ELSEVIER

Polymers to direct cell fate by controlling the microenvironment

R Warren Sands and David J Mooney

Enhanced understanding of the signals within the microenvironment that regulate cell fate has led to the development of increasingly sophisticated polymeric biomaterials for tissue engineering and regenerative medicine applications. This advancement is exemplified by biomaterials with precisely controlled scaffold architecture that regulate the spatio-temporal release of growth factors and morphogens, and respond dynamically to microenvironmental cues. Further understanding of the biology, qualitatively and quantitatively, of cells within their microenvironments and at the tissue–material interface will expand the design space of future biomaterials.

Address
Harvard University, School of Engineering and Applied Sciences, Cambridge, MA 02138, USA

Corresponding author: Mooney, David J (mooneyd@seas.harvard.edu)

Current Opinion in Biotechnology 2007, **18**:448–453

This review comes from a themed issue on
Tissue and cell engineering
Edited by Alan Trounson and Andrew Elefanty

0958-1669/$ – see front matter

DOI 10.1016/j.copbio.2007.10.004

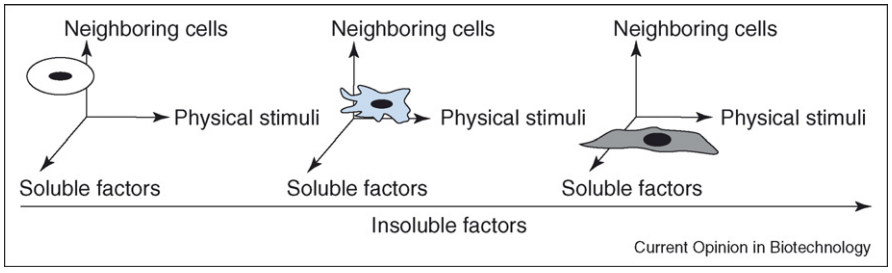
Introduction

Tissue engineering and regenerative medicine hold the promise to treat and even cure a wide range of diseases ranging from acute pathology (e.g. traumatic injury) to chronic diseases (e.g. cardiovascular disease, cancer, and diabetes) and materials will typically play a prominent role in these therapies. In addition to maintaining, replacing or regenerating lost, diseased, or damaged tissues, tissue engineering, and regenerative medicine may provide artificial tissues for extracorporeal support, pharmacologic testing, or the enhancement of normal tissue function. The field has already contributed model systems to facilitate basic biological studies and led to the development of FDA-approved therapies [1]. Materials are a cornerstone of tissue engineering and regenerative medicine and have grown from inert mechanical supports, physical bridges, or cell and drug delivery vehicles with poorly understood biologic functions or limited control to dynamic substrates that serve as cell instructive materials by directing interactions at the tissue–material interface. By better understanding and incorporating elements of the cellular microenvironment, this new generation of materials promises to allow greater control over cell fate and ultimate tissue structure and function. This review will address the recent progress in material designs and fabrication approaches that are leading to the development of increasingly multifunctional mimics of the native cellular microenvironment. As the fundamental biology of the cellular microenvironment is often the inspiration for material design, this review will begin with a brief discussion of the cellular milieu, and then highlight polymers that direct the tissue–material interface through the controlled presentation of specific cues in time or space, or in response to external signals. Finally, a discussion of current and potential future approaches to further develop a quantitative understanding of the biology within cellular microenvironments and at the tissue–material interface will be provided as this knowledge will enrich the palette for future polymer design. The chemistry and physical properties of materials are critical parameters for directing cell fate and are discussed as they pertain to the spatial control of the scaffold architecture, the spatial and temporal control of morphogen and growth factor delivery, and dynamic polymer design; for a more comprehensive review on these topics the reader is encouraged to refer to other recent articles [2,3].

The cellular microenvironment

The cell is immersed in a dynamic landscape composed of insoluble macromolecules of the extracellular matrix (ECM), soluble bioactive factors, and neighboring cells (Figure 1). The landscape varies from tissue to tissue and changes during disease and aging. Three of the principle molecular signals within this environment include insoluble hydrated macromolecules, soluble molecules, and cell surface proteins [4]. These signals are sensed, integrated, and processed by the cell to determine behavior and function, and information is passed bi-directionally as the microenvironment is remodeled by the cells. Information is encoded within the chemical identity, localization, duration, and context of these molecular cues. Spatial cues are displayed in 3D [5] and can include signaling gradients such as that observed during chemotaxis, haptotaxis, and mechanotaxis. Moreover, spatial cues are found at many length scales. Architectures range from the nanometer to the centimeter length scales [2,6–10], exemplified by ECM fibers, cells, and tissue tubes, folds, and bends. In addition, the concentration, duration, and context of the molecular cues contain information that dictates cell fate. As exemplified by angiogenesis, certain growth factors initiate angiogenesis, while a second group of growth factors induces maturation. Later, a third cohort of molecules maintains the integrity of the established vasculature [11,12]. If the

Figure 1



4D pseudo-phase diagram of cell fate. The cellular microenvironment is composed of signals from neighboring cells, physical stimuli, soluble factors including growth factors, and insoluble molecules such as the extracellular matrix. The effects of these variables are plotted as different axes on this 4D diagram of cell fate (e.g. differentiation) and are symbolized in this illustration by the different shapes and colors of the cells located at different positions in space. In advanced tissue engineering and regenerative medicine the biomaterial may direct cell fate through any of the variables. The signals from the biomaterial may change over time as a result of pre-programmed spatio-temporal control or in response to the microenvironment, allowing for the recapitulation of complex signaling pathways.

appropriate concentration, duration, and context (e.g. presence and sequence of multiple factors) are not achieved, poor vascularization results. Finally, the microenvironment changes dynamically over time. The ECM is continually processed, degraded, and synthesized anew, altering the matrix's presentation of chemical cues and elasticity, and leaving behind proteolytic fragments and cryptic domains that in turn affect cellular activity [13,14]. Meanwhile, soluble bioactive factors are secreted and destroyed as the cells migrate, differentiate, proliferate, and undergo apoptosis.

Spatial control of the scaffold architecture

Polymeric materials designed in the past incorporated many signals found within the microenvironment but typically only provided one or two cues in a static manner. The focus of current efforts is to dynamically encode the localization, duration, and context of multiple cues to adequately integrate signaling and direct cell fate in light of the host microenvironment. This aim requires control over architecture at multiple size scales, spatiotemporally regulated release of signaling molecules, and dynamic polymer design.

Within the past decade, a dramatic increase in the resolution of control over scaffold architecture has been achieved through microfabrication technologies and has led to the recent widespread use of this technology for tissue engineering and regenerative medicine applications. In comparison to traditional polymer processing methods, microfabrication, and more recently nanofabrication, may allow for design at the nanometer to the supramillimeter length scale (Figure 2) [15,16] and for exquisite control of the internal architecture of the material *a priori*, facilitating the patterning of immobilized chemicals, cells, and mechanical gradients [17]. High-resolution spatial control could benefit a wide range of applications from artificial blood vessels with compliances that match host tissue to directional nerve guidance channels to aid neural regeneration. In many fabrication procedures, however, increased spatial resolution comes at the expense of long fabrication times. Thus, efforts are underway to create high throughput technologies suitable for bulk fabrication of a wide range of materials that can maintain spatial resolution.

Soft lithography and multiphoton photocrosslinking allow for submicrometer to supramillimeter spatial control. Soft lithography has been used with microfluidics to create hydrogels with gradients of adhesive ligands and mechanical properties [18] and complex spatial gradients can be readily generated [19]. Increased 3D resolution down to the submicron range can be achieved with multiphoton photocrosslinking but at the expense of fabrication time. To decrease processing time, mask-based methods for rapid prototyping have been developed [20] and could be further improved if used in tandem with a micro-mirror-based masking device [21•]. The utility of microfabrication techniques has been demonstrated in the design of 3D skin substitutes with an artificial epidermis containing micrometer scale features similar to the rete ridges and dermal papillae found in normal skin at the epidermal–dermal junction [22]. The depth and width of the engineered invaginations was demonstrated to influence keratinocyte stratification and differentiation.

Electrospinning has emerged as a prominent method for nanometer scale design not addressable with traditional microfabrication techniques, at the expense of control over internal scaffold architecture, void space connectivity, and mechanical properties. However, both synthetic and natural polymers can be electrospun into fibers with diameters ranging from the 10s of nanometers to several micrometers [23,24]. The goal of recent work has been to create more complex materials with defined internal architectures. To this end, composite materials and aligned fibers have been synthesized and utilized for vascular [25] and meniscal [26] tissue engineering applications,