YAP/TAZ AND MECHANICAL CUES AS TEMPORAL REGULATORS OF ANGIOGENESIS

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Introduction

Angiogenesis, i.e. the formation of new blood vessels, plays a crucial role in both health and disease. Better understanding and controlling this process could improve treatment strategies for associated diseases (e.g. cancer) and unlock the development of large tissue-engineered constructs.

Angiogenesis could be regulated by tuning the extracellular matrix (ECM), as suggested by experiments showing that ECM stiffness affects the process of tip cell formation [1]. This mechanoresponse might be explained by the crosstalk between the force-sensitive proteins YAP/TAZ and Notch [2], a key pathway for angiogenic EC fate selection. However, the underlying mechanisms are not fully clear yet.

Here, by coupling computational models of YAP/TAZ and Notch signaling, we investigated the effects that ECM stiffness, via the YAP/TAZ-Notch crosstalk, has on the temporal dynamics of endothelial cell (EC) fate selection, one of the key determinants of the density of the formed vascular networks.

Methods

An ordinary differential equation (ODE) model of the YAP/TAZ mechanoresponse [3] and an ODE model of Notch and VEGF signaling during angiogenesis [4] were coupled by assuming Dll4 inhibition by YAP/TAZ activation, as motivated by previous experiments [2] (see Fig. 1 for the model overview). These ODE models were extended to simulate rows of ten cells interacting via Notch. The YAP/TAZ-mediated Dll4 inhibition was fitted against *in vitro* qPCR data linking stiffness to Dll4 expression [5]. To simulate the temporal dynamics of EC fate selection at the onset of angiogenesis, *in silico* experiments were conducted; in particular, ECs were exposed to VEGF for 28 hours. EC fate selection times were determined based on their filopodia formation and stability, used to classify the EC phenotype.

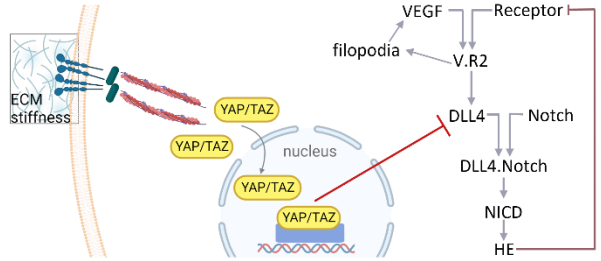

Figure 1: Schematic representation of the YAP/TAZ mechanotransduction pathway and its inhibitory relation with DLL4. The right side portrays the VEGF-Notch crosstalk in ECs. Created with BioRender.com

Results

In agreement with previous experiments [5], DLL4 production decreased with increasing stiffness. This decrease was caused by a higher YAP/TAZ nuclear fraction. Additionally, we found that stiffer environments lead to increased average amounts of filopodia prior to patterning, but also slower EC patterning (Fig. 2). If DLL4 production decreases below critical levels, no patterning is observed anymore and hypersprouting occurs.

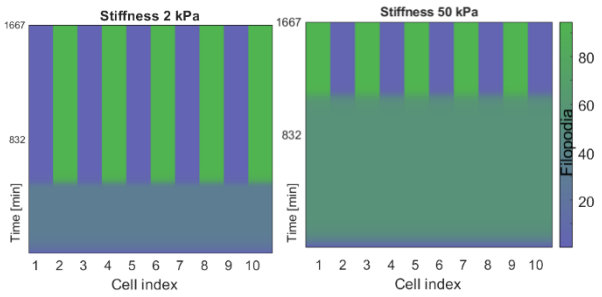

Figure 2: EC fate selection time (y-axis) for a row of ten cells (x-axis). The greener the color, the larger the filopodia content.

Discussion

Our study suggests the presence of a bi-phasic effect of stiffness on angiogenesis: a relatively small increase of the stiffness slows down EC fate selection, leading to sparser networks; whereas increasing the stiffness at higher values (e.g. 60 kPa and higher) leads to hypersprouting. While the latter has already been observed [1], the first trend could be validated in future experiments. Our study thus provides a first outlook on the YAP/TAZ-mediated influence of mechanics on the temporal dynamics of angiogenesis. In the future, the computational model will be further extended by including the effects of YAP/TAZ on other components of the VEGF-Notch crosstalk.

References

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Acknowledgements

This project was funded by the Marie-Sklodowska-Curie Global Fellowship (grant number 846617).