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MODELING THE ROLE OF OSCILLATORY FLOW AND DYNAMIC MECHANICAL CONDITIONING ON DENSE CONNECTIVE TISSUE FORMATION IN MESENCHYMAL STEM CELL DERIVED HEART VALVE TISSUE ENGINEERING

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INTRODUCTION

Living tissue engineered heart valves (TEHV) may circumvent ongoing problems in pediatric valve replacements, offering optimum hemodynamic performance and the potential for growth, remodeling, and self-repair [1]. Although a myriad of external stimuli are available in current bioreactors (e.g. oscillatory flows, mechanical conditioning, etc.), there remain significant bioengineering challenges in determining and quantifying parameters that lead to optimal ECM development and structure for the long term goal of engineering TEHVs exhibiting tissue architecture functionality equivalent to native tissue. It has become axiomatic that in vitro mechanical conditioning promotes engineered tissue formation (Figure 1), either in organ-level bioreactors or in tissue-level bioreactors with idealized-geometry TE constructs. However, the underlying mechanisms remain largely unknown. Efforts to date have been largely empirical, and a two-pronged approach involving novel theoretical developments and close-looped designed experiments is necessary to reach a better mechanistic understanding of the cause-effect interplay between MSC proliferation and differentiation, newly synthetized ECM, and tissue formation, in response to the controllable conditions such as scaffold design, oxygen tension, nutrient availability, and mechanical environment during incubation. We thus evaluate the influence of exterior flow oscillatory shear stress and dynamic mechanical conditioning on the proliferative and synthetic behavior of MSCs by employing a novel theoretical framework for TE. We employ mixture theory to describe the evolution of the biochemical constituents of the TE construct and their intertwined biochemical reactions, evolving poroelastic models to evaluate the enhancement of nutrient transport occurring with dynamic mechanical deformations, and computational fluid

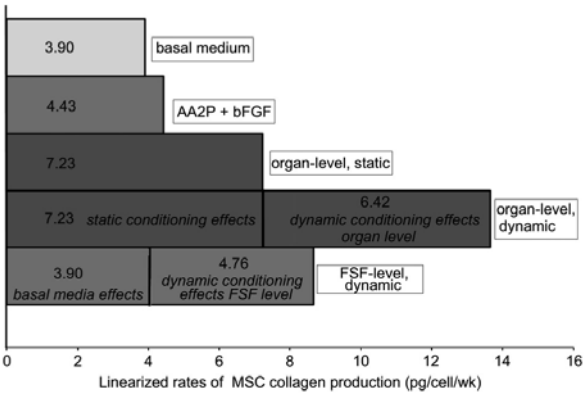

Figure 1. Linearized rates of collagen production in TEHVs at physiologically representative pulmonary artery scales (from [5]) and in comparison to specimens conditioned in a FSF bioreactor (from [2-4]).

dynamics (CFD) to assess the exterior flow boundary conditions developed in the flex-stretch-flow (FSF) bioreactor [2-4].

RESULTS

Highly oscillatory flow fields develop around flexed configurations of rectangular scaffolds in FSF bioreactors [4]. CFD simulations were conducted to assess wall shear stress profiles around the undeformed and flexed specimens (Figure 2). We hypothesize that oxygen transport is enhanced due to oscillatory exterior flow and model this effect with Neumann boundary conditions on the oxygen phase with an oscillatory shear index (OSI)-dependent oxygen transfer coefficient. Cell oxygen consumption and diffusive constraints prevent oxygen from being fully replenished inside the scaffolds. Cells in the vicinity of the boundaries are able to proliferate faster and synthesize more ECM. The flexed configuration introduces a large degree of oscillatory flow in the bottom surface and spatial inhomogeneity in growth and matrix synthesis is observed (Figures 2 and 3).

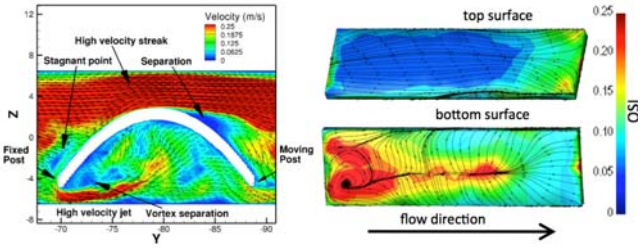

Figure 2. Velocity flow field and distribution of oscillatory shear index on construct surfaces (Re=1376).

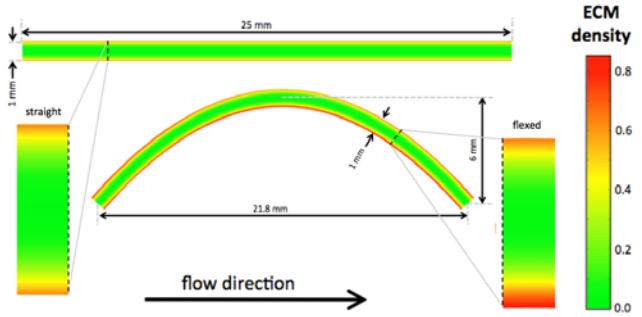

Figure 3. Spatial distribution of ECM (non-dimensional) in a cross section of the non-deformed and flexed TEHV leaflet constructs. Highly oscillatory flows enhance oxygen transport, cell growth and matrix production in the bottom surface of the flexed scaffold.

DISCUSSION

With the goal of obtaining improved homogeneous tissue distribution and higher quality extracellular matrix, a multitude of external conditions are available in bioreactors, e.g. oscillatory flows, mechanical conditioning, scaffold design, among others. The ability to quantify and predict cell growth and matrix production (outputs) in response to a multitude of controllable stimuli (inputs) is of the utmost importance for successful clinical development of all TE applications. Starting from this preliminary modeling step, our future objective is to improve our modeling capabilities towards a useful and robust TE design tool, supported by carefully designed experiments, accounting for multiple inputs available to the tissue engineer, and predicting their effect and impact on the evolving TE construct.

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