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REVIEW ARTICLE

Application of bone growth factors—the potential of different carrier systems

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Abstract
Aim The aim of the present review was to characterize the potential of different biomaterials as carriers for bone growth factors.
Introduction Beyond mechanical and structural characteristics, one of the features that account for a potential carrier is the possibility to couple growth factor molecules to it. As simple adsorption of the growth factor to the carrier surface by soak loading produces a burst release of growth factors with rapid decrease of biological activity, the ability to accomplish controlled release of functional growth factor molecules is one of the crucial characteristics for an appropriate carrier material.
Conclusion The variety of carrier materials requires different strategies to either couple growth factors to the material surface or to incorporate them into the carrier matrix. The present review outlines current technical approaches and discusses future trends in the use of carrier materials for bone growth factors.

Keywords Growth factors · Carriers · Biomaterials · Osteoinduction · Regenerative medicine

Introduction

Applications of biological signals in regenerative medicine require carrier systems for targeted delivery with respect to both location and dosage. Bone growth factors are expected to enhance or to accomplish bone formation in defects that would otherwise require autogenous bone tissue transfer for repair. In order to fulfill these expectations, the ideal carrier system would provide mechanical strength for bridging of bone defects and resistance against soft tissue pressure on the one hand as well as interconnecting porosity and degradability for unrestricted bone ingrowth and final replacement by regenerated bone on the other. Many biomaterials can act as passive scaffolds in this way; however, in order to qualify for a growth factor carrier, they have to be loadable with biologically active molecules and allow for retarded delivery and controlled presentation. The carrier systems for osteogenic growth factors that are in clinical use or undergo current clinical testing are loaded either by soaking the carrier into the growth factor solution for immediate application or they are submitted to soaking and lyophylization for storage and later use. Delivery from these carriers occurs through a burst release with loss of up to 80% of activity within the first 48 h after implantation [39]. Although the dosage requirements for osteogenic growth factors have not yet been clearly defined, there is wide agreement that controlled release of growth factors is more likely to approximate natural delivery characteristics than the burst release provided by the carriers currently in use.

Loading of a potential carrier with growth factors can be accomplished either through various ways of binding the growth factor molecules to the material surface or by incorporating them into the biomaterial itself. The strategies for biofunctionalization of carriers with growth factors, thus, depend very much on the characteristics of the carrier material with respect to degradability. For permanent materials, loading of the carrier surface with growth factors would be an appropriate approach, whereas for degradable carriers, incorporation of these molecules into the carrier

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matrix for gradual release during degradation would be desirable. Sophisticated technology to anchor biologically active molecules to the surface of degradable materials would not be useful as surface erosion during early stages of degradation would rapidly extinguish the biological activity and leave a passive scaffold behind.

All biomaterials that are potential candidates as growth factor carriers have their individual limitations with respect to binding or incorporation of growth factors that are based on their chemistry and have to be specifically addressed by individually adapted technology. With respect to material chemistry, a gross distinction between inorganic and organic carriers may be useful for a systematic approach. While most of the former ones fall into the realm of dental implants and bone replacement materials, the latter ones provide a wide variety of new polymeric materials, most of them being still under development.

Inorganic carriers

Inorganic carriers can be grouped into metals and mineralized carriers, the latter ones being split up into scaffolds of natural and synthetic origin. The conditions and temperatures used during fabrication of inorganic carriers commonly preclude the inclusion of bioactive molecules into the material itself. Only nanocrystalline calcium phosphate cements that are prepared at room temperature and cure at body temperature may be suitable for the integration of growth factors into the biomaterial itself. However, the approaches that have been evaluated in preclinical experimental settings have not been successful yet [18]. Thus, inorganic carriers can be considered as being functionalized merely by coupling biologically active molecules to the material surface.

The least complex way of binding growth factor molecules to the surface of an inorganic biomaterial is adsorption during immersion of the material into the solution of the respective growth factor. Adsorptive binding can occur through physisorption or chemisorption [28]. Physisorption is based on the fact the most inorganic biomaterial surfaces are negatively charged and that positively charged proteins can bind to these negative surface charges. Release of physisorbed molecules is influenced by the chemical nature of the material and the actual chemical status of its surfaces. Titanium surfaces that have been loaded with bone morphogenic proteins (BMPs) by physisorption have lost 99% to 96% of their bioactivity during the first hours of release depending on their microstructure [11]. In contrast, diamond coating of titanium surfaces could achieve a much stronger binding of BMP molecules to the surface [36] with a considerably retarded release in vitro and increased bone formation in vivo depending on its oxidative status [20]. Physisorption has also been used to bind structural proteins such as collagen to titanium surfaces. Collagen provides numerous bindings sites for integrin receptors on the surface of osteoblasts and precursor cells and can act as well as a reservoir for growth factors in conjunction with other bone matrix components such as glycosaminoglycans. In this way, coadsorption of collagen and chondroitin sulfate to titanium surfaces has been applied to bind BMP molecules [4]. This matrix engineering approach has enhanced bone formation, but specific effects of released growth factors could not be shown [30].

An alternative way of coupling growth factors to inorganic carrier surfaces is a chemisorptive process using linker molecules. With one end, the linker molecules bind to the surface of the carrier and with the other end to the growth factor. The chemical nature of the carrier surface and the molecular structure of the growth factor to be attached frequently determine the choice of the linker molecules. Thiol anchors have been employed for this purpose that bind to cysteine residues of organic molecules using maleimide chemistry [29]. Phosphonate anchors are commonly used to couple BMP2 to a carrier surface because the seven cysteine residues are engaged in disulfide bonds within the molecule and in the intermolecular disulfide bond of the dimeric protein [1]. Phosphonate anchors bind to the oxide groups of the material surface through their phosphonate groups. Modification of these anchor molecules using *N*-hydroxysuccinimide/*N*-ethylcarbodiimide (NHS/EDC) or *N*,*N*-carbonyldiimidazol chemistry on the free end of the anchor molecule allows for covalent binding of the primary amino groups of growth factor molecules. Chemisorptive coupling of BMP has been reported to retard release from the surface and enhance bone formation in a significant manner [1, 33].

Valve metals like titanium can be also coated using nanomechanical anchorage of organic molecules. This strategy is based on the growth of oxide layers on the titanium surface under anodic polarization. Molecules or nanoparticles that are preliminary adsorbed on the initial surface can be incorporated into the growing oxide layer. Nanomechanical fixation has already been used for the partial incorporation of a cyclic RGD-peptide conjugated to phosphonate anchors [3] and fixation of adsorptively immobilized fibrillar collagen [29]. Additional binding of selected proteins such as RGD motifs can be accomplished using thiol anchors [30].

Nanomechanical fixation as well as chemisorptive binding of biologically active molecules to a biomaterial surface, however, has the disadvantage that the sterilization procedures which all implants have to undergo prior to insertion could easily render the coated implant surface inactive. Therefore, the concept of nanomechanical anchorage has been recently expanded to the regioselective

incorporation of terminally functionalized oligonucleotides. As the structure of oligonucleotides are much more likely to survive sterilization procedures, they could act as anchor strands for bioactive molecules by using hybridization with complementary strands conjugated with biologically active molecules after sterilization [21]. Different oligonucleotide sequences would then allow for anchorage of more than one growth factor molecule, and different strand lengths can provide variable release kinetics. Nevertheless, this concept requires further in vitro evaluation and assessment of preclinical proof of principle.

Organic carriers

Like inorganic carriers, organic carriers can be divided into those that originate from natural precursors and those that are produced from purely synthetic polymers. Because organic carriers allow for engineering of material composition and surface properties in conjunction with proteins to a higher extent than inorganic carriers, they are likely to have a higher potential to provide controlled release characteristics.

Among the carriers of natural origin, collagen has undergone the widest application as carrier for many different biologically active molecules. Its potential as a carrier for bone growth factors has been thoroughly evaluated [2, 9, 40, 41]. Although it is the only carrier that has received Food and Drug Administration (FDA) approval for BMPs so far, native collagen sponges have only inferior characteristics for retarded growth factor delivery [39]. Therefore, chemical modifications of the collagen fibers have been performed to enhance the binding of the growth factors and slow down the release. These modifications have made use of the fact that collagen contains multiple heparin binding sites on the one hand and that heparin also acts as binding molecule for many growth factors. Coupling of heparin to the collagen fibrils can allow for stronger binding of growth factors and result in a slower release from the collagen carrier. This approach has been successfully performed for binding and release of vascular endothelial growth factor [35, 43]. Alternative routes for coupling of growth factors have been pursued using chemical modifications of the growth factor itself. Binding and release of human recombinant bone morphogenic protein 2 (rhBMP2) to collagen scaffolds have been improved by adding a collagen binding domain to the N-terminal of the growth factor molecule. In this way, bone formation could be significantly increased in critical size defects compared to controls [5].

Another organic carrier of natural origin is silk, a fibrous protein, which is composed of fibroin and sericin proteins. Silkworm silk in its original composition has shown to be strongly immunogenic. Removal of the glue-like sericin proteins, which act as binding agents for the native silk fibroin threads, has rendered this material highly biocompatible [34]. The fibroin protein is a degradable protein that can be regenerated as gels, films, or fibers for various applications [22]. Coupling of biologically active molecules such as RGD peptides, parathormone, and BMP2 to silk fibers has been performed using NHS/EDC chemistry [22]. This type of coupling had resulted in retention of higher amounts of growth factors on the biomaterial surface as well as increased mineralization in vitro [16]. In vivo testing of silk as carrier for BMP2 has also been successfully demonstrated; however, in these applications, the growth factor had been only adsorbed to the carrier surface without using specific means of coupling [17, 19].

A third carrier of natural origin is chitosan, a degradable polyaminosaccharide which is derived from the chitin shell of shrimps. High molecular mass chitosan is fabricated as fibrous textile structure by electrospinning. Growth factor molecules can be coupled to chitosan using maleimide chemistry [26]. This chemical conjugation has been shown to be associated with significantly retarded release of BMP from the surface of chitosan fibers as well as significantly increased accumulation of calcium in MC3T3 cell cultures when compared to carriers with adsorptive coating only [24]. Preclinical testing of this carrier in conjunction with BMP2 has shown significantly enhanced bone formation using adsorbed and not chemically conjugated growth factor molecules [7]. However, this carrier had failed to produce sufficient bone tissue when being tested in a clinical setting later on [6].

The majority of organic carriers of pure synthetic origin are polymers of poly-α-hydroxy acids with polylactic acid (PLA) and polyglycolic acid (PGA), and their derivatives being the most common ones. These polymers degrade through hydrolysis. Their degradation time can vary considerably depending on composition, molecular weight, and crystallinity.

Synthetic polymers derived from poly-α-hydroxy acids have been tested extensively as carriers for bioactive substances. Both PLA and PGA as well as combinations of both have been used as delivery vehicles for bone growth factors. Incorporation of growth factors into the polymer matrix requires additional technology as the glass transition temperature (the temperature at which the polymer becomes liquid) of both PLA and PGA is well above the temperature at which proteins denaturate. One intensely researched way of integrating growth factors into the polymer matrix is the application solvent technology. During this procedure, the polymer is liquefied using organic solvents such as dichloromethane or methylene chloride after which the growth factor is added. During evaporation of the solvent, the polymer becomes solid and can release the incorporated growth factor during degradation [42]. Porous carriers can be derived by

combining solvent casting with particle leaching methods, during which sodium chloride particles are added and removed from the solid polymer afterwards by salt leaching. More recent approaches have used amino terminated poly(L-lactic-*co*-glycolic acid) and combined this technology with NHS activated heparin which in turn allows for targeted growth factor binding [12]. When combined with BMP2, this amino-terminated heparin-conjugated polymer has resulted in growth factor release for more than 14 days in vitro and has significantly enhanced bone formation compared to conventionally prepared polymer carriers. However, concerns have been raised in conjunction with this technique that residues of organic solvents remain after evaporation which could cause toxic reactions and lead to tissue irritation in vivo.

An alternative way of incorporating growth factors into the polymer matrix that could avoid the use of organic solvents is gas foaming. Gas foaming is performed using high-pressure carbon dioxide and is particularly suitable for amorphous poly-DL-lactic acid. Under high-pressure conditions (approximately 100 bar), the carbon dioxide molecules diffuse into the polymer between the PLA chains and lead to reduction of the glass transition temperature so that the polymer becomes liquid at body temperature. If a lyophilized mixture of polymer granules and growth factor is submitted to gas foaming in a mold, the polymer can incorporate the growth factor that had been adsorbed and lyophilized on the surface of the polymer granules [23, 38]. During decompression, the liquid polymer transforms into a solid foam that fills the mold. The incorporation of growth factors using this technology has shown to be superior to adding growth factor to the solid porous matrix after gas foaming of the polymer alone [25]. Implants produced with this technology have been successfully tested as slow release devices for BMP2 in vitro and preclinically [10, 31, 32].

One major drawback of the use of poly-α-hydroxy polymers is the fact that their degradation is associated with a periimplant drop in pH, which can cause tissue irritation and produce detrimental effects on bone formation. Moreover, during degradation, thorough initial hydrolysis fragmentation of the polymer occurs, which elicits cellular uptake and degradation. This cellular degradation process can cause features of sterile inflammation with resorption of adjacent bone tissue. Addition of neutralizing components such as calcium carbonates and/or calcium phosphates can help to reduce the acidic degradation products occurring during resorption of the carrier [8, 27].

Another synthetic polymer which is currently being researched intensely is polyethylene-glycol (PEG). PEG molecules form a three-dimensional network in which water can be absorbed to a multiple of its dry weight forming a hydrogel. In this way, PEG offers the opportunity to retain active factors in the matrix and to release them in a controlled manner. Proteins and peptides can be bound into the network via cystein groups and are released during degradation of the network. Degradation occurs through hydrolysis. Mechanical strength, degradation characteristics, and, thereby, release kinetics of growth factors are strongly depending on the molecular weigth of the PEG carrier.

PEG has been used in conjunction with parathormon and with BMP2 [13, 15]. As it has little mechanical stability, it has been combined with calcium phosphate carriers [14] or polymers that provide greater stability such as PLA [37]. All combinations had been successful in inducing new bone formation; however, detailed release characteristics with respect to molecular weight of the PEG polymer and corresponding data that support a controlled release function have not been reported yet.

Conclusions

Today, a large variety of scaffold materials exist that can be used as carriers for bone growth factors. Loading of these carriers through simple adsorption produces a burst release of biological activity that is considered inappropriate from a physiological point of view. Therefore, a critical feature for the suitability of these materials is the ability to provide controlled release of the growth factor molecules. An important precondition for this quality is a defined coupling method that is used to bind the growth factor to the carrier.

Inorganic carriers, which are currently widely used as bone replacement materials and dental implants, are merely loaded with growth factors by binding them to the material surface. This can be accomplished by chemisorption using linker molecules of various chemistry or, if valve metals like titanium are involved, by nanomechanical anchorage of anchor strands that then can bind growth factors. Preclinical evidence for the efficacy of the majority of these approaches exists; however, in clinical settings, only simple adsorption of the growth factor to the carrier through soak loading has been applied yet.

Organic carriers provide a higher variability with respect to degradation characteristics, chemical modification, and, thus, binding of growth factors. A number of promising approaches exist that use polymers of both natural and synthetic origin, which have been modified to accommodate or bind bone growth factors for a controlled or at least retarded release. Many of these materials have undergone successful preclinical testing in various models. Clinical approval of these concepts remains to be shown. Currently, the only organic carrier in clinical use is collagen.

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