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Fabrication and characterization of hierarchically organized nanoparticle-reinforced nanofibrous composite scaffolds

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ABSTRACT

Two different techniques were used to fabricate nanoparticle-reinforced nanofibrous scaffolds with different organizations of the minerals. First, a three-dimensional (3D) cylindrical nanofibrous scaffold made of poly-L-lactide and poly(L-lactide)/collagen (1:1) was fabricated using a modified electrospinning method. An alternating dipping method and a flow version of it were used to mineralize the 3D scaffolds. Flow mineralization was found to significantly improve the distribution of the mineral nanoparticles throughout the 3D nanofibrous scaffold, while mineral nanoparticles were found only on the periphery of the static mineralized scaffold. As a result of the mineral nanoparticle distribution, the compressive strength and modulus of the flow mineralized scaffold was found to be significantly greater than that of the static mineralized scaffold, despite having a lower mineral content. Energy-dispersive X-ray analysis and X-ray diffraction studies suggest that the mineral was composed of heterogeneous phases of calcium phosphates. This study demonstrates the importance of hierarchical and deliberate organization of the nanocomponents to optimize the mechanical properties, as is often found in nature.

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1. Introduction

Bone is one of the best known hierarchically organized natural structures known to man. Its structure and mechanical properties have fascinated materials scientists and engineers as the basic components of bone are inherently weak individually but when combined together are able to give a strong composite material. In-depth studies into the structure of bone have shown that the strength is due to the hierarchical organization of nano-sized building blocks. Nature has used this technique to assemble numerous structures, such as wood and tendons, with various mechanical demands [1]. Fracture mechanics concepts have been proposed to explain the intriguing interactions between nanocomponents that give rise to the amazing mechanical properties [2,3]. This has led to great interest in replicating such hierarchical organizations. Molecular self-assembly techniques have been used to fabricate nanofibers from peptides [4,5] and this technique was able to mimic the hydroxyapatite nanofiber organization in bone on the nano-scale level [6]. Although this technique is able to achieve excellent control on the nano-scale level, organization at higher levels and the generation of a sufficient volume for structural usage are still major challenges.

Despite evidence from natural structures on the importance of hierarchical organization to achieve desirable mechanical requirements, replicating such an organization and verifying its mechanical properties is vital in terms of material construction for various applications. Researchers are still searching for the ideal synthetic bone graft. Replicating the structure of bone for use as bone grafts based on nature's building blocks (nanofibers and nanoparticles) is highly challenging, as there is currently no technology available to physically handle nano-sized materials. Other than meeting the mechanical requirements, it should promote osteogenesis, osteoinduction and osteoconduction [7,8]. Medically, many studies have shown that calcium phosphates such as hydroxyapatite and tricalcium phosphate in synthetic bone grafts aid in osteoconduction and osteointegration. Thus, most commercially available bone grafts and bone fillers are made up of ceramics [7,8]. While earlier generations of bone graft were mainly sintered hydroxyapatite, which is highly crystalline and not readily resorbed by the body [9], the new generation of bone grafts are made out of amorphous hydroxyapatite and its composites. Native

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bone is composed of 70% nanohydroxyapatite, with the rest consisting mainly of collagen nanofibers and trace amounts of organic molecules. Research has demonstrated that osteoblasts respond well to nano-textured surfaces, showing enhanced mineral deposition and osteointegration [10].

Recently, advances in nanotechnology have allowed researchers to replicate natural structures on the nano-scale level. In particular, electrospinning is a commonly used method for generating nanofibrous constructs. This is mainly due to the ease of fabricating nanofibers from a variety of materials and it allows a certain level of control over the nano-structures that can be constructed [11]. This has allowed researchers to investigate cell–nanofiber material interactions and cell–nanotopography interactions. Similarly, researchers have attempted to mimic various extracellular matrices (ECMs) in the search for ideal regenerative grafts. However, most electrospun scaffolds are restricted to planar structures. This limits the application of electrospun nanofibers in tissue regeneration and makes their use in tissues which are inherently three-dimensional (3D), such as bone, very difficult. Over the last couple of years researchers into electrospinning have developed techniques which are able to fabricate 3D scaffolds [12]. In the development of bone grafts this allows nanofibrous scaffolds to be used as fillers and to bridge critical size defects. The next step is to develop nanofiber–calcium phosphate composites.

Several techniques have been developed to generate and incorporate amorphous nanohydroxyapatite. Studies have shown that nanohydroxyapatite in a polymer nanofiber matrix was able to increase mineral secretion by osteoblasts cultured on it [13]. Since the minerals in native bone are predominantly found on the surface, other researchers have used surface mineralization techniques to deposit hydroxyapatite nanoparticles on the surface of fibers. The most commonly used surface mineralization techniques include soaking the scaffold in simulated body fluid (SBF) [14] and the alternating dipping method [15]. Of these two techniques, the alternating dipping method has the advantage of significantly faster mineral deposition, requiring hours to complete rather than days for the SBF soaking technique. However, until now all mineralization on nanofibers has been restricted to nanofibrous sheets [16–18]. 3D block nanofibrous scaffolds pose several challenges over nanofibrous sheets during mineralization. In particular, the chemistry must proceed in the interior of the nanofibrous block. While two-dimensional (2D) membranes can be mineralized using alternating dipping, since much of its surface is exposed to the solution, 3D block scaffolds require the solution to reach the inner core and this may require modifications to the alternating dipping technique.

In this paper we will demonstrate the impact of nano-size mineral distribution in a 3D nanofibrous scaffold on the mechanical properties. This will allow us to appreciate the importance of hierarchical organization in nature. To vary the distribution of nano-size minerals, two modified mineralization techniques based on the same principle were used. Polylactide, a biodegradable polymer, and collagen were used in this study as both materials have been used commercially as replacement scaffolds. Numerous studies have also demonstrated the biocompatibility of these two materials in the form of nanofibers [19–24]. The compressive strengths and moduli of the scaffolds were tested and the challenge presented by mineralization of 3D scaffolds will be discussed. In this study, we have demonstrated a simple method of obtaining a hierarchically organized nanocomposite scaffold (Fig. 1). The nanocomposite scaffold was in the form of a rod with a nanofibrous bundle microstructure, which was in turn made out of nanofibers and nanoparticles. We also provide clear evidence that the distribution of the nanoparticles on nanofibers significantly influences the compressive mechanical properties of the scaffold.

2. Materials and methods

2.1. Materials

Collagen type I (Col) (Koken, Japan) and poly(L-lactide) (PLLA) (molecular weight 300,000, Polyscience) were dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (Aldrich) (HFP) at a ratio of 1:1 (wt.%) and a concentration of 0.03 g ml^{-1}. A pure solution of PLLA at a concentration 0.03 g ml^{-1} was prepared using HFP as the solvent. For mineralization a 0.5 M $CaCl_2$ and 0.3 M Na_2HPO_4 solution was used.

2.2. Scaffold fabrication

Electrospinning was carried out using the dynamic fluid flow method described by Teo et al. [12]. Briefly, a high voltage of 15 kV was applied to the prepared blended solution with a 27G ground tip needle as the spinneret. A feed rate of 1 ml h^{-1} was

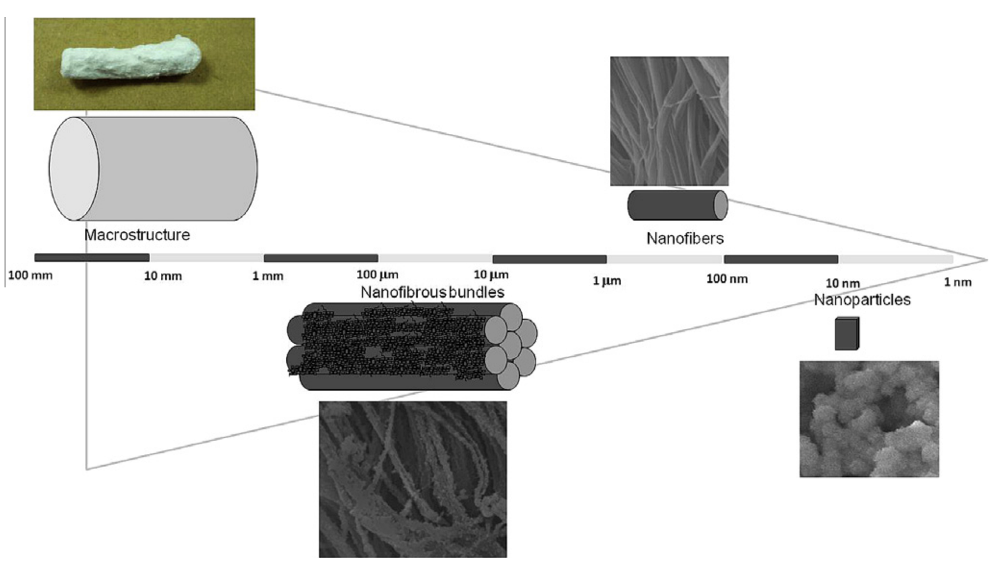

Fig. 1. Hierarchically organized nanocomposite scaffold.

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