Opinion

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Cytomechanical Alterations Induced by Inorganic NPs

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ABSTRACT

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Opinion

In the last decade, the rise of nanoparticles (NPs) in commercial products and in biomedical applications has urged the understanding of potential risks and harmful effects induced by their exposure at cellular level due to their biological interactions [1,2].

The physico-chemical properties of NPs, such as size, shape, surface charge etc. influence their interaction with the cell membrane, organelles and cytoskeleton structures changing critical cell functions [3,4]. Differently from the wide scientific literature already available dealing with standard in vitro and *in vivo* toxicity tests [5-7], the impact on cell mechanic has not been deeply investigated so far. Several experimental evidences suggest that cell mechanics is directly involved in many cellular functions, such as proliferation, polarization and shape, differentiation, apoptosis, adhesion, tissue integrity and motility by cytoskeleton components reorganizations (F-actins, microtubules and intermediate filaments) [8,9]. In addition, cytoskeleton affect cell stiffness (commonly expressed by the Young's Modulus) [10,11] and contractility properties of cells, as reported in different works [12]: consequently, any unbalance of this state can induce malignant transformations [13].

Considering the strong correlation between biomolecular features and the mechanical behavior, the elastic properties of cellular structures represent important parameters to characterize both the physiological cellular conditions and the advancement of certain diseases (e.g., atherosclerosis, heart failure, asthma, pulmonary fibrosis, preeclampsia, cancer), inducing destabilization and degradation of actin by different ways [14,15]. Healthy cells are stiffer and show an organized actin structure compared to tumour cells that present a soft and flexible behavior: in this perspective, Atomic Force Microscopy (AFM) represents an effective technique, able to measure cell elasticity and other biomechanical properties under physiological conditions (in culture medium buffer, pH and temperature) [16]. In addition, it simultaneously provides a topographical imaging of cell surfaces. The AFM has been used in many investigations to quantify morpho mechanical alterations induced by disease progression and/or to evaluate the effects produced by specific drugs [17]. At the same way, this technique could be used to understand how NPs act on cell mechanics, affecting specific cellular functions. In a recent work [18] the biomechanical changes induced by selenium NPs (SeNPs) in Breast cancer cells (MCF-7) at concentrations of 2.5 and 5μg/mL for 24h was investigated: NPs triggered several alterations of actin filaments and induced an increase of Young 's modulus (measured by means of AFM). De Matteis, et al. [19], showed how the exposure of MCF-7 to 0.05nM and 0.5nM of citrate-capped AgNPs (20nm) induced a structure modification of organelles (lysosomes and mitochondria) together with actin reorganization. Also, in this case, the authors showed a noticeable reduction of cell stiffness, reporting high values of Young's modulus: this effect could promote a detachment from basal membrane, triggering the mediatization process [20]. However, the use of other types of NPs with different physico-chemical properties induced an opposite effect of the mechanical cellular behavior which also depends on the characteristics of the cell line. Indeed, Ogneva et al. [21] found an increase of cell stiffness after exposure of SiO_2NPs (100μg/mL) to mesenchymal stem cells (MSCs), concluding that F-actin/G-actin ratio alterations provoked cytoskeleton reorganization. Similar evidences were reported for HEY A8 ovarian cancer cells exposed to AuNPs [22]: AuNPs were localized in nucleus region, enhancing the expression level of lamin A/C protein (localized in the inner nuclear membrane) increasing nuclear stiffness. Regarding zinc oxide NPs (ZnONPs), mechanical

behavior depended on NPs concentrations: the exposure of human aortic endothelial cells (HAEC) to 10μg/mL of ZnONPs resulted in stiffness enhancement, whereas cells were softer when the concentration was 50μg/mL [23].

The increase or decrease of Young's Modulus induced different impact on cells. The decrease of this value is a key factor in the tumor progression because indicated the disruption of cell junctions that is responsible of cell migrations in surrounding tissue [24]. On the contrary, the injury of cell migration in all stages of development can induced early embryonic lethality and multiple human syndromes. In this way, different kinds of NPs may alter or inhibit cell locomotion and also promote cell migrations by several mechanisms. The effects on cells are strictly correlated with physico-chemical properties and uptake phenomena. In this scenario, the bionanomechanic investigation represent a powerful tool to investigate the cytotoxicity of NPs in order to develop new standard procedures, apart from the standard toxicity test. In this way, the mechanical behavior of cells could predict the fate of cells and, consequently, the correlated diseases.

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