Harnessing Cell-instructive Hydrogels and Spheroid Bioassembly Technologies for Biofabrication of Functional Tissues

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Biofabrication technologies, including 3D bioprinting and bioassembly, enable the generation of engineered constructs that replicate the complex 3D organization of native tissues via automated hierarchical placement of cell-laden bioinks, tissue modules, and/or bioactive factors. Photo-initiated radical polymerization combining light and photo-initiators to generate radicals for crosslinking photo-polymerizable macromers, has been widely employed in 3D bioprinting of cell-laden hydrogels [1,3]. Despite rapid advances in biofabrication technologies, no universal bioink exists, requiring optimization of each bioink for each individual biofabrication technique and specific tissue niche. Bottom-up spheroid biofabrication strategies offer the flexibility to precisely arrange cellular modules to mimic the zonal structure of the tissue as well as uncouple the reliance on narrow biofabrication windows to manipulate cell signaling processes through spatial presentation of different biomolecules.

This presentation discusses alternative strategies to provide highly tuneable bioinks that 1) promote a specific cell-instructive niche using light-activated crosslinking in high throughput modular spheroids, and 2) are printable across multiple biofabrication technologies, including extrusion-, lithography- and microfluidic-based bioprinting.

We describe the design of versatile photoinitiator system (Ru/SPS) and photo-clickable, cell-instructive gelatin-based bioinks and bioresins for biofabrication of 3D *in vitro* models. Importantly, tailoring macromolecular chemistry offered by the platform by varying photoinitiator and thiolated crosslinker (DTT, PEG-SH) concentration, we modulated the cell-instructive tissue niche for multiple cell types via: covalent incorporation of thiolated bioactives (e.g. heparinSH), nanocomposites (e.g. strontium, Laponite), di-tyrosine cross-linking of decellularized extracellular matrix (ECM) bioinks, and tailored Ru/SPS photoinitiator delivery presenting stiffness gradients in cell-laden bioinks. Examples discussed include yielding enhanced chondrogenic and osteogenic differentiation and vascular network formation [2,3,5,9].

We further discusses our experiences in developing hybrid tissue constructs and convergence with 3D spheroid bioassembly platforms for probing multicellular spheroid fusion, extracellular matrix (ECM) formation and stem cell niche, offering new paradigms for high-throughput screening, “on-chip” and osteochondral tissue repair applications.

This work demonstrates a significant breakthrough in development of cell instructive universal bioink platforms for 3D bioprinting and regenerative medicine, and advances biofabrication and bioassembly of functional tissues and clinical translation of the technology.

References

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