

The role of macrophages in immune-induced contractile dysfunction and vascularization of hearts-on-a-chip

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For decades, macrophages were thought of as a single monocyte derived subset and it was not clear how they could simultaneously mediate both injury and repair. Recent studies demonstrate that in contrast to monocyte derived macrophages, resident macrophages, arising from the yolk-sac, can facilitate cardiac repair. In this presentation, I will discuss the incorporation of macrophages from two different sources: human peripheral blood and differentiated hESC to facilitate cardiac disease modelling and vascularization of hearts-on-a-chip.

To model COVID-19 induced acute myocarditis, we perfused hearts-on-a-chip with peripheral blood mononuclear cells. This model demonstrated that immune cells increased proinflammatory cytokines, impaired contractile function, and disrupted calcium handling. Elevated circulating cell-free mitochondrial DNA (ccf-mtDNA) was observed, a hallmark of COVID-19-induced cardiac dysfunction confirmed in the plasma of COVID-19 ICU patients. Endothelial cell-derived exosomes effectively rescued contractile function, normalized calcium handling, increased contraction force, and reduced ccf-mtDNA and cytokine release, suggesting a promising therapeutic approach.

In contrast, when human pluripotent stem-cell-derived primitive yolk-sac-like macrophages were integrated within vascularized heart-on-chip platforms, macrophage incorporation profoundly impacted the functionality and perfusability of microvascularized cardiac tissues up to 2 weeks of culture. Macrophages mitigated tissue cytotoxicity and the release of cell-free mitochondrial DNA (mtDNA), while upregulating the secretion of pro-angiogenic, matrix remodeling, and cardioprotective cytokines. Bulk RNA sequencing (RNA-seq) revealed an upregulation of cardiac maturation and angiogenesis genes. Further, single-nuclei RNA sequencing (snRNA-seq) and secretome data suggest that macrophages may prime stromal cells for vascular development by inducing insulin like growth factor binding protein 7 (IGFBP7) and hepatocyte growth factor (HGF) expression. Our results underscore the vital role of primitive macrophages in the long-term vascularization of cardiac tissues, offering insights for therapy and advancing heart-on-a-chip technologies.