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Review

Scaffolds for Bone Tissue Engineering: State of the art and new perspectives

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ABSTRACT

This review is intended to give a state of the art description of scaffold-based strategies utilized in Bone Tissue Engineering.
Numerous scaffolds have been tested in the orthopedic field with the aim of improving cell viability, attachment, proliferation and homing, osteogenic differentiation, vascularization, host integration and load bearing. The main traits that characterize a scaffold suitable for bone regeneration concerning its biological requirements, structural features, composition, and types of fabrication are described in detail.
Attention is then focused on conventional and Rapid Prototyping scaffold manufacturing techniques. Conventional manufacturing approaches are subtractive methods where parts of the material are removed from an initial block to achieve the desired shape. Rapid Prototyping techniques, introduced to overcome standard techniques limitations, are additive fabrication processes that manufacture the final three-dimensional object *via* deposition of overlying layers. An important improvement is the possibility to create custom-made products by means of computer assisted technologies, starting from patient's medical images.
As a conclusion, it is highlighted that, despite its encouraging results, the clinical approach of Bone Tissue Engineering has not taken place on a large scale yet, due to the need of more in depth studies, its high manufacturing costs and the difficulty to obtain regulatory approval.
PUBMED search terms utilized to write this review were: "Bone Tissue Engineering", "regenerative medicine", "bioactive scaffolds", "biomimetic scaffolds", "3D printing", "3D bioprinting", "vascularization" and "dentistry".

Contents

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1. Introduction

Bone loss has, in general, significant effects on patient's quality of life. As a consequence, bone-related medical treatments and costs are increasing. Moreover, because of a prolonged life expectancy and an aging world population, there is a rapid increase in musculoskeletal pathologies such as fractures, low back pain, scoliosis, osteoporosis, bone infection or tumors, congenital defects and oral and maxillofacial pathologies, as well as rheumatic diseases like osteoarthritis [1].

Recently, more attention has been given to osteochondral defects, mostly concerning a young, athletic population. Such lesions, if untreated within subchondral bone, do not heal properly and osteoarthritis may develop over time [2].

Bone dynamic structure displays remarkable regenerative properties [3,4]. However, complicated larger defects can delay or impair healing, thus needing additional treatment before they can regenerate. In particular, a main issue yet to be solved is represented by the decrease in vascular supply [5].

The development of bone lesion treatment techniques starts from the understanding of bone biology [6,7]. Bone is a mineralized connective organ exerting important functions in the body: locomotion, soft tissue support and protection, calcium and phosphate storage and bone marrow harboring. Mechanical properties vary according to location and function [4]. Due to its complex and hierarchical structure, such a tissue can be defined as a nanocomposite consisting of inorganic nanocrystalline hydroxyapatite (HA), organic components (mainly collagens) and water. Proteins assemble together to form a nanostructured extracellular matrix (ECM) which influences adhesion, proliferation, and differentiation of several cell types: osteoblasts, bone lining cells, osteocytes, and osteoclasts [8–11].

This review gives a state of the art description of the scaffold-based strategies used in Bone Tissue Engineering (BTE). Critical issues and obstacles are highlighted. Applications and advances are described, figuring out possible scenarios and future directions. Our finality is to consider not only the engineering point of view, but all aspects of the BTE complex scenario: medical, economic-industrial, legal-ethical and patient perspective.

2. Strategies for bone regeneration

Different techniques have been proposed over the years to cure bone lesions, but they still represent a challenge in the orthopedic field [1].

Bone is the most commonly transplanted tissue after blood [12]; however, despite having been used for over a decade in the clinical setting, bone grafts display some disadvantages that limit their applications in therapy. The drawbacks in autograft technique (either vascularized or not), which represents the current gold standard, are: supply limitation, variable resorption, risk of donor site morbidity, high rate of failure in specific sites and the need of a second surgery [1]. The problems associated with allografts (from human cadavers or living donors), such as Demineralized Bone Matrix and xenografts (animal source) can be pathogen transmission and rejection by the recipient's body [1,13]. Metal implant strategy (titanium alloys and stainless steel) such as joint prostheses, plates and screws, currently utilized to provide mechanical and structural support for joint arthroplasties and long bone and vertebral fractures [1], presents limitations due to non-degradability, high rigidity, fatigue, fracture, lack of integration into the host tissue, extrusion and infection.

In the last decades, tissue engineering and regenerative medicine have emerged as promising strategies for bone reconstitution, with the ambition to circumvent the complications associated with traditional techniques [14–17]. Recently, their role has become more strategic, due to an ever-increasing demand for organ transplantation and, at the same time, to a severe shortage of donor availability [1,12]. Indeed, a potential solution to fix these problems is the development of engineered structures through the combination of scaffolds, cells and/or soluble/mechanical factors.

In BTE, a biomaterial can be defined as a temporary matrix that provides a specific environment and architecture for bone growth and development. A scaffold can be described as an artificial structure used to support three Dimensional (3D) tissue formation [16,18]. Scaffolds can be used as acellular systems or as vehicles for cells and/or drugs. Once implanted into the injured site, acellular materials should allow proper host cell colonization for regeneration purposes. Alternatively, scaffolds can be combined with different types of cells able to promote bone formation *in vivo* either by differentiating towards the osteogenic lineage or releasing specific soluble molecules. These cells may be expanded *ex vivo* before the implant. The most commonly utilized expanded cells are adult stem cells (bone marrow-, adipose tissue-, tooth-, peripheral blood-derived Stem Cells), Embryonic Stem Cells, induced Pluripotent Stem Cells and genetically modified cells. Conversely, non-expanded cells are, for instance, Bone Marrow aspirate concentrate supplemented with Platelet-Rich Plasma [14,17,19]. Another possibility is the use of scaffolds primed with soluble molecules such as antibiotics,