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# Electrospun materials as potential platforms for bone tissue engineering ☆

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ABSTRACT

Nanofibrous materials produced by electrospinning processes have attracted considerable interest in tissue regeneration, including bone reconstruction. A range of novel materials and processing tools have been developed to mimic the native bone extracellular matrix for potential applications as tissue engineering scaffolds and ultimately to restore degenerated functions of the bone. Degradable polymers, bioactive inorganics and their nanocomposites/hybrids nanofibers with suitable mechanical properties and bone bioactivity for osteoblasts and progenitor/stem cells have been produced. The surface functionalization with apatite minerals and proteins/peptides as well as drug encapsulation within the nanofibers is a promising strategy for achieving therapeutic functions with nanofibrous materials. Recent attempts to endow a 3D scaffolding technique to the electrospinning regime have shown some promise for engineering 3D tissue constructs. With the improvement in knowledge and techniques of bone-targeted nanofibrous matrices, bone tissue engineering is expected to be realized in the near future.

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**Contents**



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## 1. Introduction

The treatment of bone defect sites with medical-grade materials is widely performed with some degree of clinical success. The manipulation of biomaterials in concert with tissue cells is considered a promising and alternative therapy to the autologous surgery [1]. This tissue engineering approach to bone reconstruction, having gained significant interest and research input over the last decade, requires a suitable cell supporting matrix, namely a scaffold, to provide a 3-dimensional substrate for cells to populate on and function appropriately during the formation of bone analog tissue [2,3].

There have been significant advances in the development of bone scaffolds with various compositions and 3-dimensional configurations using a variety of techniques [4,5]. Recently, the electrospinning process and the nanofibrous matrices thus fabricated have gained tremendous interest, mainly due to the structural similarity to the tissue extracellular matrix (ECM), the processing availability to a wide range of materials, as well as simple set-up and operation at low cost [6–10]. Several studies have reported the performance of nanofibrous materials in guiding cells to initially adhere to and spread over the material, as well as further triggering them to secrete the appropriate ECM molecules targeted to the skin, blood vessel, cartilage, muscle, adipose, nerve and bone. The intriguing features of a fibrous morphology with diameters ranging from tens of nanometers to a few micrometers have attracted considerable attention focused on exploiting the properties as well as structural tuning to the tissue of concern for the applications as a tissue engineering scaffold.

In the bone reconstruction area, the electrospun nanofibers have also attracted considerable attention aimed at identifying suitable material compositions and exploiting them into electrospinning [11,12]. As the bone-associated cells and their progenitor/stem cells show initial responses in a similar manner to those in other tissues, which are anchorage-dependent, the nanofibrous substratum may provide favorable conditions for cell anchorage and growth. In tandem with the initial cell responses, further osteoblastic differentiation and mineralization have also been reported to be regulated in a positive manner on nanofibrous surfaces compared to a dense substrate of polymers [13].

Although studies on the *in vivo* feasibility of electrospun nanofibers in bone reconstruction and tissue engineering progress are currently in the early stages, recent reports of electrospun nanofibers with new compositions targeted for bone as well as some processing tools to design 3-dimensional scaffolding and tissue engineering have highlighted the potential use of electrospun materials in bone tissue engineering.

This review consists of three parts: a brief introduction of the bone structure, which is to be mimicked by electrospun nanofibrous matrices, and the bone tissue engineering concept; a research summary of electrospun materials targeted for bone regeneration, including polymers, inorganics and their composites/hybridized compositions; and a description of on-going efforts aimed at employing nanofibrous matrices for drug delivery and tissue engineering, which was facilitated by surface functionalization, drug encapsulation and 3D scaffolding technique.

## 2. Bone and tissue engineering

### 2.1. Bone structure and ECM mimics

#### 2.1.1. Bone structure: bone cells, ECMs and organization

It is important to understand the biomechanical and biological properties of bone in order to gain insight into choosing the type of materials that can best be used to reconstruct the degenerative functions of bone. Bone is a complex, highly organized and specialized connective tissue. Compared to soft tissues, bone is physically hard, rigid and strong, and microscopically contains relatively few cells with abundant intercellular matrix in the form of collageneous fibers and stiffening inorganic substances. There are three types of cells comprising bone as illustrated in Fig. 1.

Osteoblasts located on the surfaces of bone are responsible for the formation and organization of the extracellular matrix of bone and its subsequent mineralization. These cells are responsible for the synthesis of organic components of the bone ECM. They are derived from mesenchymal precursor cells in the marrow, which also has the potential to differentiate into fat cells, chondrocytes or muscle cells [14]. The principal products of mature osteoblast are type I collagen (90% of the protein in bone), bone specific vitamin-K dependent proteins, osteocalcin and matrix Gla protein, phosphorylated glycoproteins including bone sialoproteins I and II, osteopontin and osteonectin, proteoglycans and alkaline phosphatase.

A proportion of osteoblasts become trapped as osteocytes in the lacunae within the bone matrix. These cells may be responsible for intercellular communication. They possess long thin cytoplasmic processes called filopodia located in thin cylindrical spaces or canals in the bone matrix. Nutrients and oxygen pass between the blood vessels and distant osteocytes via the arrangement of the canaliculi. Osteocytes also break down the bone matrix through osteocytic osteolysis to release calcium for calcium homeostasis [15].

Osteoclasts are polarized cells with a ruffled border region of the cell membrane that is surrounded by an organelle-free region, or 'clear zone'. They adhere to the bone surface via integrins, which are specialized cell surface receptors [16]. Osteoclastic bone resorption initially involves mineral dissolution, followed by degradation of the organic phase. These processes take place beneath the ruffled border and depend on lysosomal enzyme secretion and an acid microenvironment [17]. Osteoclasts actively synthesize lysosomal enzymes, particularly the tartrate-resistant isoenzyme of acid phosphatase (TRAP) (used as a marker of the osteoclast phenotype), and cysteine-proteinases, such as cathepsins, which are capable of degrading collagen. Lysosomal enzymes are released only at the ruffled border region of the osteoclast cell membrane [18].

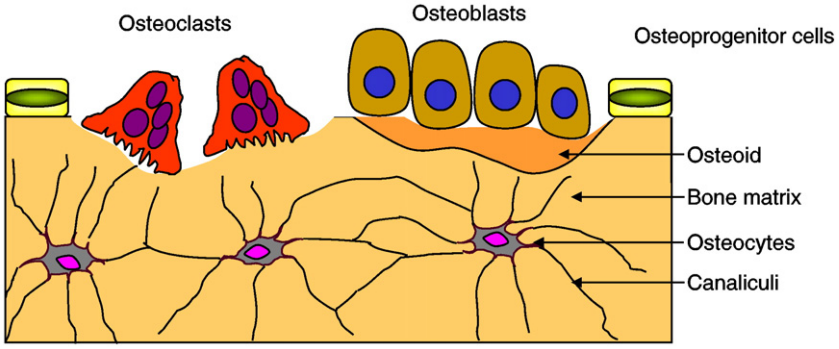


**Fig. 1.** Schematic diagram of bone structure at cellular level.

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