QUANTIFYING CELL FORCES EXERTED BY CHONDROCYTES IN THE CONTEXT OF OSTEOARTHRITIS

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Introduction

Osteoarthritis (OA) is the most common chronic joint disease. During disease progression, cartilage degeneration occurs, with associated changes in all other joint tissues. To date, OA is the leading cause of disability among elderly, and no known cure or proven strategy exists for reducing progression from early to end-stage OA. OA progression affects the function of integrins, focal adhesion proteins, which impairs the ability of cells to generate forces and interact with the extracellular matrix (ECM). Cellular forces are therefore an important indicator of disease progression. The Wnt signalling pathway is a key regulator and activator of cellular and molecular processes during the development of OA. During the course of OA, this pathway has been shown to be abnormally activated or suppressed [1], and the GSK3 inhibitor CHIR99021 (CHIR) may be used to promote its activation [2]. This study investigates the cellular forces generated in healthy and in CHIR-treated chondrocytes, as a chemical model of Wnt-hyperactivation, as previously reported in OA primary chondrocytes.

Methods

Traction Force Microscopy (TFM) is the most well-known method for calculating cellular forces in both 2D and 3D. In the past years, the Van Oosterwyck group has developed experimental procedures and computational algorithms for 3D time lapse TFM allowing the quantification of traction maps around cells embedded in an ECM-mimicking hydrogel [3, 4]. TFM infers cell-generated forces (tractions) from the measurement of hydrogel deformation combined with its mechanical (elastic) properties. In this work, TFM is applied to study force generation by chondrocytes in both 2D (using collagen-coated PAA substrate) and 3D (using RGD-functionalized PEG hydrogel) cases.

Results

To the best of our knowledge, for the first time the use of 3D TFM on chondrocytes has been shown. The 2D case is also being studied and compared with previously published data from the literature. Chondrocytes pull on the ECM in both 2D and 3D environments, as indicated by displacement vectors pointing towards the cell center. Preliminary results show a decrease in cell-generated tractions from 74±23 Pa to 61±10 Pa (n=3) in CHIR-treated chondrocytes. These results validate the use of these in vitro systems as platforms for further study of the OA impact on cellular force generation.

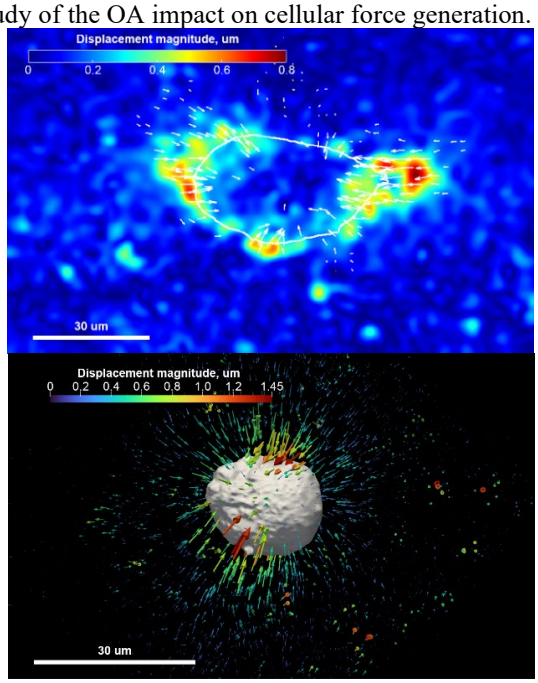

Figure 1: displacement fields generated by chondrocyte on a 2D polyacrylamide substrate (top) and 3D polyethylene glycol hydrogel (bottom). Unpublished data.

Discussion

The hypothesis that OA-chondrocytes generate lower tractions than healthy cells seems to be confirmed in our preliminary data based on the C28/I2 cell line. With the experimental and computational workflow here described, in follow-up experiments we will expand this analysis to primary human OA and non OA cells, where more profound PCM generation is expected.

References

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