Abstract—Microscale technologies are emerging as enabling tools for tissue engineering and biology. Here, we present our experience in developing microscale technologies to regulate cell-microenvironment interactions and generate engineered tissues. Specifically, we will describe the use of microengineered shape-controlled hydrogels to generate biomimetic 3D tissue architectures, the utility of surface patterning approaches for controlling cell-cell interactions and engineered microchannels for controlling cell-soluble factor interactions.

INTRODUCTION

Tissue engineering, is an interdisciplinary research field that aims to generate transplantable tissues that can restore, maintain, and enhance tissue function[1, 2]. However, despite significant advances in tissue engineering, a number of challenges limit the therapeutic applications of tissue engineering approaches.

Microscale technologies are enabling tools for addressing the challenges imposed by conventional tissue engineering methods. Microscale technologies enable the control of cell-microenvironment interactions, such as cell-cell, cell-extracellular matrix (ECM), and cell-soluble factor interactions[3]. One such technique is soft lithography. In soft lithography, elastomeric poly(dimethylsiloxane) (PDMS) stamps made from photore sist- patterned silicon masters can be used to manipulate the topography of a surface at sub-micron resolution in a rapid and inexpensive manner. Moreover, microengineering approaches are used to create tissue scaffolds with enhanced physical, mechanical, and biological properties. In this paper, we present various microscale technologies (i.e. surface patterning, microfluidics, microengineered hydrogel arrays) for tissue engineering applications.

Surface patterning for regulating cell-cell contacts

Microscale surface patterning can be used to control cell-cell contacts and cellular shapes. Various microscale technologies, such as microtopography[4-9], microfabricated stencils[10-12], and layer-by-layer deposition[13], have been used to pattern cells within geometrically defined substrates. For example, hyaluronan modified with photoreactive methacrylates has been used to make microstructures[5].

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Microfluidics for spatial control of cell-soluble factor interactions

Microfluidic systems are powerful tools for controlling the spatial and temporal aspects of cell-soluble factor interactions. Microfluidic systems have been used to control cell docking[14] and cell-soluble factor interactions. For example, a multiphenotype cell array inside a microfluidic channel was fabricated by reversibly sealing a PDMS mold with the impression of the fluidic channel to a microwell-containing substrate. Cells and fluids were selectively delivered to the microwells. This microfluidic device containing sequentially aligned orthogonal microchannels is a potentially useful approach for the high-throughput experimentation.

Microfluidics has also been used to create stable hydrogel gradients and generate cell-laden hydrogel scaffolds. These microfluidic devices can address several challenges associated with current scaffolds, such as the inability to
control the complex cellular interactions in the scaffolds and the lack of vascularization. Microfluidic systems can be used to synthesize microengineered scaffolds that can overcome these limitations[15]. To generate hydrogel scaffolds with gradients, materials can be generated with embedded gradients by using a microfluidic device[16]. By creating gradients of adhesive peptides conjugated within hydrogels, the attachment of endothelial cells along the material can be controlled.

Microfluidic devices have also been shown as a promising tool to facilitate the exchange of nutrients and oxygen in 3D tissue constructs. We have recently developed cell-laden hydrogel microfluidic channels and demonstrated that (just like in real tissues) only cells near microfluidic channels remained viable after three days in vitro [17]. These cell-laden hydrogel microfluidic devices can be scaled up by stacking the vascular patterns to create biomimetic multi-layer vascularization. Therefore, microfluidic devices are powerful tools for controlling cell-soluble factor interactions and are increasingly used by biologists and tissue engineers to study cell behavior and create tissue constructs.

**Microengineered hydrogel arrays for tissue engineering**

Recently the merger of microengineered hydrogels and microscale techniques has been used to develop new approaches to create 3D tissue constructs. We have developed bottom-up tissue engineering technique that use directed assembly of hydrogels. In this approach, tissue-mimetic building blocks are generated and subsequently assembled to create larger structures. The shape of the individual pieces can be controlled to enable their assembly by using directed self-assembly[18, 19] or stop-flow lithography in a microfluidic device[20]. Therefore, the modular design and assembly of these approaches can influence many areas of tissue engineering.

**CONCLUSIONS**

The merger of microscale technologies and hydrogels offers new opportunities to address the challenges imposed by existing technologies to create 3D tissue scaffolds and control cellular behavior.

**REFERENCES**


