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A novel microvascular-on-chip device for studying angio- and vasculogenesis under cyclic mechanical stress

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***Abstract*— A novel, double vessel chip exposed to three dimensional cyclic stretch, varying extracellular matrix stiffness and biochemical signals is presented in this work, in an effort to better mimic the *in-vivo* tissue environment and to provide a platform combining multiple mechanical and biochemical stimuli.**

***Clinical Relevance*— The integration of the blood microvasculature is one of the key challenges for the next generation Organs-on-Chip (OOC) platforms to enable the recapitulation of intricate biological processes involving the circulation of immune or cancer cells.**

I. INTRODUCTION

In-vivo, endothelial cells forming blood vessels are exposed to several mechanical and biochemical cues that influence their morphology and functions. OOCs incorporating vasculatures have mostly focused on the effects of shear forces through perfusion [1] and recently on the effect of a uniaxial cyclic stretch (CS) [2]. Our group recently developed a single vessel chip, where 3D strain can be induced [3]. Here, we present a double vessel chip with which the formation of new vessels from existing one (angiogenesis) and the *de novo* vessel formation (vasculogenesis) are investigated upon exposure to mechanical and biochemical cues.

II. METHODS

A polydimethylsiloxane (PDMS) chip is created using soft lithography. A central well with suspended needles and an underlying PDMS membrane serve as main culture area. This central well is filled with fibrin gel. After crosslinking and needle removal, circular channels for cell seeding are formed. The 100um thin membrane can be deflected by applying a cyclic vacuum underneath. This allows for a 3D CS of the gel-cell construct. Human umbilical vein endothelial cells (HUVECs) and fibrin of 20mg/ml or 30mg/ml concentrations are used. Additional treatments with vascular endothelial growth factor (VEGF, 50ng/ml) or CS (0.2Hz frequency, 12% linear strain) are applied.

III. RESULTS

Vasculogenesis was observed when cells were loaded between the tubes. HUVECs were added to the fibrinogen solution between the vessels, allowing for complementary vasculogenesis through cellular self-assembly. The impact of the CS on the self-assembled vessels resulted in a larger vascularized area and changed vessel dimensions (Fig. 1).

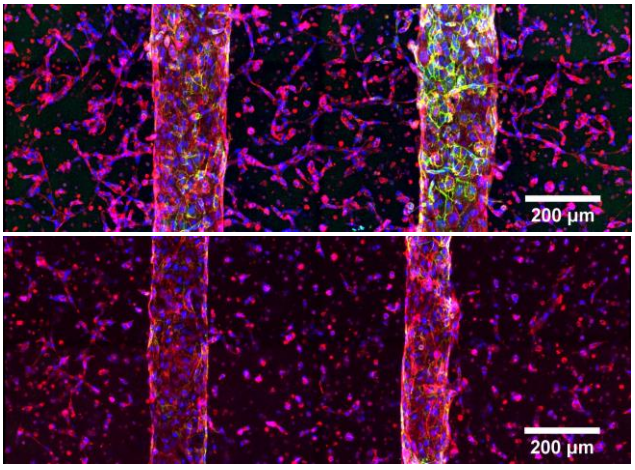

Figure 1. Representative images of the vasculogenesis model under CS (top) and static (bottom) conditions. (z-projected immunofluorescence images, blue: Hoechst, green: PECAM-1, red: F-actin).

Angiogenesis was investigated without cells between the vessels. Here, the length and the number of sprouts were assessed to evaluate angiogenesis under different conditions. Interestingly, the amount of sprouts between the two vasculatures was lower than lateral of the vessels, presumably due to a locally increased uptake of nutrients.

IV. DISCUSSION & CONCLUSION

With this novel, double vessel chip platform we could show the influence of biological and mechanical stimuli on the development of artificially created vasculature. This versatile model enables to further investigate the effect of continuous perfusion, create anastomotic capillaries and the use of other cell types for tissue barrier models.

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