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Harnessing Topographical Cues for *Tissue Engineering*

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Biomaterials play a pivotal role in the field of tissue engineering as their surface can influence cell behavior. Initially, biomaterials such as polymers from natural (collagen, fibrin, hyaluronic acid, alginate, hydroxyapatite, β-tricalciumphosphate, etc.) or synthetic (polylactic acid, polyglycolic acid, polyethylene glycol, polycaprolactone [PCL], etc.) origin primarily had a passive scaffolding function. However, it has become increasingly appreciated that biomaterials can directly instruct cell behavior through physical and biochemical signals such as their stiffness, micro/nanotopography, surface chemistry, cell adhesivity, crystallinity, release dynamics, degradation-by-products, and so on. Moreover, the interactions at the cell–biomaterial interface are a dynamic interplay of ''give-and-take,'' where, for example, cells degrade the biomaterial and the degradation-by-products can in turn influence cells' behavior.

Despite the fact that it has been extensively shown that surface topographies greatly affect cell behavior, they have only been recently explored for applications in tissue engineering (first publication in *Tissue Engineering* in 2007). In this special collection, we will highlight articles that exploit the power of surface topography for applications in retinal regeneration,[1] nerve regeneration,[2] cartilage repair,[3] bone repair,[4] dermal wound healing,[5] and vascularization.[6] For example, Yao *et al.*[1] fabricated a biodegradable PCL scaffold with varying surface topographies using microfabrication techniques. They showed that the PCL scaffolds induced the differentiation of mouse retinal progenitor cells toward a photoreceptor fate *in vitro* and that the tissue-engineered constructs could be delivered into the subretinal space of mice with minimal disturbance. Moreover, functional integration was assessed by the expression of photoreceptor markers (i.e., Crx, Recoverin, and Rhodopsin). Yoon *et al.*[4] demonstrated that microgrooves with radial arrangement more efficiently recruited osteoblasts, correlating with the upregulation of cell migration signaling molecules (i.e., E-cadherin, Rac1, and PI3K). *In vivo*, these implants resulted in improved bone repair in mouse calvarial defect models. Interestingly, Chaterji *et al.*[6] used nanotopographies to engineer an *in vitro* testing environment that is able to induce various vascular smooth muscle cell phenotypes corresponding to healthy, diseased, and aged arterial beds.

To fully harness the potential of surface topographies, future research should address the challenges associated with topographical diversity, combinatorial complexity of biomaterial properties, and more fully understanding the cell signaling pathways that are involved in topographical sensing. First, most studies to date focus on limited topographical shapes such as pits, pillars, or grooves. However, using computational tools, libraries of surface topographies can be designed and microfabricated to increase the diversity of patterns and the identification of hit surfaces.[7] Alternatively, diverse surface topographies can be inspired by nature-derived surface structures, such as shark skin, which prevents bacteria attachment and biofilm formation.[8] Second, only a small number of biomaterial properties are typically analyzed simultaneously, neglecting potential synergies or even antagonistic effects between multiple biomaterial properties (stiffness, surface topography, composition, cell adhesivity, etc.). The same applies to the soluble biochemical environment where, for example, limited growth factor types and concentrations are explored. In this respect, the study of Chaterji *et al.*[6] nicely demonstrates the synergistic effects of nanotopographical cues and substrate stiffness on vascular smooth muscle function. Due to the complex interplay between cells and substrates and the daunting number of ways in which biomaterials can be modified, combinatorial screening approaches, typically used in the pharmaceutical industry for drug discovery, are an exciting avenue to tackle this combinatorial complexity (''materiomics'').[9] Finally, to further optimize and advance current topographical designs, a fundamental understanding of the mechanisms of action underlying topography-induced cellular behavior is required. In this respect, Stukel *et al.*[10] and Miyoshi *et al.*[11] provide an informative overview of this area of investigation.

In conclusion, there are many exciting ideas on how to diversify surface topographies and tailor them together with other properties to accelerate the transition of biomaterials from passive space-filling scaffolds to bioactive, cell-instructive materials.

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