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Mini review

Alveolar bone tissue engineering using composite scaffolds for drug delivery

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Summary For many years, bone graft substitutes have been used to reconstruct bone defects in orthopedic and dental fields. However, synthetic bone substitutes such as hydroxyapatite or β-tricalcium phosphate have no osteoinductive or osteogenic abilities. Bone tissue engineering has also been promoted as an alternative approach to regenerating bone tissue. To succeed in bone tissue engineering, osteoconductive scaffolding biomaterials should provide a suitable environment for osteogenic cells and provide local controlled release of osteogenic growth factors. In addition, the scaffold for the bone graft substitute should biodegrade to replace the newly formed bone. Recent advances in bone tissue engineering have allowed the creation of composite scaffolds with tailored functional properties. This review focuses on composite scaffolds that consist of synthetic ceramics and natural polymers as drug delivery carriers for alveolar bone tissue engineering.

1. Introduction

Osteogenesis, osteoinduction, and osteoconduction are the three essential elements of bone regeneration, along with the final bonding between the host bone and the grafting material, which is called osteointegration [1]. "Osteogenesis" is the process of new bone formation by osteoprogenitor cells living within the autograft. "Osteoinduction" on the other hand is the stimulation and activation of host osteoprogenitor cells from surrounding tissue [1]. "Osteoconduction" describes the facilitation and orientation of blood-vessel and the creation of the new Haversian systems into the bone scaffold [2]. Finally "osteointegration" describes the surface bonding between the host bone and the grafting materials [2].

The advantage of an autograft is that it contains viable osteoblasts and osteogenic progenitor cells that can contribute to the formation of new bone [3]. In addition, the autograft possesses the three essential elements that are

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required for bone regeneration. Other options, such as allografts and xenografts, are believed to be osteoconductive, but confer the risk of disease transmission and immune rejection [4]. Therefore, autologous bone is generally considered the gold-standard graft material [5]. However, only a minimal amount of bone tissue can be harvested for autografts, the harvesting procedure may lead to donor site discomfort and morbidity, and it may be difficult to form this tissue into the desired shape [6—8], a problem that is particularly important in the craniofacial region.

To overcome these limitations, bone graft substitutes have been used to reconstruct bone defects. Synthetic ceramics made from calcium phosphate have been used in dentistry and in orthopedics since the 1980s [9—11]. A bone graft substitute should be osteoconductive, osteoinductive, biocompatible, biodegradable, structurally similar to bone, easy to use, and cost-effective [1]. Hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP) are both well-known ceramics that possess high tissue compatibility and osteoconductivity. However, neither HA nor β-TCP has osteoinductive or osteogenic abilities, and HA usually shows minimal biodegradation [12—14].

To overcome these problems, bone tissue engineering has been promoted as an alternative approach to regenerate bone tissue. This approach combines cells capable of osteogenic activity and osteoinductive signal molecules with an appropriate material [15]. For bone tissue engineering to succeed, osteoconductive scaffolding biomaterials must provide a suitable environment for the cells. Furthermore, it is desirable that the scaffolds can control the release of growth factors. Accordingly, biodegradable composite scaffolds for bone tissue engineering have been developed in combination with synthetic ceramics and natural polymers. In this mini review, we focus on biodegradable osteoconductive composite scaffolds for alveolar bone regeneration.

2. Osteoconductive scaffolds: HA and β-TCP

Commercial HA and β-TCP have been examined in terms of suitability as a bone substitute in the clinical setting [16]. Radiological evaluation during clinical investigations of implanted HA and β-TCP in humans has revealed satisfactory osteoconductive qualities of both materials [17,18]. It is known that ceramics with higher porosity and lower density provide greater surface area for vascularization and bony ingrowth. Furthermore, the regular and uniform surface morphologies of HA and β-TCP affect cell proliferation and differentiation [19,20]. When the ceramics are implanted and attached to healthy bone, osteoids are produced directly on the surfaces of the ceramic in the absence of a soft tissue interface [1]. Thus, osteoconductive scaffolds such as HA and β-TCP provide an appropriate environment for bone cells. However, neither HA nor β-TCP have osteoinductive or osteogenic abilities, two factors that are important for successful bone regeneration.

In addition, synthetic ceramics should be biodegradable to support the reconstruction of new tissue without inflammation [21]. The current aim of the biological implant is to be indistinguishable from the surrounding host bone [22]. After implantation, a calcium phosphate compound such as β-TCP undergoes remodeling and is eventually completely replaced by new bone. The degradation rate of β-TCP is 3—12 times faster than HA [23]. Several animal experiments demonstrated satisfactory biocompatibility of commercial β-TCP as both biodegradation and bone formation began at an early stage following implantation [24—26]. Moreover, it is also possible to combine β-TCP with growth factors or bone marrow aspirate, which can potentially accelerate the process of bone regeneration [27—30].

Although the ceramics lack mechanical bone characteristics, they gradually acquire mechanical strength similar to cancellous bone after their incorporation [31,4]. In addition to low load-bearing applications such as alveolar bone, it is more important to have stability and the correct three-dimensional shapes for functional and aesthetic reasons [32]. With regard to shape, block and granule forms are available for calcium phosphate ceramics. For alveolar bone regeneration, the block shape is difficult to mold and adapt into the three-dimensional structure of the bone defect Thus, guided bone regeneration (GBR) using granule form ceramics has been used for periodontal defects or alveolar bone ridge augmentation. Such materials possess sufficient mechanical strength to sustain the shape until it is replaced by newly formed bone. Therefore, biodegradable granule ceramics such as β-TCP have been used in alveolar bone regeneration.

3. Natural polymers: collagen and gelatin

There are two types of biodegradable polymers: synthetic polymers and natural polymers. Synthetic polymers are widely used in biomaterial applications. Examples in tissue engineering include aliphatic polyesters (polyglycolic acid and poly-L-lactic acid), their copolymers (polylactic—coglycolic acid), and polycaprolactone. However, the chemicals (additives, traces of catalysts, inhibitors) or monomers (glycolic acid, lactic acid) released during polymer degradation may induce local and systemic host reactions that cause clinical complications [32].

Natural-based polymers offer the advantage of being similar to biological macromolecules, and thus the biological environment is better prepared to recognize and deal with these polymers metabolically. Because of their similarity to the extracellular matrix, natural polymers may also prevent chronic inflammation or immunological reactions and toxicity, which often occur with synthetic polymers [33]. Natural polymers used in bone tissue engineering include collagen, gelatin, fibrin, alginate, silk, hyaluronic acid, and chitosan [34]. Most natural polymers are biocompatible, degradable, and readily solubilized in physiological fluid, which can be used alone as a growth factor delivery carrier or combined with other delivery materials such as synthetic polymers and inorganic materials [35]. This mini review focuses on collagen and gelatin as drug delivery carriers for bone tissue engineering.

Collagen, as a natural polymer, is the most abundant extracellular matrix protein and is readily isolated and purified from various animal species by enzyme treatment. Because collagen type I is the main organic component secreted by osteoblasts, which then become mineralized at a later stage of bone development, collagen has been actively investigated as a favorable artificial microenvironment for bone ingrowth [36—39]. Type I collagen is not only a major component of the bone matrix and useful as a carrier of

Table 1 Scaffolding biomaterials for bone tissue engineering.

Scaffold	Osteoconduction	Osteoinduction	Osteogenesis	Biodegradation	Drug release
Autologous bone	3	3	3	2	0
HA	2	0	0	0	1
β-TCP	2	0	0	2	1
Collagen	1	0	0	3	2
Gelatin	1	0	0	3	3

Score: 0 (none) to 3 (excellent). HA: hydroxyapatite, TCP: tricalcium phosphate.

osteoblasts [40], but osteoblast cells have been shown to successfully invade a collagen sponge with a porous HA frame [41]. Collagen is easily degraded by the body and allows good attachment to cells. On the other hand, collagen as a drug delivery carrier has been fabricated as gels, nanofibers, porous scaffolds, and films to prolong the release rate of growth factors and increase the therapeutic effect of tissue engineering approaches [22,42]. By incorporating transforming growth factor-β1 into a dehydrothermally cross-linked collagen sponge, the former was released in a biologically active form as a result of sponge biodegradation, resulting in enhanced bone repair of skull defects [43].

Gelatin is a natural polymer that is derived from collagen and is commonly used for pharmaceutical and medical applications because of its biodegradability [44—47] and biocompatibility in physiological environments [48,49]. Various forms of gelatin carrier matrices can be fabricated for controlled-release studies [50]. The cross-linking density of gelatin hydrogels has been shown to affect their degradation rate in vivo, and the rate of biomolecule release from gelatin carriers has been shown to have a similar profile, suggesting that complexed gelatin/biomolecule fragments are released by enzymatic degradation of the carrier *in vivo* [50]. Indeed, the gelatin hydrogel or sponge can control the release of growth factors to enhance their biological functions on bone regeneration [51—54].

However, these natural polymers lack the initial mechanical strength needed for weight bearing. It is a serious disadvantage for implantation and makes it impossible to use them alone for bone replacement *in vivo* [55]. Therefore, additional support, such as a synthetic bone substitute, is needed for bone regeneration.

4. Biodegradable composite scaffolds for alveolar bone

Both ceramics and natural polymers have their own merits and drawbacks (Table 1), and a better solution may be to synergize the advantageous properties of both materials for composite scaffolds. For example, the addition of collagen to a ceramic structure can provide many additional advantages for surgical applications: shape control, spatial adaptation, increased particle and defect wall adhesion, and the ability to favor clot formation and stabilization [56]. In addition, the three-dimensional porous structure consisting of ceramic granules and a collagen sponge provides an appropriate spatial arrangement for osteogenetic cells as well as facilitating vascular invasion [57,58].

Many different composite forms such as sponges, gels, films, and blocks have been developed using different methods [32]. In alveolar bone regeneration by GBR, using sponges or gels composites is desirable, as they easily fit into alveolar bone defects. Sponge composites consisting of granule ceramics and natural polymers can simply be cut with scissors or a sharp knife, and can therefore be easily molded for use for various tissue disorders such as periodontal bone defects, cyst cavities, and alveolar bone augmentation [57]. The mechanical properties of the composites are relatively poor in comparison to bone, although the graft site can be reinforced using membranes during GBR. Gradually, the collagen of sponge composites degrades, and the remaining β-TCP granules in the defect come into direct contact with the newly formed bone. Finally β-TCP granules replace the original bone structure during the remodeling process [57,58]. In addition, these composite scaffolds can locally release growth factors from collagen and gelatin, used as drug delivery carriers, and enhance bone formation to treat bone defects [43,51,53,54].

5. Conclusions

Autologous bone grafting is the gold standard for regenerating alveolar bone. Alternative strategies for bone tissue engineering have also been developed involving three components: a osteoconductive scaffold, osteogenic growth factors, and osteogenic cells. However, it is difficult in clinical dental practice to harvest osteogenic cells such as mesenchymal stem cells, and the culture of the cells is also impractical. In dental practice, one strategy for alveolar bone regeneration is to induce maximum intrinsic healing potential at the alveolar bone defect "*in situ*", applying a selected "composite graft" that contains osteoinductive growth factors along with an osteoconductive composite scaffold. It is important to design the composite scaffold to guide the osteoblasts to the regeneration site. When developing a composite scaffold for alveolar bone regeneration, the choice of the appropriate biomaterials (e.g., biodegradable synthetic ceramics and natural polymers) and form (e.g., sponge or gel) is important, and should be based on several parameters that address clinical needs and local conditions. There are, however, unknown transmitting diseases by natural polymers. The trends in tissue engineering are heading for using animal product free materials. Therefore, we should be selected materials carefully for safety medicine.

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