A Programmable Biomaterial System for the Study of Cell Migration in Dynamic Microenvironments

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Statement of Purpose: Extracellular matrix (ECM) architecture is known to play a significant role in cell migratory behavior during tissue development and diseases such as cancer [1]. In previous studies, *in vitro* model microenvironments, such as systems of highly aligned collagen fibers, have been used to study the effect of ECM architecture on stem cell migration and cancer cell invasion [2]. However, how *dynamic* changes in ECM architecture affect cells *in vivo* remains poorly understood, due in large part to the stasis of current *in vitro* model systems. The goal of the present study was to establish a programmable biomaterial system for the study of cell migration in dynamic microenvironments. To achieve this goal, we employed a shape-memory electrospun scaffold that can change fiber orientation dynamically over time and studied how dynamic change in fiber alignment affects cell migratory behavior. We postulated that dynamic increases in fiber alignment could be accompanied by preferentially migration of cells along the fiber direction.

Methods: *Static* unaligned or aligned electrospun scaffolds were prepared from a custom-synthesized shape-memory thermoplastic polyurethane [3] with fiber diameter between 500 to 700 nm. Programmed, *dynamic* scaffolds that can be triggered to increase fiber alignment when warmed from 30 °C to 37 °C (Figure 1) were prepared by stretching aligned scaffolds in the direction perpendicular to fiber alignment direction to 100% strain at 65 °C using a dynamic mechanical analyzer. Fiber alignment was quantified by 2D Fast Fourier Transform (2D FFT) image analysis. C3H10T1/2 cells were cultured on the three scaffolds – unaligned, aligned, and dynamic. The cells were then stained with Hoechst 33342 nuclear dye and imaged for 24 h at 30°C or at 37°C, providing analysis of cell migration before and after change in fiber alignment for dynamic scaffolds, with the static scaffolds providing unchanging controls. Resulted time-lapse videos were process by an automated cell tracking algorithm [4] to analyze cell migration.

Results: Results from cell tracking show (Figure 2) that cells move randomly on unaligned scaffolds but move preferentially in the direction of fiber orientation on aligned scaffolds. On dynamic scaffolds, cells move without preferential direction prior to triggering of shape change (Figure 3). Following triggering of shape change, the cells switch motility behavior to directional migration along the fiber alignment direction.

Conclusions: These results suggest that the shape-memory nanofiber electrospun scaffolds are able to direct cell migration through changes in fiber architecture. Further analysis of cell migration behavior is needed to determine if pre-exposure of cells to unaligned scaffolds has an extended effect on cell migration behavior when fiber alignment increases.

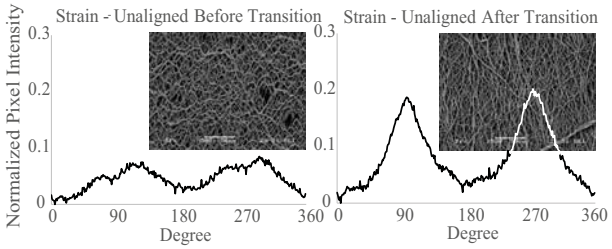

Figure 1. SEM images and 2D FFT analysis showed the programmed dynamic scaffolds have temporarily random fiber orientation at 30 °C before triggering and aligned architecture after 37 °C triggering.

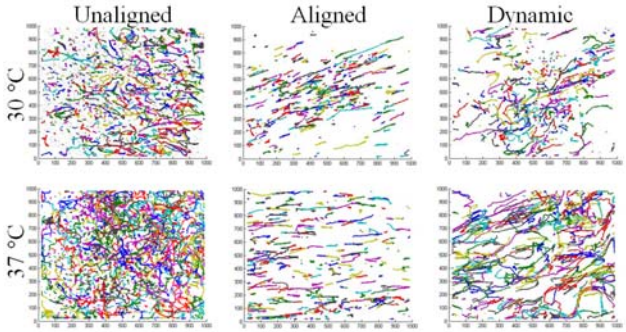

Figure 2. Cell nuclear trajectory information obtained from the automated cell tracking algorithm show distinct cell migration pattern on static unaligned, aligned scaffolds, and switched migration pattern on dynamic scaffolds before and after fiber alignment increase.

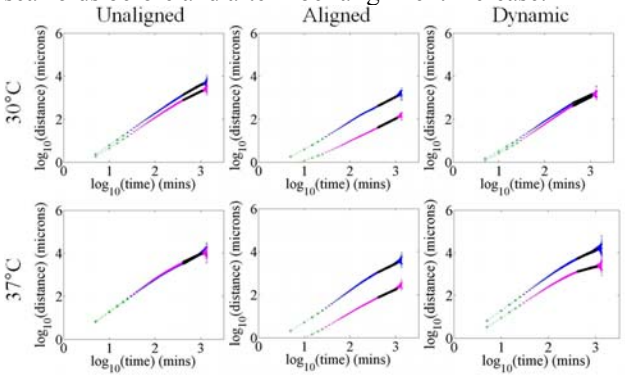

Figure 3. Representative mean squared displacement analyses obtained from the cell tracking algorithm showed distinct cell velocity difference in fiber alignment direction (x-direction in blue) and the direction perpendicular to fiber direction (y-direction in pink) in aligned and triggered dynamic scaffolds.

References: 1. Keely PJ. J Mammary Gland Biol Neoplasia. 2001; 16:3 205-219. 2. Provenzano PP. BMC Medicine. 2006;4:38. 3. Tseng LF. Acta Biomaterialia. 2013; 9:11 8790-8801. 4. Baker RM, Brasch ME. In review. 2013.