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Review article

Silk scaffolds in bone tissue engineering: An overview

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ABSTRACT

Bone tissue plays multiple roles in our day-to-day functionality. The frequency of accidental bone damage and disorder is increasing worldwide. Moreover, as the world population continues to grow, the percentage of the elderly population continues to grow, which results in an increased number of bone degenerative diseases. This increased elderly population pushes the need for artificial bone implants that specifically employ biocompatible materials. A vast body of literature is available on the use of silk in bone tissue engineering. The current work presents an overview of this literature from materials and fabrication perspective. As silk is an easy-to-process biopolymer; this allows silk-based biomaterials to be molded into diverse forms and architectures, which further affects the degradability. This makes silk-based scaffolds suitable for treating a variety of bone reconstruction and regeneration objectives. Silk surfaces offer active sites that aid the mineralization and/or bonding of bioactive molecules that facilitate bone regeneration. Silk has also been blended with a variety of polymers and minerals to enhance its advantageous properties or introduce new ones. Several successful works, both *in vitro* and *in vivo*, have been reported using silk-based scaffolds to regenerate bone tissues or other parts of the skeletal system such as cartilage and ligament. A growing trend is observed toward the use of mineralized and nanofibrous scaffolds along with the development of technology that allows to control scaffold architecture, its biodegradability and the sustained releasing property of scaffolds. Further development of silk-based scaffolds for bone tissue engineering, taking them up to and beyond the stage of human trials, is hoped to be achieved in the near future through a cross-disciplinary coalition of tissue engineers, material scientists and manufacturing engineers.

Statement of Significance

The state-of-art of silk biomaterials in bone tissue engineering, covering their wide applications as cell scaffolding matrices to micro-nano carriers for delivering bone growth factors and therapeutic molecules to diseased or damaged sites to facilitate bone regeneration, is emphasized here.
The review rationalizes that the choice of silk protein as a biomaterial is not only because of its natural polymeric nature, mechanical robustness, flexibility and wide range of cell compatibility but also because of its ability to template the growth of hydroxyapatite, the chief inorganic component of bone mineral matrix, resulting in improved osteointegration.
The discussion extends to the role of inorganic ions such as Si and Ca as matrix components in combination with silk to influence bone regrowth. The effect of ions or growth factor-loaded vehicle incorporation into regenerative matrix, nanotopography is also considered.

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Contents

1. Introduction

1.1. Bone biology and construction

Bone supports movement, provides skeleton to body, and provides protections to organs; while also regulating the storage of minerals and blood pH. It actively participates in generation of blood cells and maintains homeostasis [1]. Bone's multifunctionality is imparted by its unique hierarchical structure of self-assembled macromolecules (~30%) within the bed (~70%) of hydroxyapatite (HA) and carbonate—both inorganic compounds [2–6]. Collagen makes up around 90–95% of the macromolecules, along with osteocalcin, osteonectin, osteopontin, hyaluronan, bone sialoprotein (BSP), and proteoglycans [7]. Hydroxyapatite nanoparticles (HAp) within collagen fibers act as reinforcing agents by upregulating the synthesis of alkaline phosphatase within bones, thus imparting bone its remarkable strength [8]. The nano size ($50 \times 25 \times 3\ nm^3$) of HAp is critical for favorable proliferation of bone cells within the bone matrix [9]. In biologically occurring HAp, the Ca to P ratio is 1.67 [10], which needs to be mimicked in artificially fabricated HAp to achieve the desired biological response, solubility and mechanosensitivity.

Cellular components such as osteoblasts (bone-forming) and osteoclasts (bone-resorbing) harbor the intrinsic plasticity of bone in response to mechanical loading [11]. Osteoblasts synthesize bone tissue extracellular matrix and are embedded within it. With time, they evolve into a stellate morphology, becoming osteocytes. While originating from hematopoietic stem cells, osteoclasts, the chief cellular component of mature bones; digest HAp crystals (by hydrochloric acid release) and collagen fibers (by proteases) through catalytic or enzymatic degradation at the fracture site. They have been hypothesized to play a critical role in responding to hormonal and/or mechanical stimuli, coordinating osteoblast and osteoclast functions, expressing the bone formation inhibitor sclerostin, and initiating bone remodeling [12]. Osteoclasts also actively participate in degradation of bone implants through resorption, i.e., cellular degradation due to osteoclasts. However, osteoclast-guided degradation is highly dependent on the implant composition [13]. Adult bone structure is grouped into two categories: cortical and trabecular. Cortical bone is a compact bone with blood vessels and osteocytes [14]; while trabecular bone contains pores of variable sizes filled with bone marrow or fat [15]. Osteocytes are present in the close packed spaces of the haversian systems (osteons) of cortical bone, referred to as lacunae. While the tight packing of the haversian system gives the impression of a solid mass, haversian canals possess blood vessels that run parallel to the bone's long axis. The blood vessels interconnect through perforating canals with each other on the bone surface. However, trabecular bone is made of trabeculae and cavities containing red bone marrow; there is no haversian system. Instead of a central haversian canal, canaliculi interconnect neighboring cavities to receive their blood supply. The arrangement of trabeculae is not random, and the precise organization provides maximum strength to the bulk structure.

1.2. Bone degeneration and therapeutic approaches

Postnatal bone inherits the capability of remodeling in response to mechanical stimuli or damage. Failure in this process because of significant trauma, disease, or pathological conditions such as osteoporosis, metastasis and malignancy or restricted blood supply limits the self-healing capability of the bone. Moreover, ever-increasing incidents of musculoskeletal disease and rising cost of treatment have been reported by WHO that analyzed data from

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