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Dynamically tunable cell culture platforms for tissue engineering and mechanobiology

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ABSTRACT

Human tissues are sophisticated ensembles of many distinct cell types embedded in the complex, but well-defined, structures of the extracellular matrix (ECM). Dynamic biochemical, physicochemical, and mechano-structural changes in the ECM define and regulate tissue-specific cell behaviors. To recapitulate this complex environment *in vitro*, dynamic polymer-based biomaterials have emerged as powerful tools to probe and direct active changes in cell function. The rapid evolution of polymerization chemistries, structural modulation, and processing technologies, as well as the incorporation of stimuli-responsiveness, now permit synthetic microenvironments to capture much of the dynamic complexity of native tissue. These platforms are comprised not only of natural polymers chemically and molecularly similar to ECM, but those fully synthetic in origin. Here, we review recent *in vitro* efforts to mimic the dynamic microenvironment comprising native tissue ECM from the viewpoint of material design. We also discuss how these dynamic polymer-based biomaterials are being used in fundamental cell mechanobiology studies, as well as toward efforts in tissue engineering and regenerative medicine.

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1. Introduction

The cellular microenvironment regulates many important biological functions, including adhesion, growth, migration, and differentiation [1,2]. In addition to the biochemical properties of the extracellular matrix (ECM), mechano-structural cues such as elasticity and topography are of great importance in microenvironmental-based governance of cell function [3,4]. Growing evidence suggests that mechano-structural cues differentially modulate cell fate in a hierarchical response [5–8]. Efforts to elucidate the effects have primarily centered on static systems where the biochemical and biophysical properties of matrices remain constant over time. Studies focused on the effect of static topography and elasticity of the ECM in artificial materials have enabled the advanced interrogation of cellular mechanotransduction responses to these cues [9–14]. Biochemical cues also play a crucial role in directing cellular function and fate, and the relationship between their 'static' effect and cellular responses has been addressed by material-based and molecular biology approaches [15,16]. However, we know that cellular microenvironments *in vivo* gradually change their physicochemical properties, as evidenced in cardiomyopathies and in cancer progression [17–19]. This dynamic nature, in turn, is closely related to tissue/organ development, regeneration, wound healing, and disease progression over time [20]. Therefore, *in vitro* platforms that recapitulate dynamic *in vivo* signaling may provide for an enhanced understanding of fundamental biological processes, and could lead to eventual advances in tissue engineering and regenerative medicine.

Recently, the scientific community has attempted to mimic dynamic ECM signaling through the development of cell culture platforms with tunable properties. Within this context 'stimuli-responsive' or 'smart' materials and systems represent useful tools for mechanobiology studies [21,22]. These material systems can change their properties on demand in response to user-defined triggers (*e.g.*, pH, temperature, light). As we will discuss in further detail, recent examples of dynamic cell culture platforms involve tunable surface properties such as elasticity and topography, spatiotemporal presentation and removal of biochemical signals, and applied force loading against cultured cells. Inspired by dynamic, tissue-dependent microenvironments *in vivo*, the use of dynamic cell culture platforms to create sophisticated matrices *in vitro* has been attractive to engineers and biologists in the fields of classic cell biology, tissue engineering, and regenerative medicine.

Although excellent reviews of stimuli-responsive polymers and their biomedical and tissue engineering applications have been published [23–35], few comprehensive reviews summarize how stimuli-responsive polymers and systems enable newfound mechanobiological studies as well as the development of artificial matrices that better mimic the dynamic biophysical aspects of native tissue [21,22]. In this review, we focus on recent efforts to construct synthetic cell culture microenvironments, discussing the dependence of cell-specific function on individual environmental cues. First, we briefly review dynamic aspects of the human body, motivating the rational designs of *in vitro* cell culture platforms. We then review different stimuli-responsive polymeric substrates that have been recently developed for dynamic cell-matrix mechanobiology. Lastly, we describe the design of artificial matrices offering four-dimensional (4D) control of material properties and highlight future trends in the field.

2. The dynamic *in vivo* cellular microenvironment

The human body represents a complex collection of dynamic environments where biochemical, physicochemical, and mechano-structural interactions serve to regulate cell behavior and fate [17]. In addition to these environmental cues, various types of regulatory mechanical stimuli exist within the human body (Fig. 1A). Cells are constantly subjected to shear flow, stretching, cyclic strain, and generated tensions, where stimuli magnitude is highly dependent on the tissue itself. These tissue-dependent mechanical stimuli ultimately dictate cellular function and fate [36]. Mechanobiology is an emerging field of science interfacing engineering and biology. Understanding mechanotransduction, or how cells of various tissues sense, recognize, and respond to mechanical stimuli, is a major challenge that has become increasingly important in mechanobiology. Here, mechanical stimuli are not limited to externally-imposed forces, such as fluidic shear stress, but also include the intrinsic tensions generated by active cell contraction that occur in the absence of external forces. Thus, the mechanotransduction process can be described as a simple model where mechanical input influences cells' intrinsic mechanical properties which is then transduced into specific cellular outputs (Fig. 1B). Furthermore, the biological output can change the cellular microenvironment, altering the initial mechanical input. In other words, the mechanotransduction process is equipped with a feedback system, which generates a highly complex and dynamic mechanical environment that mechanobiological studies have until recently largely ignored.

On the other hand, all cell types are in contact with their ECM, a complex and dynamic network of macromolecules with different physicochemical natures. By modulating the production, degradation, and remodeling of its components, the ECM can support organ development, function and repairing [17,37,38]. Williams et al. recently reported that the ECM is gradually altered during heart development and demonstrated its importance in cardiac regeneration [39]. They determined ECM composition at different developmental ages – fetal, neonatal and adult – by liquid