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Preservation of FGF-2 bioactivity using heparin-based nanoparticles, and their delivery from electrospun chitosan fibers

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ABSTRACT

Here we present a novel matrix-mimetic nanoassembly based on polysaccharides. Chitosan electrospun fiber networks are decorated with heparin-containing polyelectrolyte complex nanoparticles (PCNs) that present basic fibroblast growth factor (FGF-2), both stably adsorbed to the surfaces and released into solution. These FGF-2/PCN complexes can be released from the fibers with zero-order kinetics over a period of 30 days. Further modification of fibers with a single bilayer of polyelectrolyte multilayer (PEM) composed of *N*,*N*,*N*-trimethyl chitosan and heparin completely prevent release, and the FGF-2/PCN complexes are retained on the fibers for the duration of the release experiment (30 days). We also compare the mitogenic activity of these FGF-2/PCN complexes delivered in two different states: adsorbed to a surface and dissolved in solution. FGF-2/PCN complexes exhibit mitogenic activity with respect to ovine bone marrow-derived mesenchymal stem cells, even after being preconditioned by incubating for 27 days at 37 °C in solution. However, when the FGF-2/PCN complexes are adsorbed to chitosan and coated with PEMs, the mitogenic activity of the FGF-2 steadily decreases with increasing preconditioning time. This work demonstrates a new system for stabilizing and controlling the delivery of heparin-binding growth factors, using polysaccharide-based matrix-mimetic nanomaterials. This work also contributes to our understanding of the preferred mode of growth factor delivery from porous scaffolds.

1. Introduction

The use of growth factors to guide the differentiation of stem cells is a particularly promising strategy for engineering slow-healing tissues such as bone and cartilage, to treat a variety of injury and disease states [1]. Growth factors from the fibroblast growth factor (FGF) family and transforming growth factor-β (TGF-β) superfamily, which includes the bone morphogenetic proteins (BMPs), affect wound healing, tissue synthesis and mesenchymal stem cell (MSC) differentiation. For example, FGF-2 is involved in osteogenesis [2,3], chondrogenesis [4] and angiogenesis [5]. However, many therapeutic strategies based on growth factor delivery are impeded by the relative instability of growth factors on time scales associated with these biological processes. Members of the FGF family and TGF-β superfamily have plasma half-lives on the order of minutes (1.5 min for FGF-2, and between 11 and 160 min for TGF-β1, for example) [6]. FGF-2 and BMP-2 have been demonstrated to lose their activity within 24 h and become completely degraded within 3 days when adsorbed to and released from mineral-based and ceramic scaffolds for bone tissue engineering [7,8]. Materials for skeletal tissue engineering that use growth factors should be developed that can present the growth factor in a structural and biochemical context similar to native tissue. This could mean presenting the growth factor bound to a surface or slowly releasing the growth factor into nearby tissue [9].

In mammalian tissues, polysaccharides are found in nanostructured proteoglycans, like aggrecan, which impart both biomechanical and biochemical function to the extracellular matrix (ECM) [10]. One of the most important of these biochemical functions is to serve as a reservoir for the binding and stabilization of growth factors. Heparin is a glycosaminoglycan that protects FGF-2 from proteolytic and chemical inactivation [11]. This stabilization likely results from the binding of FGF-2 to specific sulfation patterns in

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