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Heart-On-A-Chip Platform For The Study Of Myocardial-Vascular Interactions

INTRODUCTION: Although cardiac microphysiological systems hold great promise for drug testing and disease modeling, their physiological relevance is limited by anabsence of functional vasculature. Vessels are key regulators of mechanical and inflammatory signaling, but vascularization of microtissues remains a largetechnical hurdle. We report a heart-on-a-chip system that integrates cardiac spheroids within self-assembled, perfusable microvascular networks using a microfluidic device with circulating flow. This platform builds on our studies establishing perfusable vascular networks using an endothelial-based flow sensor driven by the expression of the transcription factor Krüppel-like factor 2 (KLF2), a key regulator of endothelial phenotype. Moreover, this platform incorporates two important nnovations: 1) We assess the impact of flow on the self-assembled vascular networks in 3D. 2) We control the levels of intravascular flow and assess vascular function in the self-assembled vascular networks and also determine contraction in the cardiac spheroid.

METHODS: Cardiac spheroids formed by aggregating human induced pluripotent stem cell-derived cardiomyocytes (CM), primary endothelial cells (EC) with a KLF2-GFP reporter that is activated by flow, and fibroblasts (FB) were suspended in a fibrin gel along with additional EC and FB and injected into our microfluidic device to form a heart-on-a-chip preparation. A pump attached to each chip was used to circulate media through the microvasculature and perfuse the cardiac spheroid. We measured changes in the vascular networks by assessing KLF2-GFP expression, measuring permeability to fluorescent dextran, staining for junctional proteins, and measuring changes in vessel morphology. We also measured changes in contraction from videos of beating spheroids.

RESULTS: Engineered vessels within our microfluidic device form a fully perfusable network with complex geometry. Application of flow activates the KLF2 pathway in the EC of these vessels, evidenced by increases in GFP fluorescence throughout the networks and the upregulation of endogenous endothelial KLF2. Further, flow conditioned vascular networks exhibit increased diameters, decreased branching, and decreased permeability. Importantly, we also demonstrate the full vascularization, perfusion, and contraction of cardiac spheroids in the platform. Finally, we measure changes in CM contraction driven by pharmacological agents that are introduced through the vasculature.

These data indicate that we have developed a fully vascularized and perfusable heart-on-a-chip system. In doing so, we present a new platform for dissecting flow mediated EC-CM interactions and define an approach for vascularizing a broad range of organoid models.