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What controls endothelial sprouting? Interstitial flow vs. shear stress

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INTRODUCTION: During angiogenesis, endothelial cell (EC) sprouting occurs when select ECs lining a vessel are exposed to stimulatory factors. Growth factor gradient has been proved to stimulate angiogenesis. However, the effect of shear stress on cell sprouting has been controversial [1-2]. Since certain level of media perfusion is required to support cell viability as well as to maintain the stability of the newly formed vascular network, it is necessary to fine-tune shear stress in engineered tissues. In the present study, we investigated the effect of different amounts of shear stress and interstitial flow on EC sprouting with the aim of finding a new approach to control vascular formation in thick engineered tissues.

METHODS: To determine how different ranges of interstitial flow and shear stress modulate sprouting, we developed a microfluidic platform that contains a crinkle line with different angles (Channel 1), a straight line (Channel 2) and a hydrogel channel in between. Both channels 1 and 2 were lined with a monolayer of ECs. Mural cells and ECs were mixed with the hydrogel and filled in the channel between the two EC lined channels. To assess the effect of shear stress on cell sprouting, the pressure drop in different parts of the channel 1 was kept constant. To apply interstitial flow in different directions, positive or negative pressure difference was considered between two channels. Shear stress and interstitial flow profiles were calculated using COMSOL simulation.

RESULTS & DISCUSSION: Biological self-assembling of ECs resulted in tube formation within the hydrogel after one week. ECs lined the channels 1 and 2 started to sprout and connect to the capillary bed based on the amount of shear stress they experienced. High amounts of shear stress restricted angiogenesis. In contrast, low amount of shear stress was suitable to initiate and support ECs sprouting. Interstitial flow was required to direct ECs connection to the capillary bed within the hydrogel, and making perfusable vascular networks.

CONCLUSIONS: Using a microfluidic platform, we found that biomechanical forces at special ranges direct sprout formation and can be used to control vascularization within engineered tissues.

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