



Review

Bone regeneration: Biomaterials as local delivery systems with improved osteoinductive properties



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ABSTRACT

Bone is a mineralized conjunctive tissue, with a unique trauma healing capability. However, the replacement or regeneration of lost bone is not always successful and becomes more difficult the wider the bone defect. A significant growth in the demand for orthopedic and maxillofacial surgical procedures as a result of population aging and increase in chronic diseases as diabetes is a fact and successful approaches for bone regeneration are still needed. Until today, autogenous bone graft continues to be the best solution even with important limitations, as quantity and the requirement of a donor area. Alternatively, local delivery systems combining an osteoconductive biomaterial with osteoinductive compounds as hormones, growth factors or drugs is a popular approach aiming to replace the need for autogenous bone grafts. Nevertheless, in spite of the intense research in the area, presently there is no system that can mimic all the biological functions of the autogenous bone grafts. In this context, the present work provides an overview of the most recent advances in the field of synthetic bone grafts. The opportunities and limitations are detailed along with the remaining gaps in the research that are still preventing the successful translation of more products into the market able to be a valuable option in comparison to the autogenous bone grafts.

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1. Introduction

Bone is a mineralized conjunctive tissue, with a unique trauma healing capability [1]. Osteoblasts, osteocytes and osteoclasts are the specialized bone cells (Fig. 1).

When a bone defect occurs due to injury, cells are supplied from the periosteum and the regeneration occurs [1,2]. However, satisfactory regeneration becomes more difficult the wider the bone defect. That is why even with this property of healing in many situations bone graft is necessary [3]. Orthopedic procedures, like pseudoarthrosis, hip or knee arthroplasty, arthrodesis, and tumor removal commonly require bone graft [4]. Furthermore, oral and maxillofacial procedures often demand replacing the missing bone (Fig. 2). For example, to allow the correct implant insertion, based on the

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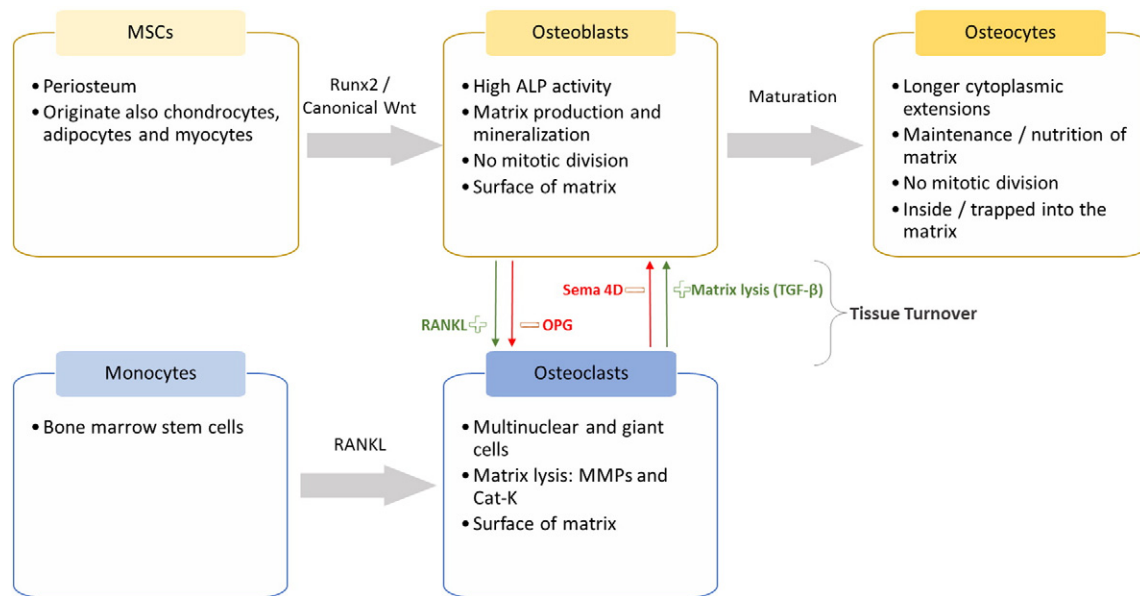


Fig. 1. The specialized bone tissue cells: origin and characteristics. Abbreviations: alkaline phosphatase – ALP, cathepsin K – Cat-k, matrix metalloproteinase – MMP, mesenchymal stem cell – MSCs, osteoprotegerin – OPG, receptor activator of nuclear factor κ B ligand – RANKL, Runt-related transcription factor 2 – RUNX2, semaphorin-4D – SEMA 4D and transforming growth factor beta – TGF- β .

prosthesis ideal position when the residual bone is not enough, to optimize functional/biomechanics results and to improve gingival and facial aesthetic [3].

Also important is the expected population aging along with the increasing on chronic diseases as obesity and diabetes, meaning that the number of patients undergoing orthopedic and/or dental procedures will raise and, consequently, the need for optimal bone grafts will greatly increase.

To date, the main approach for replacing missing bone is by using grafts. Bone grafts may be autogenous, homogenous, heterogeneous or synthetic. Autogenous means that the bone is removed from the patient's own body, often from the iliac crest, skullcap, mandible or tibia. To the present it is considered the gold standard (Fig. 3) once it contains growth factors for osteoinduction (i.e. to promote the differentiation of cells into active osteoblasts), cells for the osteogenesis and the framework for osteoconduction (meaning bone growth on the surface) [5]. However, it presents fast remodeling and limited source, once a donor area is required. In addition, autogenous grafts are often associated with high surgical risks and morbidity [3].

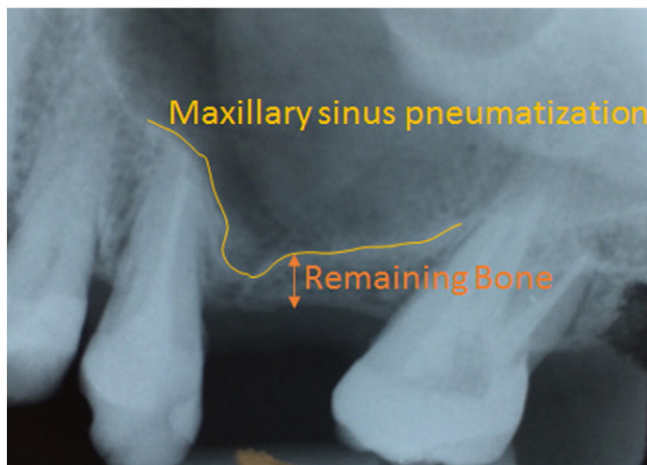


Fig. 2. Example of bone graft demand in oral surgery. Maxillary sinus pneumatization caused by loss of tooth, where the installation of dental implant is not possible by the lack of bone height. Radiograph assigned by Victor Z Martin DDS.

The second most common type of bone grafts is homogenous or allograft, which is a graft removed from human cadavers and it is available in bone banks [5]. Heterogeneous or xenograft is a graft obtained from species other than human, as bovine bone [3]. These types of bone grafts often require sterilization and deactivation of proteins, remaining only the mineral matrix. Homogenous or heterogeneous grafts are only osteoconductive, meaning that these grafts are often combined with patient's own stem cells (also termed mesenchymal stem cells) or growth factors [6]. That is, osteogenic as bone marrow aspirate (BMA) [7] or osteoinductive compounds as bone morphogenetic proteins (BMPs) or platelet rich plasma (PRP) [8,9] must be also used in the procedures (Fig. 3).

Alternatively, research has been focusing on finding, safer, less expensive and easier to use synthetic bone grafts. These bone substitutes can be created from biomaterials as hydroxyapatite (HA), tricalcium phosphate (TCP), bioactive glass, ceramics and polymers [5]. To date, those types of grafts can provide only osteoconduction, limiting its usage in bone reconstruction [3].

To improve biomaterials clinical outcome as bone grafts, researchers are trying to combine different compounds as hormones, growth factors and drugs with the materials. Synthetic scaffolds are being developed to deliver different compounds in the target area, aiming to achieve a high local concentration with minimum side effects (Fig. 4), besides maintaining the space, so that defects can be adequately replaced by newly formed bone. These grafts can facilitate the surgical procedure, reduce the time of the surgery, as well as the morbidity and provide an unlimited source.

With the ongoing intensive research in the field, there is a need to review and update the current advances on the novel approaches in terms of biological and synthetic compounds release by local scaffolds, designed to provide osteoinduction in osteoconductive materials, favoring the enhancement of bone regeneration, in the attempt of replacing the autologous grafts.

Up to date, published reviews are mainly focused on the biomaterial as a bone graft or growth factors role, either without exploring or comparing the enormous potential of local delivery systems in the context of bone regeneration. With that in mind, the present review aims to emphasize the current strategies, including their opportunities and limitations, which explore the role of biomaterials as local delivery systems to improve bone regeneration.

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