Nano-mechanical characterization of human brain tumor

Minelli E. [a], *Ciasca G.* [a], *Sassun T.E.* [b], *Antonelli M.* [c], *Papi M.* [a], *Santoro A.* [b], *Giangaspero F.* [c,d], *Delfini R.* [b°], *De Spirito M.* [a°]

[a] Istituto di Fisica, Universita Cattolica del Sacro Cuore, Largo F. Vito 1, 00168 Rome, Italy
[b] Department of Neurology and Psychiatry, Neurosurgery, Sapienza University, 00181 Rome, Italy
[c] Department of Radiological, Oncological and Anatomo Pathological sciences, Sapienza University, Rome, Italy
[d] IRCSS Neuromed, Pozzilli (IS), Italy.
° These authors share equal credit for seniorship
e-mail: minelli.eleonora@gmail.com

Keywords: cancer microenvironment, biomechanics, AFM

It is already becoming apparent that the mechanical properties of cells and their microenvironment may profoundly affect tissue homeostasis. In physiological conditions, cells are susceptible to physical and mechanical forces, mediated by the extracellular matrix (ECM), which play a fundamental role in the development and maintenance of organs and tissues. The perturbation of this biophysical interplay between cells and ECM has therefore emerged as a key signaling pathway regulating diseases growth and progression. Tumour onset and advancement indeed influenced, and are influenced by, modifications in the mechanical properties of cells and their surrounding ECM [1].

Atomic Force Microscopy (AFM), have allowed scientists to probe the mechanical properties of cells and tissues, demonstrating that cancer cells in vitro are softer than their healthy counterparts, while cancer tissues appear to be significantly stiffer than healthy ones. The cellular modified deformability is associated to alterations in the cytoskeletal architecture and it is strictly related to their malignant behavior, instead, the tumor tissue rigidity is due to the accumulation of ECM fibrous protein, such as collagen, laminin, and fibronectin[2-3].

This is particularly true in the case of glioblastoma multiforme (GBM), a highly invasive brain tumor with a unique infiltrative pattern, strictly related the typical composition of the brain ECM[4]. In this work, we provide the first study of the nano-mechanical properties of human GBM tissue, obtained after surgical resection. In order to achieve a more in-depth understanding of the role of the mechanical landscape, we investigated Young's modulus (E), to obtain information about the tissue elasticity, and the Hysteresis (H), the energy dissipated during the indentation cycle, to quantitatively evaluated the role of the viscous forces. We compared the GBM results with that of human meningothelial meningioma (MM) tissue, a benign brain lesion which does not infiltrate the normal parenchyma.

Normal brain ECM is composed of glycosaminoglycan, hyaluronan, and proteoglycans, and it is very soft with an average Young's modulus of 1-2 kPa (fig 1a) and high H value, while both GBM and MM microenvironment are characterized by high rigidity 10 kPa and 15 kPa, respectively, and lower Hysteresis values (fig. 2).

The stiffness increase of GBM tissue is related to its spread mechanism; GBM cells motility is higher on stiff structures, so they actively modify their microenvironment. Moreover, being GBM a high-grade tumor, necrosis is always present and it is a hallmark for the diagnosis. We provide the mechanical characterization of necrosis, finding out an extremely low Young's modulus and high viscous behavior, E~300 Pa H ~ 0.7 (fig.1b)

These results confirm the important role played by the mechanical cues in the spreading and the progression of brain tumors, further stressing the need to elucidate the mechanical modifications occurring during the genesis and progression of the pathology. In this regard, it is important to evaluate the key role played by the extracellular microenvironment We report a comprehensive study on the nano-mechanical properties of human GBM and MM tumor tissues obtained after surgical resection and analysed by indentation-type atomic force microscopy (IT-AFM).

[1] Suresh, S. Acta Materialia 55, 3989-4014 (2007)
[2] Alibert, C., et.al Biology of the Cell (2017).
[3] Plodinec, M., et al. Nature nanotechnology 7.11 (2012): 757-765.
[4] Ciasca, G., et al. Nanoscale 8.47 (2016): 19629-19643.

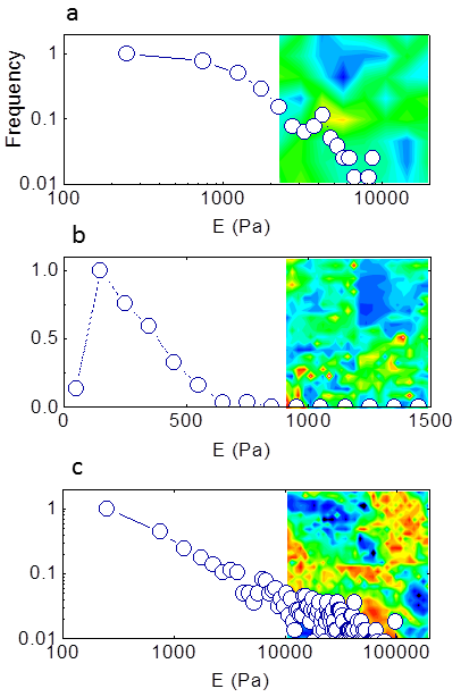

Figure 1. Normalized frequency histogram of the apparent Young's modulus and the relatives maps. a) healthy brain tissue, b) GBM necrosis, c) GBM tumor tissue.

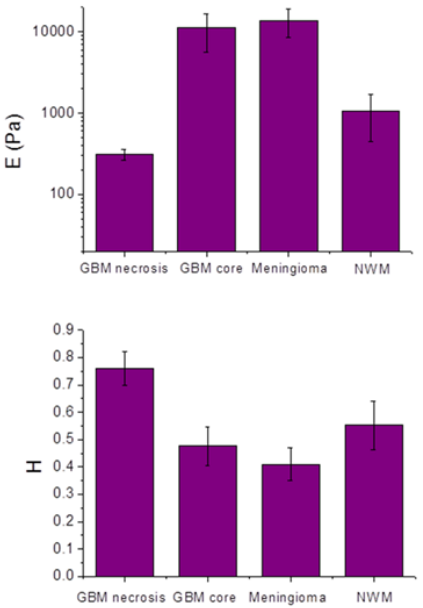

Figure 2. Average E and Hysteresis value for GBM necrosis, GBM tumor tissue, meningioma and normal white matter (NWM)