MICROVASCULAR ENGINEERING: DYNAMIC CHANGES IN MICROGEL-ENTRAPPED VASCULAR CELLS CORRELATES WITH HIGHER VASCULOGENIC/ANGIOGENIC POTENTIAL

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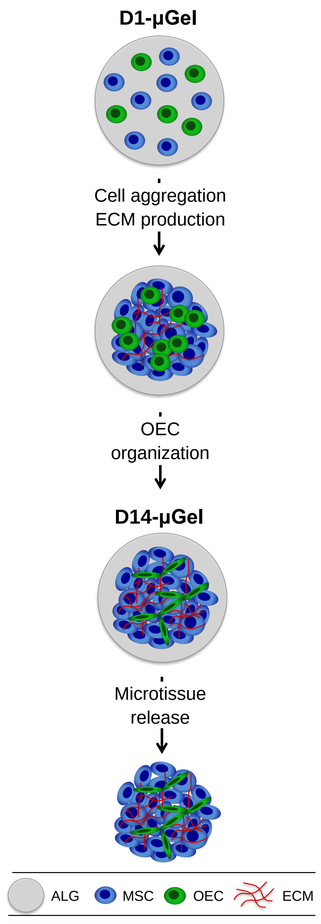
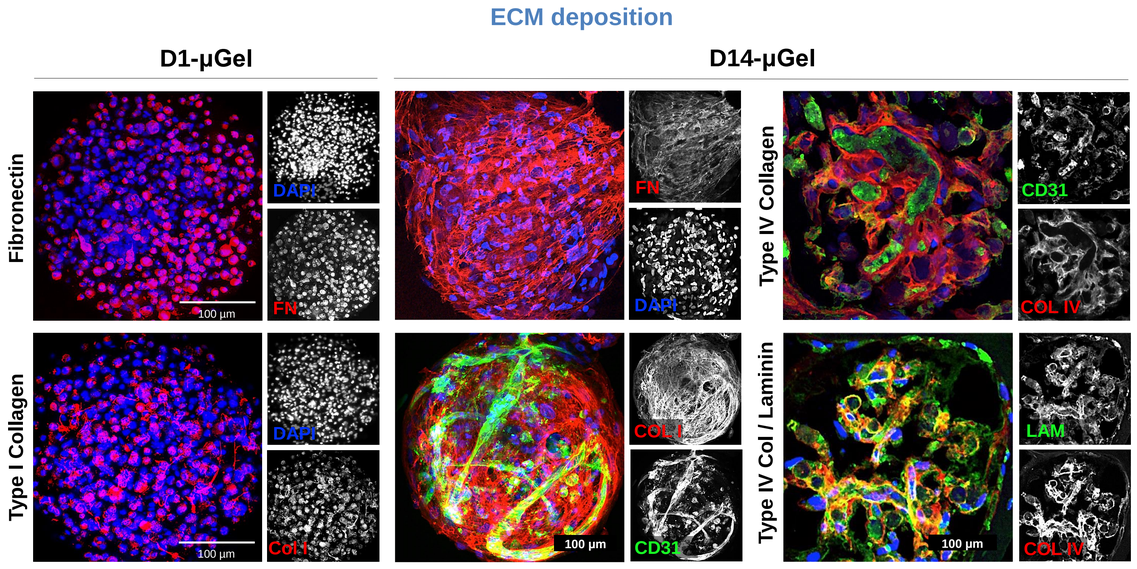
OVERVIEW Ischemic vascular diseases are the leading cause of mortality worldwide, but several remain untreatable. While advanced therapies combining vessel-forming cells and biomaterials to induce vascularization show promise, those involving in vitro formation of primitive vascular beds prior to transplantation are still scarce. Microparticles are appealing for minimally invasive therapeutic vascularization. In those systems, in vitro priming can enhance endothelial vessel formation, but associated cellular changes remain elusive. Here, outgrowth endothelial cells (OEC) and mesenchymal stem cells (MSC) self-organized into vascularized microtissues within bioengineered microgels. During in vitro maturation, OEC formed vessel-like networks enveloped in newly-formed ECM. Gene expression profiling showed that MSC remained transcriptionally stable, while OEC acquired a more mesenchymal-like phenotype, suggesting the occurrence of a partial endothelial-to-mesenchymal transition (EndMT). The secretome of entrapped cells was also altered, creating a pro-angiogenic niche, while not affecting the inflammatory profile. Importantly, In vitro maturation of microgels translated into improved cell survival/retention after transplantation in mice, with preservation of capillary-like networks and de novo formation of human vascular structures. These findings support that in vitro priming and morphogenesis of vessel-forming cells, prior to implantation, improves their vasculogenic/angiogenic potential, which is therapeutically relevant, shedding some light on associated mechanisms.

Microgel-entrapped cells co-assemble into vascularized microtissues

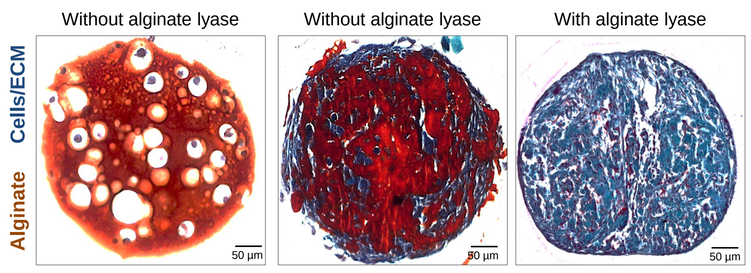
MICROTISSUE formation



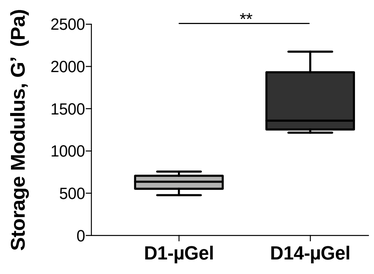
ECM deposition



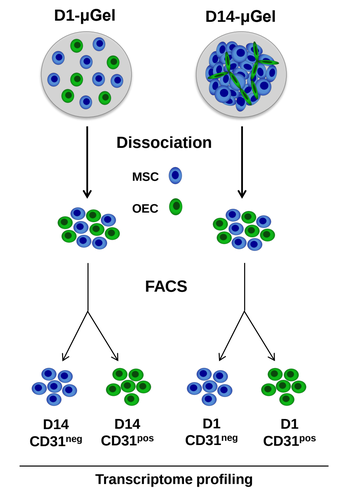
Microtissues remain cohesive upon alginate degradation



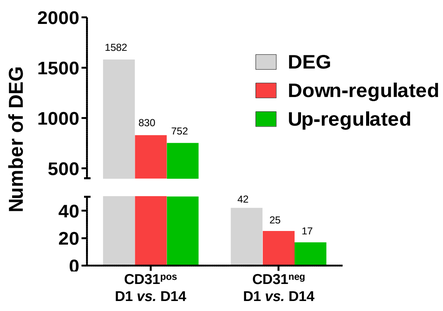
Viscoelastic properties



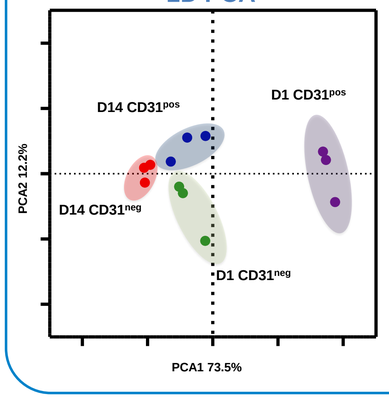
OEC gene expression profile changes along microgel maturation



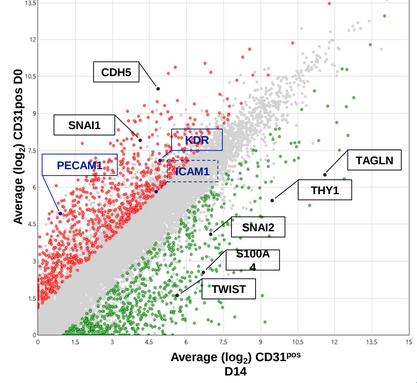
Differentially expressed genes



2D PCA

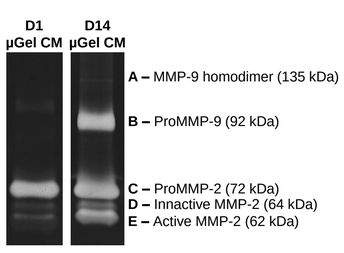


MA plot



Cells in matured microgels: more pro-angiogenic secretome with similar inflammatory profile

MMP activity (zymography)



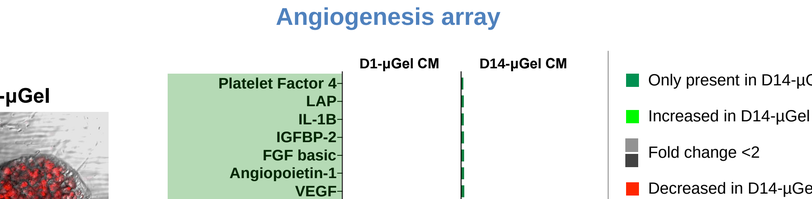
Angiogenesis array

Only present in D14-µGel CM
Increased in D14-µGel CM
Fold change <2
Decreased in D14-µGel CM

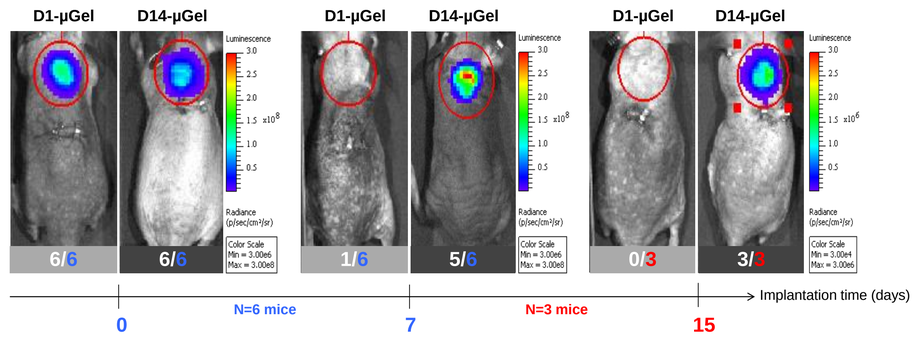
CAM assay

Cytokine array

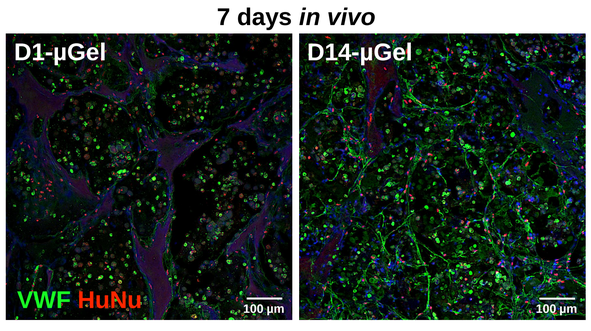
Air-pouch mice model



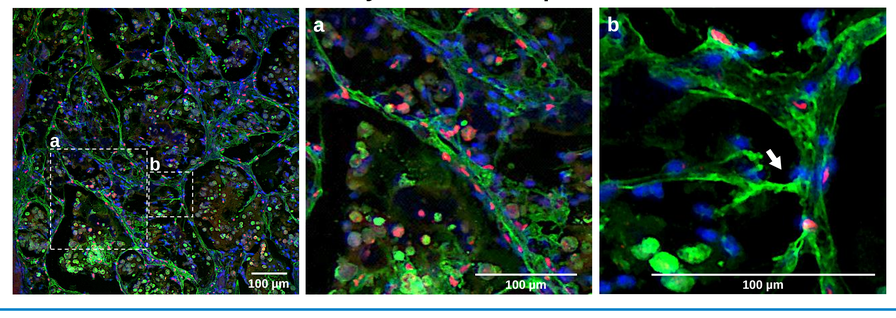
Cells in matured microgels: enhanced *in vivo* survival/engraftment & vessel-formation ability



7 days *in vivo*



15 days *in vivo:* D14-µGel



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