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Review

Development of polyurethanes for bone repair

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ABSTRACT

The purpose of this paper is to review recent developments on polyurethanes aimed at the design, synthesis, modifications, and biological properties in the field of bone tissue engineering. Different polyurethane systems are presented and discussed in terms of biodegradation, biocompatibility and bioactivity. A comprehensive discussion is provided of the influence of hard to soft segments ratio, catalysts, stiffness and hydrophilicity of polyurethanes. Interaction with various cells, behavior in vivo and current strategies in enhancing bioactivity of polyurethanes are described. The discussion on the incorporation of biomolecules and growth factors, surface modifications, and obtaining polyurethane-ceramics composites strategies is held. The main emphasis is placed on the progress of polyurethane applications in bone regeneration, including bone void fillers, shape memory scaffolds, and drug carrier.

1. Introduction

The aim of tissue engineering is to assemble constructs that provide mechanical, cellular, and molecular signals in order to restore, maintain, or improve damaged tissues or whole organs. Therefore, bone tissue engineering strives to restore a normal physiology or to speed up healing of bone in musculoskeletal disorders, injuries or deformities. Nowadays, autografts and allografts are commonly used in clinics in restorative therapy. However, bone harvesting is traumatic, causes pain and infections at the donor site, and very often results in complications. Hence, the use of synthetic grafts is emerging as an alternative treatment. Potentially, candidate materials for bone substitutes are a bioresorbable or biodegradable polymers and among them polyurethanes (PUR). PURs are non-toxic, biocompatible, biodegradable and they calcify in vivo. Properties of the PURs can be shaped by the various chemical compositions in the wide range of mechanical properties from rigid to flexible. Very broad assortment of products like foams, coatings, fibers, films etc. can be obtained from them [1–2]. PURs support cell adhesion and proliferation of human osteoblasts and other cell types [3]. PURs are very important biomaterials in tissue engineering. Numerous publications describing the possibility of PUR application in bone regeneration are published each year. There is a need to give critical review over current status on this subject. Thus, the aim of this work is to present why PURs are one of the most prominent materials in the bone tissue engineering application. Different PUR systems will be discussed in terms of biodegradation, calcification, biological activity taking into account their various applications in bone repair.

2. Bone structure and repair

Bone is a specific form of connective tissue, composed of collagen scaffold impregnated with calcium salts Ca^{2+} and PO_4^{3-} [4]. Bones protect the internal organs, act as a lever to which muscles are attached. Bone tissue is constantly resorbed and replaced with a new tissue. This process removes small defects and allows the bone to remodel in response to pressure and gravity loads. In the adult, healthy human about 10% of bone is replaced within a year, which implies that approx. after 10 years bone composition is exchanged at 100% [5]. Bone is also an important reservoir of calcium, 99% of this element present in our body is localized in this tissue.

2.1. Bone structure

The bone consists of cells (approx. 5% by weight of tissue), and extracellular matrix (ECM) (Fig. 1). Osteoblasts or osteogenic cells (20–30 μm) differentiate from bone marrow stem cells. They produce organic components of ECM: collagen and proteoglycans, and secrete proteins that regulate bone mineralization process [4]. Osteocytes are an osteoblasts surrounded by an impermeable, mineralized bone matrix, and their main role is to exchange nutrients and metabolites in the bone, but also they act as mechanosensors. Through numerous canaliculi, osteocytes remain in contact with each other and with cells on the

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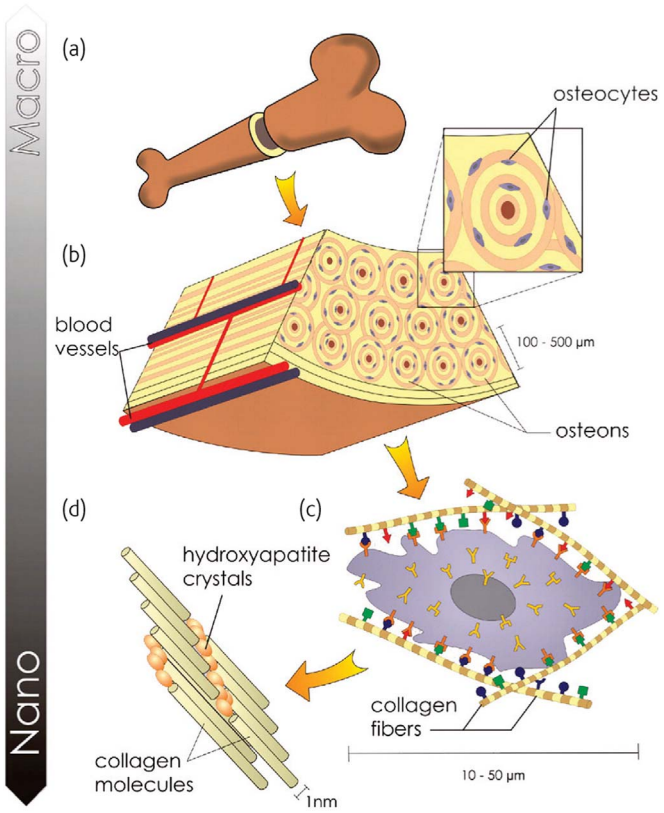

Fig. 1. Schematic bone structure.
Reproduced with permission from The American Association for the Advancement of Science [6].

bone surface (Fig. 1b). Osteoclasts or osteoclastic cells (up to 100 μm) are multinucleated and of hematopoietic origin. Their main function is bone resorption which is controlled by enzymes - hydrolases, that decompose the organic bone components by acidification of the surrounding environment with H^+ and Cl^- ions [4].

Bone ECM is made up of organic component - approx. 30%, and inorganic component of 70% of dry weight. Organic components include primarly collagen type I, but also proteoglycans and other matrix proteins such as growth factors (GFs), which regulates bone mineralization. The hydroxyapatite (HA) is the major component of inorganic phase (60–70% of bone mass) and is localized in the ECM in the form of small crystals (10 × 15 nm) (Fig. 1d).

The first type of bone formed developmentally is woven bone (immature), later replaced by lamellar bone (mature) and is further classified as two types: trabecular bone (also called cancellous or spongy bone) and compact bone (also called dense or cortical bone). The cancellous bone is located at the ends of the long bones as well as at the core of vertebral bones in the spine, the pelvic bones, ribs, and skull. It is built from bone trabecules, which size and shape depend on the direction of force acting on the bone and contains bone marrow. The cortical bone is located in the external layer of flat bones and in the diaphysis [4]. Selected physical properties of cancellous and cortical bone are presented in Table 1.

The outer surface of the bones (with the exception of the articular surface) is covered with a periosteum, while the inner surface, from the medullary canal side with a endosteum. The periosteum is built from connective tissue, which contains collagen fibers and a large number of cells, including stem cells, which are capable of dividing and can differentiate into osteoblasts. There are nerves and blood vessels as well, therefore periosteum also provides nourishment. Endosteum forms a film separating the trabecules from the medullary cavity. It contains both mesenchymal and hematopoietic stem cells, and together with periosteum residing cells takes part in bone remodeling and repair of bone defects.

Table 1
Selected physical properties of cancellous and cortical bone [7–8].

Property	Bone type - direction			
	Cortical - longitudinal	Cortical - transverse	Cancellous - longitudinal	Cancellous - transverse
Porosity [%]	5–10		75–90	
Density [g/cm^3]	1,99		0,05–1,0	
Volume fraction [mm^3/ mm^3]	0,85–0,95		0,05–0,60	
Young Modulus [GPa]	17–20	6–13	20	14,7
Tensile strength [MPa]	79–151	51–56	10–20	
Compression strength [MPa]	131–224	106–133	2–12	

2.2. Bone repair

In depth understanding of injured bone healing process lays at the base of biomaterials design for bone regenerative purposes. Bone healing consists of three consecutive processes: inflammation, repair and remodeling phases. To ensure bone regeneration, interplay between four elements need to be provided: 1) osteoconductive matrix (tissue scaffold); 2) osteoinductive signals (growth factors), 3) osteogenic cells (osteoblasts and stem cells); and 4) supply of blood and nutrients [9].

Osteoconductive, osteoinductive and osteogenic properties posses autologous bone graft. Autologous bone grafts have excellent biologic and mechanical properties, however their application may cause donor site morbidity, chronic postoperative pain, nerve damage and the limited volume available. The goal of tissue engineering is to assemble constructs that provide mechanical, cellular, and molecular signals in order to restore, maintain, or improve damaged tissues or whole organs. Scaffolds play a very important role in tissue engineering, by providing appropriate support for tissue growth and cell proliferation [10]. In 2010 Kommareddy et al. have proposed a mechanism of bone tissue regeneration on scaffolds [11]. The first stage is dominated by cell adherence and is highly dependent on the scaffold surface properties, such as chemistry and topography [12–13]. Next, cells proliferate and migrate into the pores. After a delay time of a few weeks, which depends mainly on material stiffness, cells begin to form an ECM. Seeding density has a dramatic effect on the delay time, because cells need time to proliferate before they can migrate into the pores. When the cell seeding density is increased, cells take a very short time to reach confluence and the migration starts much earlier resulting in little dependence of the delay time on pore parameter. The extracellular tissue layer is thick enough to support the cells independent of the scaffold and the growth kinetics depends only on the interaction between the cells and their own ECM, not the scaffold material properties.

To summarize, during bone regeneration both structure and properties of the material and cell-material interactions are critical. There are already published some reviews describing bone tissue scaffolds requirements, in example those written by Carvalho et al. describing the interactions between cells, scaffolds and signaling molecules, and providing extensive information on bioactive constructs requirements [14], by Puppi et al. about design, synthesis, characterization of polymeric scaffolds for bone repair [15], by Pilia et al. giving comprehensive review on commonly used ceramics and polymers in bone repair [16], and by Janik and Marzec discussing benefits and drawbacks of classical scaffold fabrication methods [1]. Firstly, the physiochemical