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On-command on/off switching of progenitor cell and cancer cell polarized motility and aligned morphology via a cytocompatible shape memory polymer scaffold

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ABSTRACT

In vitro biomaterial models have enabled advances in understanding the role of extracellular matrix (ECM) architecture in the control of cell motility and polarity. Most models are, however, static and cannot mimic dynamic aspects of *in vivo* ECM remodeling and function. To address this limitation, we present an electrospun shape memory polymer scaffold that can change fiber alignment on command under cytocompatible conditions. Cellular response was studied using the human fibrosarcoma cell line HT-1080 and the murine mesenchymal stem cell line C3H/10T1/2. The results demonstrate successful on-command on/off switching of cell polarized motility and alignment. Decrease in fiber alignment causes a change from polarized motility along the direction of fiber alignment to non-polarized motility and from aligned to unaligned morphology, while increase in fiber alignment causes a change from non-polarized to polarized motility along the direction of fiber alignment and from unaligned to aligned morphology. In addition, the findings are consistent with the hypothesis that increased fiber alignment causes increased cell velocity, while decreased fiber alignment causes decreased cell velocity. On-command on/off switching of cell polarized motility and alignment is anticipated to enable new study of directed cell motility in tumor metastasis, in cell homing, and in tissue engineering.

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1. Introduction

Extracellular matrix (ECM) architecture plays a critical role in guiding cell motility during both tissue development and disease progression. During tissue development, the local ECM architecture can, for example, guide cells to migrate along elongated collagen fibers where tissue branching occurs [1], and fibrillar fibronectin is necessary to maintain cell polarity and guide many morphogenic movements [1–3]. Similarly, ECM fiber architecture has been implicated in the control of cell motility in diseases ranging from cancer to tissue hyperplasia [4] and fibrosis [5], with pregnancy-associated breast cancer being one of the most studied and well-understood examples. During breast cancer progression, radially aligned collagen fibers provide “tracks” for cancer cells to invade into the surrounding stroma [6–8]. Collagen alignment is thought to facilitate tumor cell invasion and, as a result, is being studied as a marker for diagnosis.

In vitro biomaterial models have been developed to study the architectural effects of the microenvironment on cell motility and cell morphology. These *in vitro* biomaterial models include naturally occurring polymeric three-dimensional (3D) matrices and synthetic polymeric two-dimensional (2D) substrates or 3D scaffolds. For example, collagen gels and cell-derived matrices are widely used natural polymeric 3D matrices [9–11]. With respect to synthetic models, electrospun scaffolds have been widely used as *in vitro* models due to their nano- to micro-fibrous architectures, which can mimic some aspects of the fibrillar structure of many native ECMs [12–15].

Both naturally occurring and synthetic matrices have been used to study cell motility. For example, Friedl and colleagues [16] showed that highly invasive melanoma cells in 3D collagen

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matrices follow the protrusion, attachment, and contraction three-step model of cell motility. Such invasive motility results in cell-driven reorganization of the ECM. Dubey and colleagues [17] found that magnetically aligned collagen fibrils can guide Schwann cell invasion into aligned collagen gel matrix. Such findings may provide improved methods of directing and enhancing axonal growth for nerve repair. Johnson and colleagues [18] used aligned and randomly oriented electrospun scaffolds to quantitatively study glioma cell motility on different fiber architectures. They found that cells would move along the highly aligned fibers in the aligned fiber architecture, while cells showed non-polarized motility on randomly oriented fibers. Lastly, Shao and colleagues [19] employed a polycaprolactone (PCL) electrospun mesh with a specific peptide sequence (E7) conjugated as an “MSC-homing device” to recruit mesenchymal stem cells (MSCs) for the application of tissue regeneration. Collectively, existing models such as these have proven successful in studying the response of cells to static matrices in which fiber alignment does not change.

Although many of the existing ECM models provide physiologically relevant fiber microarchitecture and biochemical composition, the models are limited by their fundamentally static nature, with reorganization of matrix architecture occurring only in models that permit cell-driven reorganization. Cells sense the surrounding matrix and, in return, remodel it by depositing additional ECM, by digesting it by secreting matrix metalloproteinase (MMPs), and also through their ability to attach to and actively pull on the fiber architecture, as is the case with cancer associated fibroblasts [20,21]. Previous studies have shown fibroblasts cultured *in vitro* can contract collagen fibers and remodel ECM architecture and density via collagen matrix remodeling through $\alpha_2\beta_1$ integrin and fibronectin matrix remodeling through $\alpha_5\beta_1$ integrin [22]. Cancer cell invasion has been found to be associated with increased collagenase activity, which digests collagen to assist cell translocation through the matrix [23,24]. Importantly, such cell-driven remodeling can result in changes in matrix biochemical composition. Many physical properties, including stiffness, are strongly coupled to the biochemical composition of the matrix. As a result, cellular remolding of model matrices leads to changes in multiple physical properties, which are hard to predict, control, and characterize. Thus, the coupling of fiber alignment to biochemistry in models involving cell-driven reorganization confounds analysis of the role of fiber alignment in cell motility and polarity.

In contrast to the static nature of most natural and synthetic materials employed in the study of cell motility and polarity, shape memory polymers (SMPs) are a class of “smart materials” that can demonstrate dynamic change in shape on command. SMPs achieve the shape memory effect by “memorizing” a permanent shape through chemical or physical cross-linking, then being manipulated and fixed to a temporary shape by an immobilizing transition, such as vitrification or crystallization, and then later recovering to the permanent shape by a triggering event, such as thermal, electrical or solvent activation [25–31]. A number of recent breakthroughs in the area of cytocompatible SMPs [32–39] have enabled application of SMP on-command functionality in cell culture application. Although SMPs have not previously been applied in the study of cell motility and polarity switching, we have recently demonstrated the feasibility of employing SMPs in the study of cell motility in a 2D system [40].

To address limitations of current static *in vitro* ECM models used in the study of cell motility and polarity, the objective of the present study was to develop a synthetic 3D biomaterial scaffold that can, with cells present, undergo programmed increases or decreases in fiber alignment on command. Furthermore, we sought to use the scaffold to demonstrate successful on-command on/off switching of cell polarized motility and aligned morphology, with decrease in fiber alignment resulting in a change from polarized motility along the direction of fiber alignment to non-polarized motility and from aligned to unaligned morphology, and increase in fiber alignment resulting in a change from non-polarized motility to polarized motility along the direction of fiber alignment and from unaligned to aligned morphology. In addition, we hypothesized that an increase in fiber alignment would cause increased cell velocity, while a decrease in fiber alignment causes decreased cell velocity, as quantified by cell average velocity. To achieve these objectives and test this hypothesis, our approach was to tailor for this purpose a 3D SMP nano-fibrous scaffold. The SMP selected was one recently demonstrated to be suitable for shape change under cytocompatible conditions, being triggered by increasing the incubation temperature from 30 °C to 37 °C when hydrated [31]. To study the cellular response of both cancer cells and progenitor cells, the human fibrosarcoma cell line HT-1080 and the multipotent murine mesenchymal stem cell line C3H/10T1/2 were chosen, as they demonstrate multipotentiality with highly metastatic cancer cell motility and classic fibroblastic motility, respectively [41,42]. Analysis of cell motility was enabled by a recently developed cell tracking algorithm [40].

2. Methods and materials

2.1. Study design

Scaffolds of four different architectures, two static and two dynamic, were developed and used in this study (Fig. 1). The two control scaffolds featured static architectures of unidirectional aligned fibers and of randomly oriented fibers, respectively. The two dynamic scaffolds featured architectures that dynamically increase unidirectional alignment and dynamically decrease unidirectional alignment, respectively, when warmed from 30 °C to 37 °C under cell culture conditions. To determine whether successful on-command on/off switching of cell polarized motility and aligned morphology was achieved, both the human fibrosarcoma cell line HT-1080 and the multipotent murine mesenchymal stem cell line C3H/10T1/2 were studied, as they demonstrate multipotentiality with highly metastatic cancer cell motility and classic fibroblastic motility, respectively. Cell motility and morphology were qualitatively and quantitatively assessed before and after thermal triggering by time-lapse imaging, computational cell tracking, and fixed time point staining.

2.2. Shape memory polymer synthesis

To produce a shape memory 3D electrospun scaffold capable of dynamical increase or decrease in fiber alignment on command, a thermoplastic polyurethane (TPU) featuring shape memory was synthesized as previously described ([31] and Supplemental Method 1). One TPU batch, which had a molecular weight of 130 kg/mol, was used for this entire study.

2.3. Scaffold fabrication

To prepare the fibrous 3D architecture that forms the basis of both the static control architectures and the dynamic architectures, scaffolds were fabricated by electrospinning the SMP TPU. Electrospinning was performed as previously described [31], but with the spinning parameters optimized to achieve sub-micron fibers of ~400 nm diameter (Supplemental Method 2). The two control static scaffold architectures were prepared by electrospinning unidirectional aligned fibers (as-spun static aligned scaffolds, “A”) or randomly oriented fibers (as-spun static unaligned scaffolds, “U”). These static control scaffolds will not change fiber architecture

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