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Tubular hydrogels of circumferentially aligned nanofibers to encapsulate and orient vascular cells

Mark T. McClendon [a], Samuel I. Stupp [b,c,d,e,*]

[a] Department of Chemical and Biological Engineering, Northwestern University, Evanston, IL 60208, United States
[b] Department of Chemistry, Northwestern University, Evanston, IL 60208, United States
[c] Department of Materials Science and Engineering, Northwestern University, Evanston, IL 60208, United States
[d] Institute for BioNanotechnology in Medicine, Northwestern University, Chicago, IL 60611, United States
[e] Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, United States

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ABSTRACT

There is a great clinical need for tissue engineered blood vessels that could be used to replace or bypass damaged arteries. The success of such grafts will depend strongly on their ability to mimic the cellular and matrix organization found in native arteries, but currently available cell scaffolds such as electrospun fibers or hydrogels lack the ability to simultaneously encapsulate and align cells. Our laboratory has recently developed liquid crystalline solutions of peptide amphiphile nanofibers that form aligned domains at exceedingly low concentrations (<1wt%), and can be trapped as gels with macroscopic alignment using low shear rates and ionic crosslinking. We describe here the use of these systems to fabricate tubes with macroscopic circumferential alignment and demonstrate their potential as arterial cell scaffolds. The nanofibers in these tubes were circumferentially aligned by applying small amounts of shear in a custom built flow chamber prior to gelation. Small angle X-ray scattering confirmed that the direction of nanofiber alignment was the same as the direction of shear flow. We also show the encapsulation of smooth muscle cells during the fabrication process without compromising cell viability. After two days in culture the encapsulated cells oriented their long axis in the direction of nanofiber alignment thus mimicking the circumferential alignment seen in native arteries. Cell density roughly doubled after 12 days demonstrating the scaffold's ability to facilitate necessary graft maturation. Since these nanofiber gels are composed of >99% water by weight, the cells have abundant room for proliferation and remodeling. In contrast to previously reported arterial cell scaffolds, this new material can encapsulate cells and direct cellular organization without the requirement of external stimuli or gel compaction.

1. Introduction

Heart disease is an unsolved problem accounting for over 30% all US deaths in recent years, and it is most often caused by damaged or weakened coronary arteries [1]. In such cases the affected blood vessels can be bypassed to restore blood supply to cardiac tissue. Synthetic materials have poor patency when used to bypass small diameter blood vessels (>5 mm) and autologous grafts are in short supply [2,3]. Therefore, there is a critical need for tissue engineered blood vessels that can be used to replace damaged and blocked arteries. After the pioneering work of Weinberg and Bell [4], a significant focus of vascular engineering has been the development of methods that mimic the native microscopic organization found in arteries [5–10]. The functions of arteries are dependent upon their cellular organization, and are known to fail when this organization is not present [11,12]. The key feature of arterial microarchitecture is the alignment of smooth muscle cells (SMCs) with their long axis extending in the circumferential direction in the medial layer [13]. Vasoactivity, the constriction or dilation of blood vessels, is controlled by the contractile force produced by circumferentially aligned SMCs, and the durable mechanical properties of arteries can be attributed to the circumferential alignment of SMCs and their fibrous extracellular matrix (ECM). Therefore, it has been established that the circumferential alignment of contractile SMCs is necessary for the successful design of artificial blood vessels [10].

* Corresponding author. Department of Materials Science and Engineering, Northwestern University, 2220 Campus Dr., Evanston, IL 60208, United States. Tel.: +1 847 491 3002; fax: +1 847 491 3010.
E-mail address: s-stupp@northwestern.edu (S.I. Stupp).

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