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A crimp-like microarchitecture improves tissue production in fibrous ligament scaffolds in response to mechanical stimuli

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ABSTRACT

The aim of this study was to determine the influence of a crimp-like microarchitecture within electrospun polymer scaffolds on fibroblast extracellular matrix (ECM) production when cultured under dynamic conditions. Electrospun poly(L-lactide-*co*-D,L-lactide) scaffolds possessing a wave pattern similar to collagen crimp (amplitude: 5 μm and wavelength: 46 μm) were seeded with bovine fibroblasts and mechanically stimulated under dynamic uniaxial tension. The effect of strain amplitude (5%, 10% and 20%) was investigated in a short-term stimulation study. The 10% strain amplitude in the stimulated crimp-like fibre scaffold increased only collagen synthesis, while the 20% strain amplitude increased both collagen and sulphated proteoglycan synthesis compared to stimulated uncrimped (straight) fibre scaffolds and unloaded controls (crimp-like static fibre scaffolds). Alternatively, mechanical stimulation of fibroblasts seeded on uncrimped fibre scaffolds induced significant fibroblast proliferation compared to the stimulated crimp-like fibre scaffolds and no-load controls. Long-term, dynamic mechanical stimulation of fibroblasts seeded on crimp-like fibre scaffolds at 10% strain amplitude resulted in significantly up-regulated collagen accumulation and down-regulated sulphated proteoglycan accumulation. Additionally, the fibroblasts seeded on dynamically stimulated crimp-like fibre scaffolds appeared to form bundles that resembled fascicles, a characteristic hierarchical feature of the native ligament. Our findings demonstrate that fibroblasts seeded on crimp-like fibrous scaffolds respond more favourably (increased ECM synthesis and fascicle formation) to dynamic mechanical loading compared to those grown on scaffolds containing uncrimped (straight) fibres.

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1. Introduction

The anterior cruciate ligament (ACL) is a fibrous load-bearing connective tissue found in the intra-articular space of the knee that helps stabilize the knee joint [1–3]. In 2002, there were 200,000 ACL reconstruction surgeries reported in the USA alone with associated costs exceeding the US$5bn mark [1–6]. The number of ACL injuries per year is expected to increase, due to an increase in the number of people involved in physical and recreational activities, with professional athletes being affected the most [7–9]. By nature, the ACL has a low self-healing propensity as it is surrounded by synovial fluid, which is designed to lubricate the joint as well as prevent clot formation [6]. Additionally, its high extracellular matrix (ECM) density and organization, along with the presence of few or no blood vessels, further impede its capacity to heal itself [5,6]. The inability of the ACL to self-repair has led to the study and design of functional synthetic constructs to replace damaged ACL using tissue-engineering principles [5,6]. Even though tissue engineering holds much promise, the constructs developed to date do not completely restore normal tissue function [10–12], primarily because they lack the microstructural architecture (crimp pattern) and mechanical properties of native ACL [10–12], thereby increasing the propensity of premature construct failure.

Several research groups have studied the beneficial effects of repetitive cyclic stimulation of fibroblasts [13–16] on the production of ECM components such as collagen, fibronectin and tenascin-C [14,17]. However, the majority of these studies have been conducted over short periods of time [13,14,16] and the effect of long-term stimulation is presently unknown. Additionally, there may be drawbacks with the use of straight, uncrimped fibres in tissue engineering ACL scaffolds [18,19] as the appropriate mechanical stimuli may not be imparted to the cells during normal function [18,19]. It is well known that collagen fibres in ligaments and tendons possess a distinct crimp pattern (amplitude: 5–10 μm and wavelength: 45–60 μm, respectively [4]) and that tenocytes (and

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