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STRESSING CHROMATIN, FROM THE CELL TO THE NUCLEOSOME SCALE

The physical impact of the nucleus on cellular function becomes evident during migration in 3-D environments. With its large volume and relative rigidity, governed by the nuclear envelope proteins and chromatin organization, the nucleus acts as physical barrier, particularly relevant to immune cells and invading cancer cells. These must move through tissue pores and clefts often smaller than the size of the nucleus, which induce substantial compressive and shearing stresses, and may also lead to the temporary rupture of the nuclear envelope. Recent studies amply demonstrated that extreme nuclear deformations during confined migration can lead to DNA damage and increased genomic instability in cancer cells.

Here we shed a first light on the molecular processes of stress transfer and relaxation down the scale of the individual chromatin units, the nucleosomes. In this talk, we will briefly outline our innovative experimental techniques aimed at measuring and biophysical signatures of cancer cells, notably single-cell MEMS nanotweezers that provide high sensitivity to examine different biophysical properties (size, stiffness, viscosity, etc.), and high-throughput MEMS devices oriented at clinical applications. Then, by using molecular dynamics simulations of force-induced poly-nucleosome deformation under ideally controlled conditions, we show that external forces acting on the nucleosome core particle transmit a mechanical stress, which is mainly translated as elastic energy stored in the elastic and plastic response of DNA. The ability of the double-stranded DNA helix to absorb and release this stress, most notably in the form of bending and twisting deformations, may constitute a platform to elicit or repress the interaction with remodeler proteins, by controlling their access to active histone domains.

The concerted actions of mechanical deformation and remodeler enzymes open the way for a new framework, to understand the microscopic control of chromatin organization by mechanical forces, and the attending modifications of gene expression and transcription factor activity.

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