Rapid Synthesis of Multiscale and Multicomponent 3D Tissues by Chemically Programmed Assembly

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Tissue structure underlies the physiology of development and normal tissue function, as well as the pathophysiology of many diseases. Thus, methods for reconstituting tissue structure from single cells will be critical for tissue engineering and regenerative medicine. To construct defined three-dimensional (3D) tissue structures from single cells, across centimeter distances, and in a manner that is amenable to long-term culturing and imaging, we combine microscale direct writing of oligonucleotides with Chemically Programmed Assembly (CPA). The process begins by chemically remodeling the adhesive properties of individual cells using degradable oligonucleotide "velcro," thus allowing cells to rapidly and specifically adhere to materials and other cells coated with complementary DNA sequences. Living cells are thereby rapidly assembled, layer-by-layer, onto a DNA-patterned substrate. Assembled tissues can span several centimeters and are released directly into ECM gels for 3D culture and imaging. We demonstrate schemes for the synthesis of a variety tissues having precise sizes, shapes, cellular compositions, and spatial arrangements fully embedded within ECM gels. These tissues are assembled with single cell spatial resolution and incorporate multiple cell types, providing an unprecedented means to interrogate cell-cell interactions in the context of complex 3D tissue microenvironments. For example, we quantitatively analyze cooperative and competitive interactions between malignant and non-malignant mammary epithelial cells in the same tissue, and observe physical interactions among epithelial, endothelial, and fibroblast cells assembled into a single integrated 3D tissue.