Engineering Extracellular Environments in 2D and 3D

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Synthetic tools to control the local molecular (nanoscale) and cellular (microscale) environments of individual cells and cell populations *in vitro* are emerging as important complements to *in vivo* approaches for illuminating signaling cues in the extracellular environment on cell responses and provide a foundation for controlling these responses *in vivo*. At the nanoscale, one role for synthetic tools is to parse the role of individual receptors in governing an overall cell response in ways that are difficult to do with ECM molecules that have multimeric sites for cell interactions. For example, tenascin-C, an ECM molecule upregulated in development, wound healing, and cancer, is a known ligand for several integrins but also has epidermal growth factor (EGF)-like repeats that can activate the EGF receptor. Tenascin C may thus serve to control the relative homotypic and heterotypic interactions between EGFR and integrins, and the spatial localization of EGFR to the cell surface. To parse such structure-function relationships, we have developed synthetic materials that present integrin ligands and EGF in controlled nanoscale arrangements in the cell environment and find that physical receptor interactions can control cell signaling responses in several cell types, including primary mesenchymal stem cells. At the level of the capillary bed, we have developed a microreactor system that fosters organization of isolated liver cells into tissue-like structures and that allows for local, controlled perfusion of the *in vitro* 3D tissues at the microscopic level, and substantial retention of liver-specific functions *in vitro*. A current application of this approach is to provide a tissue microenvironment for evaluating the factors regulating the growth of individual prostate tumor cells into microscale tumors in the context of liver tissue. The localized perfusion enables growth of tumors to several hundred microns without a necrotic core and may serve as a model for early stage tumor growth in tissue.