Modeling the enhancement of extracellular matrix quantity and quality in large-deformation mechanically-conditioned tissue engineering

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Abstract

A myriad of external stimuli is available in current bioreactors and it has become axiomatic that in vitro mechanical conditioning promotes engineered tissue formation. We have observed that upon mechanical conditioning, vascular smooth muscle cells are stimulated to produce not only more extracellular matrix (ECM), but also of better quality. Possible mechanisms for such are: (i) a substantial enhancement of the nutrient supply occurs due to convection of fluid inside the porous construct; and (ii) a significant change in nuclear aspect ratio occurs upon large deformation and may act as stimulatory triggers for a substantial improvement of de novo ECM properties.

We have observed that cyclic flexure (within ranges pertaining to physiological function of heart valves) promotes enhancement of the synthetic behavior of vascular smooth muscle cells in vitro, particularly in the internal regions of the constructs that usually remain devoid of cellular content during static incubation[1, 2]. We have proposed and proposed a theoretical framework to describe such phenomena based on an inter-reacting triphasic mixture of nutrient-cell-ECM coupled with an evolving deformable poroelastic body[3]. Subsequently, we have observed and quantified the effects of large deformations on ECM synthesis and ECM stiffness. We have observed that cyclic (1Hz) strip biaxial strain of 30% promotes a profound improvement of the synthetic behavior of vascular smooth muscle cells cultured in vitro when compared to static culture conditions or subjected to mechanical training with infinitesimal deformations[4, 5]. We have developed an analysis methodology to de-couple the response of the scaffold from de novo ECM, and to quantify the mechanical properties and anisotropy of de novo ECM with biaxial testing protocols. We have observed that at low strains the de novo ECM stiffness is comparable to bovine pericardium (the standard material of bioprosthetic heart valves), however its response does not possess the functional nonlinearity characteristic of dense connective tissues (exponential behavior) and is unable to stiffen and carry higher stresses within moderate

deformations[5]. The employment of structural constitutive modeling extends the experimental interpretation and yields further insight into the underlying characteristics of de novo ECM and their mechanistic effects - we infer that while de novo ECM collagen fibers show acceptable fiber stiffness, the fiber ensemble network lacks on miscrostructural organization. Collagen fiber undulation, a dense connective tissue characteristic occurring only after extensive remodeling and maturation, seems negligible in de novo ECM and may be responsible for the lack of functional stiffness at the bulk level as minimal fiber recruitment occurs upon deformation[5]. Lastly, we expand our theoretical framework to depict the substantial improvement of ECM quantity and quality in response to large deformation stimuli.

References

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