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Molecular Approaches to Functionalization of Dental Implant Surfaces

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Abstract

The present review examines several approaches to improve properties of dental implants by modifying their bioactive surfaces (functionalization) using the techniques of molecular transplantation. The first group of functional ligands is designed to enhance osseointegration of implants, it includes growth factors, promoting the formation and bone remodeling: bone morphogenetic proteins (BMPs), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and their combinations with each other, and several other ones. The second group of bioactive molecules does not directly stimulate bone formation, but it promotes osteoblast seeding on the implant surface due to the adhesive properties, thus accelerating osseointegration. Finally, the third group of substances used to increase the antibacterial properties of coatings, thereby reducing the formation of bacterial film on the implant surface and the risk of inflammatory rejection of the implant. Key issues of using biofunctional coatings, despite their obvious promise today still are relatively high cost, difficulties of controlling properties and its storage between the fabrication and installation of implants in the bone of the recipient.

Keywords: dental implantation, functional coating, bioactive surface, cellular adhesion, osseointegration, platelet-derived growth factors, bone morphogenetic proteins.

Introduction

The success of prosthetic dentistry, due to the advent of new diagnostic and therapeutic technologies have led to the fact that dental implantation claims to be a "gold standard" in the restoration after lost of teeth. The number of operations in leading dental clinics in the thousands per year with efficiency of over 95 %, and in some age groups of the urban population in developed nations, the part of people with dental implants is approaching to 20 % [16, 56].

The long-run objective of dental implantation is a stable recovery of function of dental system by restoring the three-dimensional dental occlusion, which is unconceivable without the formation of a strong bond between the implant and the recipient bone, osseointegration [2, 21, 37, 40, 57]. The failures of dental implantation specifically associated with a partial loss of foregoing connection, with bacterial population of the resulting gaps and with inflammation of surrounding tissues [49, 55].

The surface of the metal structures installed in bone tissue is continuously improves. This is one of the main approaches to solving the defined problem. Ideally, it should be absolutely biocompatible, have a high specific area and cause intensive bone tissue formation, that is, have osteoinductive effect [1, 8, 22]. The number of foreign analytical reviews [7, 44, 58] describes ways to enhance osseointegration by creating biomimetic micro-relief surfaces and by coating implants of various materials with osteoinductive properties.

Although the number of such modifications is theoretically infinite (calculated in the hundreds in practice), manufacturers seem to reach the limit improving the osseointegration by these methods. This is evident from the fact that there are no proven advantages of modified surfaces over conventional screw implants in a few clinical trials [61, 62].

The surface functionalization usage opens fundamentally different possibilities. The idea is to use them in a controlled placement on the implant' surface of active molecules with biological effect - adhesion, growth factors, etc., which allows the quickest possible osteogenesis initialization throughout the implant surface. Making the surface of the predefined useful health properties (functionalization) is achieved in this case by molecular transplantation [3, 52]. This review is devoted to observe the advantages and unresolved problems of this approach.

1. Functionalization with growth factors

The main purpose of the active biomolecules placement on the implant surface concludes in diminishing the initial inflammatory response to installation of the implant due to their gradual release into the tissue. Most intensive bone formation and reduction of surface colonization by microorganisms resulted from this action. Some growth factors and fragments of the organic matrix of bone, known biologically active peptides, are suitable on the role of these substances [23, 30].

In the detailed review I. Nishimura [41] described two dozen growth factors somehow involved in osteogenesis. Nevertheless, at the moment only four growth factors are promising for the needs of implantology: bone morphogenetic proteins (BMP-2 and BMP-7), fibroblast growth factor (FGF-2) and platelet-derived growth factor (PDGF-B). Common functional scheme of molecular interactions in system 'implant – bone' presented in Figure.

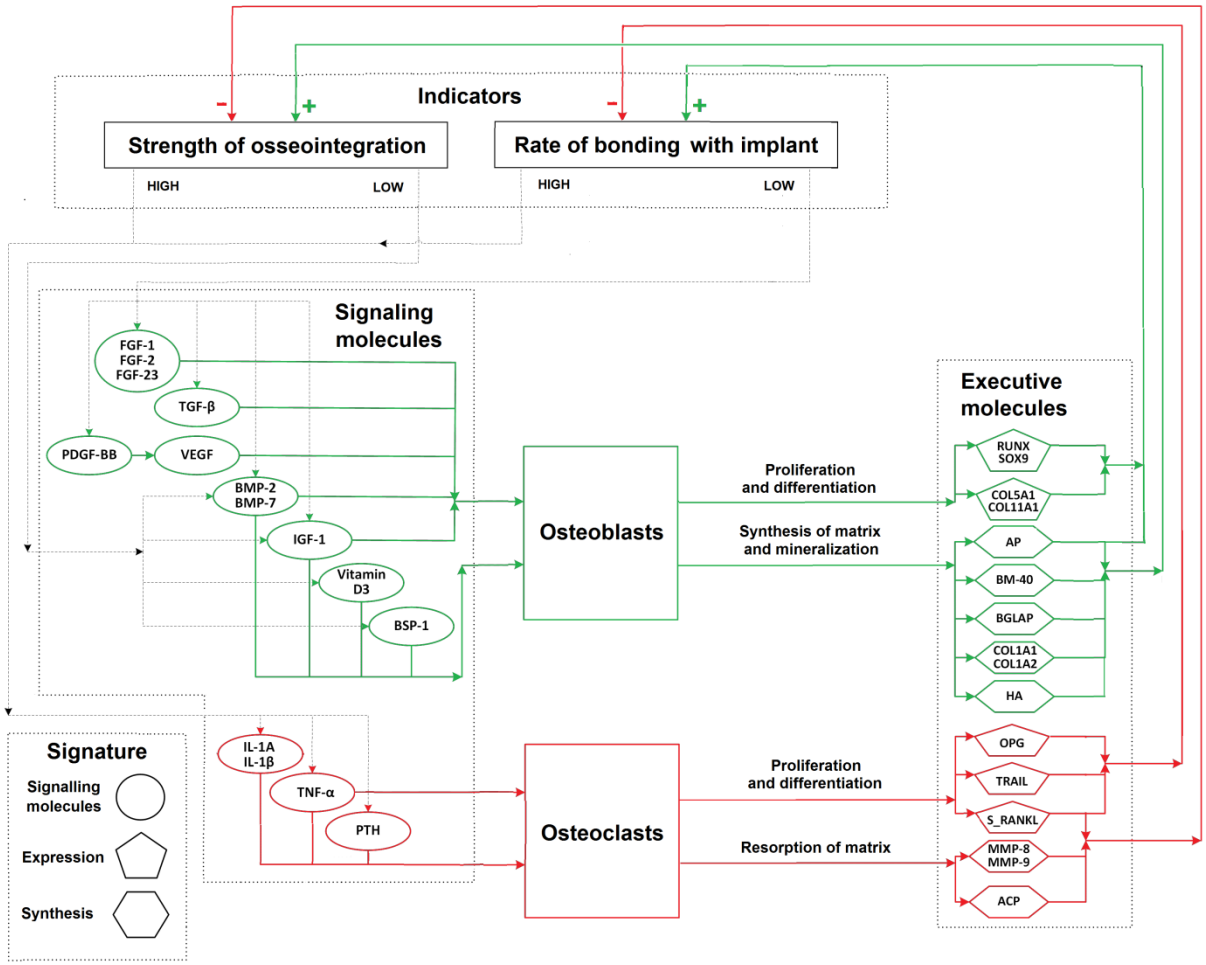

Figure. The functional system 'implant – bone' can be subdivided into three blocks. Signaling molecules form the block (I) managing the activity of the two cell populations, osteoblasts and osteoclasts. Synthesis and/or expression of executive molecules (II) reflect functional activity of these cells. A set of indicators the two final characteristics of osseointegration, such as the formation and the strength of the bond between the implant and the bone (III), can influence the concentration of signaling molecules through feedback.

Transforming growth factor (TGF-β) strongly accelerating the division and differentiation of many types of mesenchymal cells, was ineffective in these conditions, because of the considerable chondroinductive effect that could not secure the stability of implant engraftment [4]. Insulin-like growth factor (IGF-1 and IGF-2) and vascular growth factor (VEGF) have been effective only in combination with the above factors. Essentials facts about the main growth factors currently used to stimulate the osseointegration of dental implants are summarized in Table.

Table

Growth factors and biologically active peptides used for molecular transplantation due to fabrication of dental implants (on clinical trial stage)

Molecules	Mechanism of action	Ref.
Alone growth factors		
BMP-2 BMP-7	Cell differentiation and stimulation of osteogenesis	[6, 11, 14, 32, 33]
FGF-2	Mitogenesis and suppression of apoptosis in osteogenic cell population	[25, 35]

PDGF-B	Mitogenesis and chemotaxis of mesenchymal and osteogenic cells	[10, 17, 43]
Combinations of growth factors		
PDGF-B + IGF-1	Additional stimulation of osteogenesis and collagen synthesis	[45]
BMP-2 + VEGF	Additional stimulation of osteogenic differentiation and mineralization of matrix	[24, 34, 47]
BMP-2 + FGF-2	Additional stabilization of osteoblast proliferation	[29, 38]
BMP-2 + TGF-β	Most intensive production of bone matrix	[54]
Adhesive and antibacterial peptides		
RGD YIGSR REDV	Most intensive adhesion of matrix proteins to implant surface	[18, 36, 52]
GL13K	Protection of implant surface to bacterial colonization	[18, 64]

Among the BMPs belonging to the TGF-β superfamily are the most relevant for dental implantology BMP-2 and BMP-7 isoforms, which proved all the effects of bone formation stimulation *in vivo* [4, 39]. Recently a group of Russian scientists has been developed the original method of producing recombinant human BMP-2 (rhBMP-2) with a high-producing strain based on *Escherichia coli*. On the basis of rhBMP-2 the osteoplastic material «Gamalant™ - pasta Forte Plus" is created. It has high osteoinductive and effectively influence on the process of reparative osteogenesis [11]. To ensure the growth factor delivery in the osseointegration area, the BMP is applied to the surface of the implant in the form of a polymer-containing gel or emulsion of a polyelectrolyte rate of approximately 200 micrograms per one product [14, 31, 65].

Recombinant FGF-2 which increases the number of functional osteoblasts successfully used in the clinic for the augmentation of the dental arch in patients with periodontitis [25]. It is contemplated to be a osteoregeneration stimulator when dental implants are installed, but is more effective against soft tissue contacting with the cervix of the implant [35].

Platelet-derived growth factor (PDGF-B) is a potent mitogen and chemotactic agent for a variety of mesenchymal cells, including osteoblasts, and therefore its isolated usage, as expected, will have a certain effect [17]. Recently, Chang et al. [7] have demonstrated for PDGF to be able stimulating osseointegration of dental implants *in vivo*. On the other hand, it has been reported that the isolated recombinant PDGF affects bone formation adversely [27]. The successful attempt to transfer gene *pdgfb* to bone marrow mesenchymal stem cells has been reported [10], but their osteoinductive effect was shown only in rats at volume replacement of bone defects with collagen-based scaffolds.

In clinics the use of platelet-rich plasma or platelet-fibrin clot may be an equivalent of pure PDGF usage. This material comprises a mixture of biologically active substances include growth factors, and the PDGF prevails therein. This method is gaining popularity due to safety and the possibility of using autologous source of growth factors ex tempore, and it shows good results in a number of clinical studies [20, 28].

The presence of multiple growth factors involved in bone formation, has pushed developers to attempts to use them as combinations with complementary effects. Successful combinations are given in Table 1.

2. Usage of biologically active peptides

Proteins of extracellular bone matrix are logical candidates for molecular transplantation. Currently, functional coatings made with the inclusion of fibronectin, laminin and vitronectin were fabricated [1, 12]. Thus, metal processing with fibronectin stimulating osteoblasts differentiation and tissue mineralization, contributed to strong osseointegration of implants in experimental models in vivo [48].

Recently, the focus has shifted to the usage of functional domains consisting of only a few amino acids of the necessary protein because it does not require control of the bioactive group

spatial accessibility. Arg-Gly-Asp (RGD), the adhesive domain derived from fibronectin and laminin, is the most successful example of biologically active peptide [36, 52]. Other sequences, such as Tyr-Ile-Gly-Ser-Arg (YIGSR), or Arg-Glu-Asp-Val (REDV), can also accelerate osseointegration. Some modifications with covalent peptides binding with coating before the anode deposition are the most stable [5, 52].

It is known the attempt to include in the coating one of the bisphosphonates (alendronate), which was able to block fibrogenesis in favor of bone formation. This effect was confirmed at the culture of mesenchymal stem cells seeded onto titanium with a functional coating [19]. Also using cell cultures L. Russo et al. [50] showed anchor proteins, which were necessary to start a full osseointegration, to increase adhesion after raising the number of free amino groups on the implant surface by reacting HA carbonate with (3-aminopropyl)-trietoksylane.

Some osteoinductive biopolymers, in particular chitosan, are also treated as the substrate coating. The material has adequate wettability and bioresorption degree. It is capable of inducing osteogenesis on osteoblast culture [46]. The experiment shows the positive effect of chitosan surface modification of titanium implants. When titanium implants with bioactive porous surface and additional fine chitosan coating were installed, the bone formation round them accelerated and become more intensive in conjunction with morphological markers of strong remodeling and sealing the surrounding bone [42].

Common problems associated with the use of growth factors and biologically active peptides can be reduced to implants cost increase, complications with the usage and preservation of the bioactive material before implantation, and with the insufficiently developed questions of kinetics and topography of their releasing in tissues around the implant, due to combined application, in particular - [23, 52]. Apparently, to date, this approach has not yet been able to compete with varying materials and relief of implants.

3. Antibacterial coating

There are several ways to functionalize the coatings that can be used to significant improvement the durability and osseointegration of the implant in the body. One of them is to enhance antibacterial properties, since infection is the second most common cause of implant failure [53, 60].

In this role, silver ions are the most studied and close to implementation) [9, 13]. Particles of gold, copper, zinc, SeO_3^-, strontium, cerium, gallium, and a number of more exotic rare earth metals are also could be potential agents. A number of their potentially useful features are summarized in a review [26], but it is unlikely that they have near-term clinical applications because of significant rise the coatings costs.

On the basis of the concept of the surfaces antibacterial properties, K.V. Holmberg et al. [18] developed coating with GL13K peptide inclusion. Such peptide had been derived from the soluble protein fraction of the parotid gland. As a coating it showed a high bacteriostatic activity against *Porphyromonas gingivalis,* which is the main microorganism associated with peri-implant pathology. While all the required properties of the implant surface were providing: high hydrophobicity (1), mechanical and thermal stability (2), resistance to enzymatic degradation (3), and high osteoinductive effect (4). The coating was recommended for clinical trials.

In a clinical study H. Tsuchiya et al. [59] used commercial dental implants with original iodine-containing coating in 158 patients with a high risk of postoperative infection. During the year complications occurred in 3 of 158 cases in main group, and in all 64 cases of implantation without the iodine-containing coating usage.

Although most of the work supports the idea that the functionalization of the implant surface can improve and accelerate its osseointegration, the key to the commercial success of this approach (besides the absolute clench the matter of cost) is to adapt the proposed methods to the surfaces of the specific dental alloys and to conserve controlled surface properties over the time between the manufacturing and implantation.

Conclusion

The surface functionalization by dynamically related ligands, possessing adhesive, modulating cell phenotype and/or antibacterial properties, at least at the level of the preclinical and first clinical trial, demonstrates the ability to improve the dental implants osseointegration.

Apparently, controlled surface nanoscale modification of two-dimensional (nanopatterns) and one-dimensional nature (nano-pores and nano-columns) is promising approach. The key issue, given the almost infinite possibilities of variation, is to reveal patterns of correlation between the composition, surface' fine-texture and the expected biomechanical properties of the implant, the overall dynamics of osseointegration.

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Молекулярные технологии функционализации поверхности дентальных имплантатов

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Аннотация. Настоящий обзор рассматривает несколько подходов к улучшению свойств дентальных имплантатов за счет модификации их биоактивной поверхности (функционализации) с помощью технологий молекулярной трансплантации. Первая группа функциональных лигандов призвана усилить остеоинтеграцию имплантатов, и представлена факторами роста, способствующими образованию и ремоделированию костной ткани: костными морфогенетическими белками (BMPs), тромбоцитарным фактором роста (PDGF), фактором роста фибробластов (FGF), а также их комбинациями между собой и с рядом других факторов роста. Вторая группа биоактивных молекул напрямую не стимулирует образование костной ткани, но за счет стимуляции адгезии, способствует укоренению остеобластов на поверхности имплантата, тем самым уменьшая сроки наступления остеоинтеграции. Наконец, третья группа веществ используется для

увеличения антибактериальных свойств покрытий, способствует уменьшению образования бактериальных пленок на поверхности имплантата, снижает риск развития его воспалительного отторжения. Ключевые проблемы использования биофункциональных покрытий, несмотря на их явную перспективность, на сегодня по-прежнему состоят в относительной дороговизне, трудности контролирования свойств и их сохранения в период между изготовлением и установкой имплантатов в кость реципиента.

Ключевые слова: дентальная имплантация, функциональные покрытия, биоактивная поверхность, клеточная адгезия, остеоинтеграция, тромбоцитарный фактор роста, костные морфогенетические белки.