VU Research Portal

Biomimetic coating delivered BMP-2 for bone tissue regeneration

Teng, F.

2018

document version
Publisher's PDF, also known as Version of record

Dental implant treatment has been widely used for oral reconstruction in recent years thanks to the advent of osseointegration and advances in biomaterials. A prerequisite to predict long-term success for osseointegrated implants is a sufficient bone volume at recipient sites. Vertical alveolar bone loss in partially or totally edentulous patients presents a major challenge in the field of implant dentistry. Although autogenous bone is regarded as the gold standard in regenerative dentistry, its various limitations stimulate the search for alternatives. Engineered bone tissue using bone morphogenetic protein 2 (BMP-2) has been seen as a potential alternative for the conventional use of bone grafts. However, most current commercial products deliver BMP-2 in a burst release mode, which leads to a number of side effects.

In **Chapter 2**, we made a systematic literature review and meta-analysis to investigate the efficacy of rhBMP-2 in vertical bone augmentation using bone substitutes in preclinical experiments (animal studies). No statistically significant difference was found in the percentage of newly formed bone and residual materials between the groups with and without rhBMP-2. The tissue regeneration was significantly improved by the additional use of rhBMP-2. With the application of space-providing barriers, the augmented bone height was also significantly enhanced by using rhBMP-2. These results are limited by the small number of included studies and a high degree of heterogeneity. Consequently, there is not enough evidence to support the current application of rhBMP-2 for vertical bone augmentation in routine clinical work.

The key point for improving the efficacy of BMP-2 is to find an appropriate carrier which can give and maintain a sustained delivery of low doses of BMP-2 (in the microgram range). A biomimetic calcium phosphate (CaP) coating was developed in our previous study as a carrier of BMP-2. In **Chapter 3**, we functionalized the deproteinized bovine bone (DBB) block with this biomimetic CaP coating incorporating BMP-2, and evaluated the release kinetics of the incorporated BMP-2 in vitro. The results showed that BMP-2 was successfully incorporated onto and into the DBB blocks and a sustained delivery of BMP-2 from the DBB blocks was achieved with the mediation of osteoclasts.

After proving the in vitro slow-release characteristics of incorporated BMP-2, in **Chapter 4**, we investigated its potential in replacing autogenous bone in vertical bone

augmentation in vivo. DBB blocks with incorporated BMP-2 (inc.BMP-2), with superficially adsorbed BMP-2 (ad.BMP-2), or without any functionalization (negative control) are used in the one-stage onlay surgery and examined for their new bone formation. The results are compared to those from the autologous bone blocks (positive control). The inc.BMP-2 group and the positive control showed a similar efficacy for vertical bone augmentation. They both exhibited a significantly thicker and wider augmented bone area, better bone-to-implant contact, and more mineralized tissue than the negative control. Furthermore, the inc.BMP-2 group induced significantly more newly formed bone in the upper half of the volume of interest (VOI-U) than the negative control. Compared with the ad.BMP-2 group, the inc.BMP-2 group showed significantly more mineralized tissue, better bone-to-implant contact and better bone-to-graft contact. This indicates that the efficacy of BMP-2 was significantly enhanced by the biomimetic CaP coating as a carrier for the slow and sustained delivery of BMP-2. Combined with the fact that DBB block has a slow rate of degradation, we propose that DBB block with coating-delivered BMP-2 can act as an appropriate bone substitute for the vertical bone augmentation.

Another prerequisite for the successful ossteointegration is the favorable surface properties of the implant materials. Commercially pure titanium has been regarded as the gold standard for osseointegrated dental implants but its greyish color might shine through the thin peri-implant mucosa and affect the esthetical outcome. A zirconia implant has been proposed as an alternative for a titanium implant because of its toothlike color. The surface property of zirconia implants is important in peri-implant bone apposition in the same way as for titanium implants. In **Chapter 5**, we functionalized the zirconia implants with our biomimetic CaP coating with or without the incorporation of BMP-2 and investigated their histological behavior in vivo. We found that the application of the biomimetic CaP coating incorporating BMP-2 enhanced the peri-implant bone density significantly for zirconia implants. This indicates that our BMP-2 incorporated biomimetic CaP coating has a histologically positive influence on the osseointegration for zirconia implants.

While BMP-2 functionalized CaP coating enhances the osseointegration of the implants, the long-term success of dental implants is also affected by their integration

into the soft tissue. In order to enhance the attachment of the implant neck with its adjacent soft tissues, we developed a modification of the implant neck surface in **Chapter 6.** We used anodic oxidation (AO) to roughen the surfaces of implant necks and applied a layer of polydopamine (PD) on the roughened surfaces. In vitro investigations showed that the surfaces of anodized implant necks were overlaid with densely distributed pores of 2–7 μm in size with a roughness of $Ra = 1.3745 \pm 0.2016$ μm. PD was successfully deposited on the PD-modified surfaces. L929 fibroblasts developed pseudopods more quickly on the PD-modified surfaces than that on the surfaces of the control. The in vivo experiment showed a longer connective tissue seal for implants treated with AO (the AO group and AO + PD group), compared with those without (the PD group and control group). A more coronally located peri-implant soft-tissue attachment was also observed in the AO + PD group, compared with that in the control group. Therefore, the implant neck modified by anodic oxidation and polydopamin deposition can enhance the attachment of peri-implant connective tissue, inhibit epithelial downgrowth and facilitate the formation of the peri-implant soft-tissue seal, thus indicating a positive effect on maintaining its stability.

We conclude that when applied in a coating-delivered mode, bone morphogenetic protein 2 can enhance the vertical bone regeneration for one-stage onlay surgery as well as the peri-implant osteogenesis for zirconia implants. A new design of anodized implant neck with pholydopamin deposition can enhance the attachment of peri-implant connective tissue and facilitate the formation of the peri-implant soft-tissue seal.