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Nanomechanical Characterization of Healthy and Tumor Lung Tissues at Cell and Extracellular Matrix Level

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Abstract : The study of the biophysics of living cells drew attention to the pivotal role of the cytoskeleton in many cell functions, such as mechanics, adhesion, proliferation, migration, differentiation and neoplastic transformation. In particular, during the complex process of malignant transformation and invasion cell cytoskeleton devolves from a rigid and organized structure to a more compliant state, which confers to the cancer cells a great ability to migrate and adapt to the extracellular environment. In order to better understand the malignant transformation process from a mechanical point of view, it is necessary to evaluate the direct crosstalk between the cells and their surrounding extracellular matrix (ECM) in a context which is close to in vivo conditions. In this study, human biopsy tissues of lung adenocarcinoma were analyzed in order to define their mechanical phenotype at cell and ECM level, by using particle tracking microrheology (PTM) technique. Polystyrene beads (500 nm) were introduced into the sample slice. The motion of beads was obtained by tracking their displacements across cell cytoskeleton and ECM structures and mean squared displacements (MSDs) were calculated from bead trajectories. It has been already demonstrated that the amplitude of MSD is inversely related to the mechanical properties of intracellular and extracellular microenvironment. For this reason, MSDs of particles introduced in cytoplasm and ECM of healthy and tumor tissues were compared. PTM analyses showed that cancerous transformation compromises mechanical integrity of cells and extracellular matrix. In particular, the MSD amplitudes in cells of adenocarcinoma were greater as compared to cells of normal tissues. The increased motion is probably associated to a less structured cytoskeleton and consequently to an increase of deformability of cells. Further, cancer transformation is also accompanied by extracellular matrix stiffening, as confirmed by the decrease of MSDs of matrix in tumor tissue, a process that promotes tumor proliferation and invasiveness, by activating typical oncogenic signaling pathways. In addition, a clear correlation between MSDs of cells and tumor grade was found. MSDs increase when tumor grade passes from 2 to 3, indicating that cells undergo to a trans-differentiation process during tumor progression. ECM stiffening is not dependent on tumor grade, but the tumor stage resulted to be strictly correlated with both cells and ECM mechanical properties. In fact, a greater stage is assigned to tumor spread to regional lymph nodes and characterized by an up-regulation of different ECM proteins, such as collagen I fibers. These results indicate that PTM can be used to get nanomechanical characterization at different scale levels in an interpretative and diagnostic context.

Keywords : cytoskeleton, extracellular matrix, mechanical properties, particle tracking microrheology, tumor
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