TISSUE SCALE AGENT-BASED MODEL OF THE TENSION-MEDIATED REVERSIBLE FIBROBLAST TO MYOFIBROBLAST TRANSITION

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Background

In wound healing, tissue-resident fibroblasts get transiently activated by biochemical and mechanical cues and transition into myofibroblasts. Myofibroblasts are contractile cells with large focal adhesions and α-smooth muscle actin (αSMA) incorporated into stress fibers. They also deposit new extracellular matrix (ECM). After wound closure, myofibroblasts need to return to the quiescent fibroblast state, to prevent excess ECM deposition and eventual fibrosis.[1] At the center of this process is the reversible fibroblast-to-myofibroblast transition (FMT). In vitro experiments have shown that this reversible process is mainly controlled by changes in the tissue tension, i.e., Kollmannsberger *et al.* showed that high FN tension accompanied by an elevated αSMA expression and therefore myofibroblast phenotype occurs only at the growth front, while matured tissue returned to the quiescent fibroblast state in a microfabricated cleft system. Interestingly, even in absence of growth factors that initiate the FMT process, tensile forces were able to trigger the reversible FMT. [2] These results suggest FMT is regulated by mechanosensitive cellular signaling but the exact link with dynamic processes of ECM deposition has not been resolved. Here, we propose that a dynamic agent-based model is ideal to study the mechanisms of action of tensile forces in FMT.

Methods

We developed a tissue scale agent-based model using Python 3.8 to mimic the Kollmannsberger *et al.* 2018 setup *in silico*. Upper left corner of the 500 µm by 500 µm cleft was represented by a 100 by 100 grid. In this model, we accounted for the subcellular αSMA expression and YAP nuclear localization as well as active ECM protein (FN and collagen) production. The production and degradation of proteins were governed by discretized ordinary differential equations and the relationship between different variables have been determined using the in vitro data when available. We hypothesize that the change in tissue tension, due to dynamic ECM deposition, degradation and alignment, changes the mechanotransductive subcellular processes which in return change the ECM protein production, iteratively affecting the tissue tension and subcellular processes (Figure 1).

Results

We ran simulations until the *in silico* cleft was full of tissue agents and reported the tension, αSMA abundance as well as the abundance of YAP in the nuclei over the distance from the growth front (Figure 2). These results agreed well with the *in vitro* experiments. The results also suggest that FN is more abundant than collagen at the growth front where the alignment between the fibers and the cells is highest. As the tissue matures, more collagen is deposited alongside FN. Cells establish adhesions to collagen and can no longer pull on the FN fibers. Overall this is reflected in a decreased ECM-cell alignment and a decreased tension in the mature tissue. In summary our work establishes a first link between subcellular mechanosensitive processes involved in tension-mediated FMT. Future work will focus on confirming our predictions and extending the ABM with a mechanical model of the ECM tension. This multiscale framework will be an important step towards generating fundamental understanding of FMT.

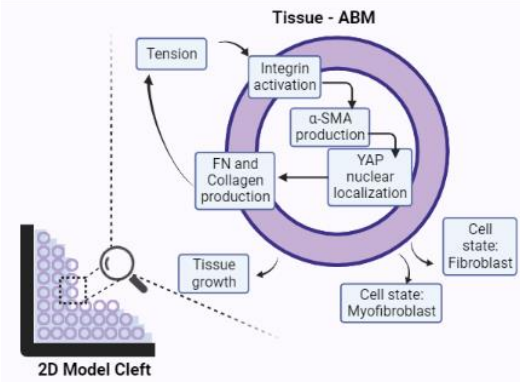

Figure 1: The tissue scale ABM processes in the model.

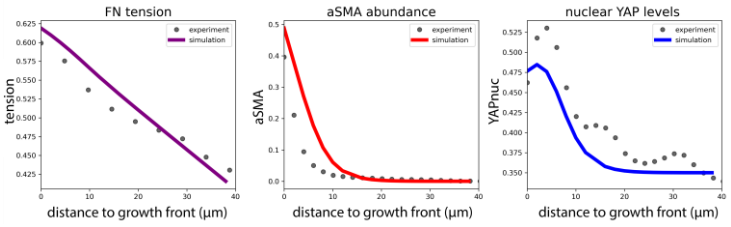

Figure 2: Distribution of tension, abundances of αSMA, YAP, ECM proteins throughout the simulated tissue space (lines) compared to experimental data (points).

References

1. M. D'Urso and N. A. Kurniawan, *Front. bioeng. biotechnol.*, vol. 8 , 2020.
2. P. Kollmannsberger, C. M. Bidan, J. W. C. Dunlop, P. Fratzl, and V. Vogel, *Sci. Adv.*, vol. 4, no. 1, 2018.

Acknowledgements

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