Manipulating Cellular Response Through Polymer Chemistry and Morphology

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Introduction

Cells respond to both physical and chemical cues and the combination of both allows us to engineer scaffolds to guide cell migration and growth. Guided tissue regeneration and controlled healing are critical goals of tissue repair strategies and require control of cell growth.

There are several tissue engineered scaffolds that have been designed with a specific porosity and pore-size distribution in mind. Taking the biology and implant morphology into consideration in the design of the scaffold has led to some success for us in bone tissue engineering strategies.

The combination of physical and chemical stimuli has allowed us to guide nerve cells and neurites. By mimicking the contact-mediated and diffusible signaling molecules that guide nerve fibers in development, we have created patterned 3-dimensional gels modified with peptides to guide nerve fiber regeneration.

These two regenerative tissues – bone and nerve – will be used as examples to describe our advanced materials strategies for controlled cell guidance.

Experimental

Detailed experimental descriptions are available in published papers. Briefly, bone tissue engineering scaffolds were prepared from poly(lactide-co-glycolide) PLGA 75/25 that was first dissolved in DMSO and mixed with polysaccharide particulates followed by freezing at – 20^{o}C and then immersed in water, where both phase inversion and particulate leaching resulted in highly interconnected macro-porous scaffolds.

Nerve guidance channels were prepared by a liquid-liquid centrifugal casting method where HEMA, MMA, redox initiators and EDMA were dissolved in excess water and polymerized within a cylindrical glass, spinning mold.

Porous scaffolds were prepared in PHEMA-AEMA gels using a fiber templating technique followed by peptide modification of primary amine groups of AEMA. Primary dorsal root ganglia neurons were plated within the resulting channels and found to be guided by both the physical cues provided by the channel and stimulated to grow by the laminin-derived peptides.

A new 3-D patterning methodology that combines laser technology with photochemistry was developed to create cylindrical volumes of peptides separated by non-cell-adhesive volumes of gel. These patterned gels were tested for guided cell and process migration of primary neurons.

Results

Biodegradable PLGA scaffolds were synthesized with a morphology similar to that of trabecular bone and found to support ubiquitous cell colonization , as demonstrated in vitro with immunolabeling, and tissue penetration, as demonstrated by in vivo studies in segmental osteotomy models in rabbit femurs.

PHEMA-MMA copolymer hollow fiber membranes were synthesized and compared for mechanical and transport properties in terms of formulation chemistry. Biodegradable polysaccharide hollow fiber membranes have been similarly prepared. Both have been studied for repair of the transected rat sciatic nerve.

Guided cell and neurite growth has been achieved in physical channels, created by fiber templating, and then chemically modified with laminin-derived peptides, YIGSR and IKVAV. Peptide modification was critical for neurite outgrowth and the channel was critical for guidance.

Similar results were achieved in biochemical rods created in agarose gels, where the only difference between the "rods" and the surrounding material was the chemistry. Using a focused laser and 2-nitrobenzyl protecting groups, peptides were immobilized within the agarose in defined volumes, but the physical properties of agarose were unchanged. Primary neurons plated on these gels aggregated on the peptide volumes and penetrated into these regions exclusively. The non-adhesive surrounding gel served to limit cell migration and neurite outgrowth to the peptide volumes that filled the gel.

Discussion

The examples described here combine morphology and chemistry of scaffold design to achieve cell and process guidance. While physical cues and chemical cues are each individually important, the synergy achieved with both is powerful. With guided cell migration, guided tissue regeneration will follow, leading to the development of new tissues and organs for ultimate application in regenerative medicine strategies. These principals are applicable to a variety of tissues and organs and have to be modified for the tissue biology; however, the underlying principals are the same.

References

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