Review

Engineering microscale topographies to control the cell–substrate interface

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Cells in their in vivo microenvironment constantly encounter and respond to a multitude of signals. While the role of biochemical signals has long been appreciated, the importance of biophysical signals has only recently been investigated. Biophysical cues are presented in different forms including topography and mechanical stiffness imparted by the extracellular matrix and adjoining cells. Microfabrication technologies have allowed for the generation of biomaterials with microscale topographies to study the effect of biophysical cues on cellular function at the cell–substrate interface. Topographies of different geometries and with varying microscale dimensions have been used to better understand cell adhesion, migration, and differentiation at the cellular and sub-cellular scales. Furthermore, quantification of cell-generated forces has been illustrated with micropillar topographies to shed light on the process of mechanotransduction. In this review, we highlight recent advances made in these areas and how they have been utilized for neural, cardiac, and musculoskeletal tissue engineering application.

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1. Introduction

The microenvironment in which cells reside in vivo exhibits a complex milieu of signals which play an essential role in a diverse set of cellular processes [1]. Cells are capable of sensing and responding to a plethora of signals, consisting of biochemical and biophysical cues, over a wide range of length scales [2]. Many of these cues are provided by the extracellular matrix (ECM), which acts as a cellular scaffold and is the primary extracellular component of tissues [3]. In vivo, the ECM, through its structure and molecular composition, presents a variety of geometically-defined, three-dimensional (3D) physical cues on the order of micron and sub-micron scale, known as topographies [4–6]. The ECM is composed of proteins and polysaccharides with structural widths and lengths in the nano- and micrometer range, respectively [7]. These individual ECM components are folded and bent to form secondary supramolecular structures—held by secondary and disulfide bonds, and hydrophobic interactions—with micron-size topographies [8]. The intestinal mucosa is a case in point illustrating the wide range of topographical length scales present in vivo. This tissue consists of finger-like projections known as villi which are epithelial folds 400–500 μm in dimension [9,10]. Each villi is further folded into smaller microvilli and at the base of each villi are epithelial invaginations known as intestinal crypts that are 100–200 μm in dimension. The intestinal mucosa is supported by a basement membrane containing surface pores 1–5 μm in diameter and 50 nm-thick collagen fibers. The interaction and response of cells with these topographies are mediated through a phenomenon called contact guidance [11]. Contact guidance is known to affect cellular behaviors such as adhesion, morphology, migration, and differentiation [12–16]. Another type of physical cue displayed by the ECM is mechanical stiffness through which, similar to topography, a diverse set of cellular functions can be modulated [17,18].

The effect of physical stimuli on cellular function has long been recognized [11,17–21]. Through a process known as mechanotransduction, various physical cues in a cell’s surrounding environment are integrated and converted to biochemical, intracellular signaling responses that lead to changes in cell function [17,19]. At the nanometer length scale, the topography of the ECM affects sub-cellular behaviors such as the organization of the cell adhesion molecule receptors, whereas at the micron level, cellular and supracellular characteristics such as cell morphology and