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ABSTRACT eBOOK

Experimental/computational approach of the nuclear pore complex mechanics

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***Abstract*—Recent findings have shown that nuclear distortions may alter the import flux of transcription factors toward the nucleus and control the expression of genes and the protein synthesis. A possible mechanism of such a mechanosensory system resides in the nuclear pore complex (NPC). NPCs are generally considered sites of active transcription. Here we hypothesized that cell-stretching forces can mechanically activate the pore, thus allowing faster diffusivity of molecules. To this purpose, we recreated the two extreme nuclear deformation conditions (spread and round). Cell nuclei were imaged by confocal microscopy and by scanning transmission electron tomography (STEM) to asses nuclear and pore features. We also developed a multyphysics model accounting for the change in permeability in response to deformation. We found an increase in the nuclear envelope (NE) surface by up to 50% in deformed cells. Non-significant differences in both shape and size of the reinforcement ring of single NPCs with NE deformation. The computational simulations show that NE-NPC structure predominates compared to the NPC structure.**

***Keywords*—Nuclear Pore Complex, Nuclear Envelope, Diffusion, Permeability.**

I. Introduction

A basic recent understanding in stem cell differentiation is that the cell is able to translate its shape (e.g. roundish or deformed) into a fate decision. However, the mechanisms by which phenotype expression is regulated by cell shape are complex and poorly understood. Our hypothesis is that cell deformation induces nuclear deformation, which in turn causes strains in the nuclear envelope (NE). This induces a change in porosity and in permeability of the NE that affects the flux of transcription factors involved in stem cell differentiation [1]. To demonstrate this hypothesis, we set-up a numerical model of the interaction between the nuclear pore complex (NPC) and the NE.

II. Material and methods

Firstly, we recreated the two extreme deformation conditions for the NE. We isolated mesenchymal stromal cells (MSC) from the bone marrow of adult rats. To recreate the deformed configuration, we processed the cells for microscopical analysis when they were in adhesion to a flat culture substrate. On the contrary, to recreate the roundish configuration, we fixed and processed the cells in suspension. In both configurations, we acquired images of the whole nuclei by scanning confocal microscopy, to measure the NE deformation. In addition, we reconstructed 3D portions of the NE by scanning transmission electron tomography (STEM), see Fig. 1 and Fig. 2, to measure geometrical parameters of the NPC size/shape.

Secondly, in order to couple a change in permeability of the NE at the microscale with a change in configuration of a single NPC at the nanoscale (in response to the deformation applied to the NE), we fed the measured data into a computational model of the NPC-NE mechanical interaction.

III. Results

Our preliminary results show an increase in the NE surface by up to 50% together with a significant change of the local NE curvature in deformed cells, compared to roundish ones. However, we found non-significant differences in both shape and size of the reinforcement ring of single NPCs with NE deformation.

IV. Conclusion

The computational simulations show that the highly different mechanical response of the NE structure, compared to the NPC structure, predominates in determining the change in porosity of the NE in response to the applied strains. This result is consistent with experimental published evidences showing a dramatic change in NPC density and shape in cells lacking lamin, an essential nuclear protein anchoring the NPCs to the NE [2].

Acknowledgement

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References

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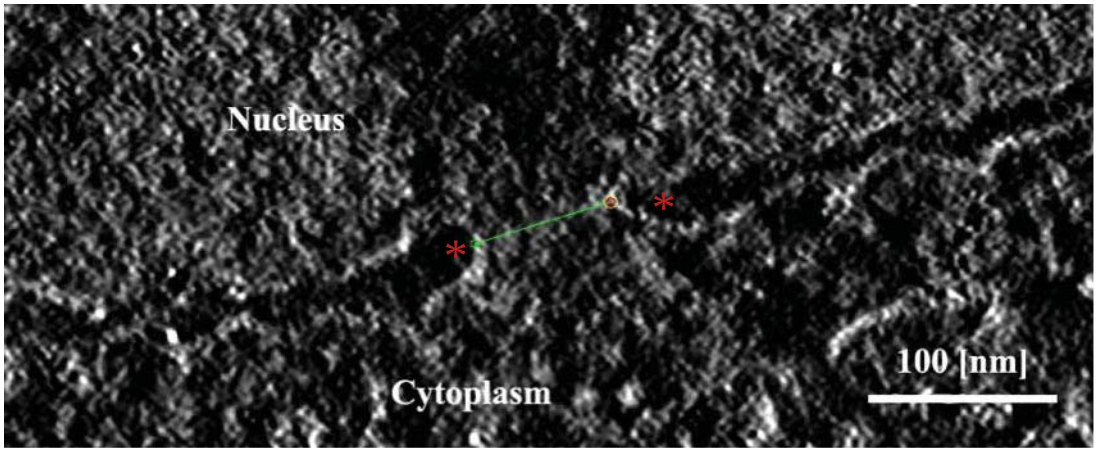

Fig. 1. Single tomographic slice through the nuclear envelope of a MSC cell grown in suspension. The highlighted distance (green) in the nuclear envelope (asterisks) corresponds to a nuclear pore complex.

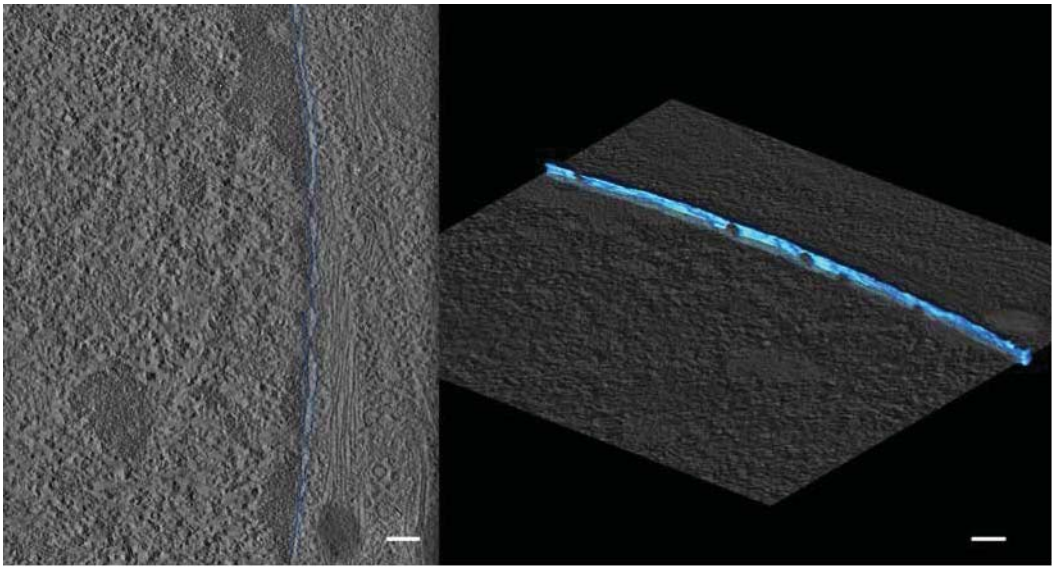

Fig. 2. Slice segmentation (blue-left image) and corresponding 3D reconstruction (blue-right image) of the nuclear envelope of a MSC. In the images it is possible to properly differentiate the location of four Nuclear Pore Complexes. The scale bar in both images corresponds to 150 [nm].

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