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Computational modelling of mechanotransduction during cell adhesion

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INTRODUCTION

Differentiation of adherent cells can be modulated by the stiffness and micro/nano-structure of substrates in controlling cell morphology and cytoskeleton tonus[1]. Changes in cell morphology during cell adhesion involve mechanotransduction process altering Rho A-mediated cytoskeleton contractility, focal adhesion assembly, downstream integrin signaling. Itano *et al*. reported that forces transmitted by the cytoskeleton may deform nuclear membrane and open ion channels allowing calcium entry inducing associated gene transcription[2].

We propose here a mechanical model of cell based on in vitro experiments so as to analyze the relation between morphology, intracellular tension and possible nucleus strain during cell adhesion on nanostructured substrates.

METHODS

Cell culture

Mesenchymal stem cells were cultured on nano-porous substrates with pore diameter of 200 nm [3]. Pores being able to trap proteins were favoured sites of adhesion. Morphology of cells and distribution of focal adhesions were reported after actin and vinculin staining.

Computational cell model

The cell model is a mechanical multi-interaction system representing the interconnected structures of cytoskeleton and nucleoskeleton. As a 3D extension of our previous 2D model[4], the present model consisted of 8500 nodes forming the cell volume and interacting together via compressive and tensile forces. Tensile interactions acted as elastic wires between nodes while compressive interactions were computed as contact forces between virtual spherical boundaries surrounding nodes. Resulting forces networks were assumed to model the various filamentous lattices of cytoskeleton such as stress fibers, actin cortex, microtubules and intermediate filaments[4]. Some nodes of cell membrane, as well as integrin receptors do, were able to connect proteins of substrate pores and form stress fibers between each others.

Intracellular tonus of adherent cell

Some adherent cells were chosen as representative of spread (Fig. 1) and round morphologies ; positions of focal adhesions were then introduced in the model. The cell model which was originally round with a diameter of 15µm spread until coinciding of focal adhesion positions.

The intracellular tonus was computed as sum of tensile forces through vertical cell section. It was modulated by increasing tensile interaction stiffness so as to obtain on pore area maximal focal adhesion tension of 0,2 nN consistently with experimental measurement[5].

Cell adhesion by modeling filopod emission

Cell model was implemented in free adhesion process. When one focal adhesion point was created, one filopod represented by a moving close node of the membrane was emitted at 1 µm away from existing focal point, so as to find more distant adhesion site and increase intracellular tonus. The spreading process was stopped when given intracellular tonus was reached.

RESULTS AND DISCUSSION

Computation shows intracellular tonus of 58nN and nucleus shear strain of 65 % for a 70 µm-diameter spread cell (Fig.1), compared to tonus of 24 nN and nucleus strain of 30 % for 35 µm-diameter round cell (not shown).

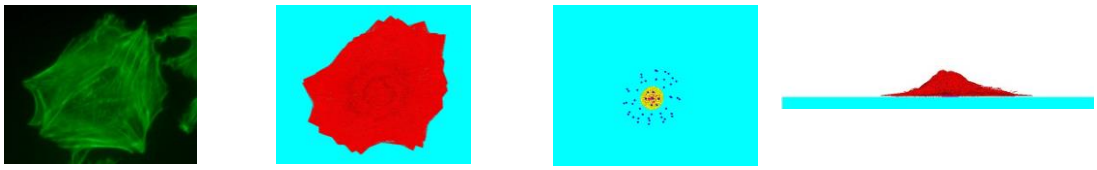

Fig. 1: Spread cell and model with coinciding focal adhesions. Tensions (red), deformed nucleus (yellow).

Free adhesion of cell model on nanoporous substrate by filopod emission led to a 75 µm-diameter spread shape with higher tonus of 220 nN due to more focal adhesion and stress fibers. In that case nucleus shear strain reached 52%. This verified previous finding that tonus and nucleus strain increase with cell spreading. Nonetheless depending on spatial distribution of focal adhesions and stress fibers, nucleus may deform in a way which is not directly coupled to intracellular tonus evolution.

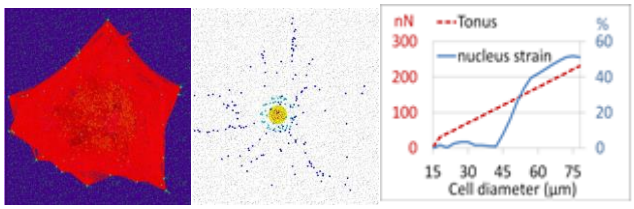

Fig. 2: Model free adhesion. Tensions (red), deformed nucleus (yellow) and focal adhesions (blue).

CONCLUSION

The present 3D cell model identified evolution of intracellular tonus and nucleus strain during cell adhesion. It may help to understand mechanotransduction involved in stem cell differentiation during adhesion on biomaterials.

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