-planar geometries and for high-throughput quantification" *Angew. Chem. Int. Ed.*, **2021**, *60*, 2.
4) "Live-cell super-resolved PAINT imaging of piconewton cellular traction forces" *Nature Methods*, **2020**, *17*, 1018.
5) "Engineering DNA-Functionalized Nanostructures to Bind Nucleic Acid Targets Heteromultivalently with Enhanced Avidity" *J. Am. Chem. Soc.*, **2020**, *142*, 9653.
6) "Tunable DNA Origami Motors Translocate Ballistically Over μm Distances at nm/s Speeds" *Angew. Chem. Int. Ed.*, **2020**, *59*, 9514.
7) "Programmable Mechanically Active Hydrogel-Based Materials" *Adv. Mater.* **2021**, *33*, 2006600.
8) "Supramolecular DNA Photonic Hydrogels for On-Demand Control of Coloration with High Spatial and Temporal Resolution" *Nano Letters* **2021**, *21*, 9958.