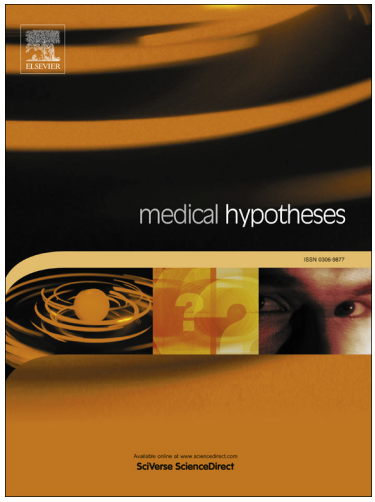

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Osteoclasts may contribute bone substitute materials remodeling and bone formation in bone augmentation

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Abstract

Bone augmentation is increasingly important in implantology. Bone substitute materials exert essential roles during bone augmentation process. However, accelerating bone substitute materials remodeling and acquiring high bone architecture quality was still the challenges of bone augmentation.

Accumulated studies had suggested osteoclasts is the key cell type to resorb bone or bone substitute materials. Our previous study and other studies suggested osteoclasts contributed to bone formation by promoting osteoblast function and facilitate angiogenesis. We hypothesized that bone substitute materials loaded osteoclastogenic cytokines or osteoclast

progenitors will help to bone substitute materials rapid remodeling and subsequent bone formation. Our hypothesis could help to lessen long-term post-bone augmentation period and acquire better bone quality for osseointegration.

Introduction

Bone augmentation is an important technique in implantology. The amount of bone and bone quality play essential role for osseointegration and implant stability. Considering the limitations of autografts and allografts[1, 2], the application of osteoinductive materials, especially calcium phosphate cement, provide a potent therapy strategy. However, bone substitute materials are very hard to be remodeled in vivo[3] and the bone formation is limited，since most osteoinductive materials due to vessels deficiency in the defect central area and capillaries deficiency lead to reduced oxygen and nutrition supply and continuous mesenchymal stem cells and osteoblasts progentiors recruit[4]. Meanwhile, about 6-12 month-time interval post-bone augmentation are needed to acquire better bone quality and bone architecture for increasing implant success[5]. Thus, accelerating osteoinductive materials remodeling and promoting bone formation of bone augmentation have drawn much attention in clinical implantist. Recent years, role of osteoclast in contributing to bone remodeling and bone formation have

been paid much attention[6].

Osteoclasts played important roles in bone remodeling

Osteoclasts are multinucleated giant cells that originate from hematopoietic stem cell and differentiate from macrophage cells under the influence of the cytokines macrophage colony stimulating factor (MCSF) and receptor activator of NF-kB ligand (RANKL)[7]. Osteoclasts degrade bone by the polarized secretion of proteolytic enzymes (e.g., cathepsin K, MMPs) and acid, which hydrolyze and solubilize the organic and inorganic components of bone, respectively[7, 8]. Proton and enzyme secretion is directed into the resorption lacunae which is partitioned from the rest of the bone microenvironment by a sealing zone of densely packed podosomes that surround the apical membrane of the osteoclast[9, 10]. During bone development and fracture healing, osteoclasts exert both indispensable roles in soft callus remodeling and hard callus remodeling[11]. Accumulated studies founded that RANKL inhibitor denosumab or mutations of osteoclastogenic-related genes (Cathepsin K, v-ATPase) result in osteoclasts deficiency and delayed fracture healing while enhancing osteoclastogenesis during fracture healing will accelerated fracture healing[12-14]. Recently，Arbez et al reported that osteoclast can resorb β-TCP material in vitro[15]. Furthermore， Choy et al reported that osteoclast resorbed β-TCP both in vitro and in vivo[16] and promoted

substitution of β-TCP ceramics by new bone[17, 18]. Consistently, Bighetti et al study also suggested osteoclast played important roles in calcium phosphate and subsequent bone formation[19]. Bone graft materials transplant's success needs well healing and remodeling with in situ bone, and osteoclast might exert powerful function during this process.

Osteoclasts contribute to the bone formation by regulating the osteoblasts differentiation and activity

Accumulated studies had proved that osteoblasts regulated osteoclasts formation and function. Recently, studies about the reciprocal impact of osteoclasts on osteoblasts showed that osteoclasts regulate osteoblasts though different mechanisms[20, 21]. During bone remodeling, many matrix-derived growth factors (TGF- β 1, IGF1) released from bone matrix by osteoclastic resorption induced osteoblastic differentiation of MSCs and bone formation, and were considered the important coupling mediators[22, 23]. Besides the resorption process, the cell-cell contact is believed the most important mechanism of osteoclast-mediated osteoblast differentiation and osteogenesis. Previous studies had proved osteoclasts can regulated the mineralization and behavior of osteoblast in the co-culture system and osteoclast deficiency will lead to disorganized collagen fibrils and matrix architecture, reduced bone mineralization and matrix deposition retention in vivo and in vitro[24]. What's more,

osteoclast-derived coupling factors recently have been identified and proved to promote osteogenesis and osteoblast differentiation in vitro assays. CTHCR1 (Collagen triple repeat containing1), sphingosine-1-phosphate (S1P), complement factor 3a (C3a), Tartrate-resistant acid phosphatase (TRAcP) are believed the important osteoclast secreted factors that can promote osteoblast differentiation[25-28].

Osteoclasts exert essential functions in angiogenesis during bone formation

Previous studies have proved that angiogenesis was coupled with osteogenesis[29] and osteoclasts are important for bone angiogenesis[30]. Impaired osteoclastogenesis will lead to defect bone angiogenesis[31]. Many molecules are known to be released by osteoclasts and to have pivotal roles in endothelial cell activities which not only VEGF but also BMP7, which promotes endothelial cell survival, induce endothelial cell migration and tube formation[30, 32-37]. Inhibition of osteoclast formation and activity with OPG or bisphosphonate reduced angiogenesis and stimulation of osteoclast activity with PTHrP increased angiogenesis in the explants[38-40]. Thus, osteoclast might be a potent target for bone angiogenesis.

Thus, a certain percent of osteoclasts might contribute to calcium-phosphate ceramics resorption, new capillaries formation and

benefit for osteogenesis by promoting and osteoblast differentiation, organizing matrix deposition and regulating osteoblast behavior in the bone augmentation process.

Hypothesis

We hypotheses that osteoclasts been recruited or application at bone augmentation site will accelerate calcium-phosphate ceramics remodeled to new bone and promote bone formation.

1. Osteoclast or osteoclast progenitors have been shown played essential roles in bone or bone substitute materials remodeling[6, 19]. During remodeling, the bone substitute materials resorbed by osteoclasts not only provide enough space for new bone formation, osteoclasts will promote osteogenesis by cell contact-mediated mechanisms or secreting cytokines to recruit MSC or osteoblast[20]. Previous studies had shown osteoclast secret or release multitudinous cytokines during bone remodeling, such as TGF-β 1, CTHCR1, TRAcP, S1P, HGF, and so on[20, 41, 42]. TGF-β 1 was released during osteoclast resorption, and induces the migration of MSC or osteoblast to bone surfaces for subsequent bone formation[43]. Our previous study suggested that osteoclasts inhibition will decrease TGF-β 1 and lead to bone remodeling suppression and impaired bone healing[44, 45]. What's more, the peptide-modifications or improved structure of bone substitute materials to accelerate bone resorption process promoted

new bone regeneration[17, 18]. Our previous study had shown osteoclasts inhibition delayed fracture healing by impaired bone remodeling[46]. These studies suggested that osteoclasts induced bone substitute materials remodeling might be a potent factor and process for bone formation during bone augmentation.

2. Osteoclast promote bone formation by regulate angiogenesis. Accumulated studies have reported angiogenesis couples osteogenesis[47]. During remodeling, osteoclasts secret BMPs, PDGF-BB and release VEGF from bone matrix to promotes endothelial cell survival, induce endothelial cell migration and angiogenesis[30, 35, 37, 48]. Increased angiogenesis not only persistently recruits osteoblasts or osteogenic progenitors to the bone augmentation site for bone formation, the O_2, nutrients and multiple growth factors carried by angiogenesis also facilitate bone formation[47, 49, 50]. Osteoclasts deficiency suppressed angiogenesis and osteogenesis while osteoclast induced angiogenesis promote bone formation[40, 48]. Thus, osteoclasts might contribute to bone formation by induce angiogenesis.

Significance of the hypothesis

In conclusion, this hypothesis is actually a supplement to the guide bone regeneration (GBR) for bone augmentation. Tardive remodeling and bone formation of bone substitution materials prolonged

pre-implant period and affect patient's life quality. To accelerate bone substitution materials remodeling and subsequent bone formation, we hypothesis that bone substitution material-loaded osteoclastogenic cytokines or pre-osteoclasts, or low-level-laser-treatment (LLLT) application on the bone augmentation site to enrich and active osteoclasts during remodeling could accelerate remodeling and promote osteogenesis. This hypothesis might be useful to advance new medical approaches for lessening long-term post-bone augmentation period and acquire better bone quality for osseointegration. Further studies deserved to prove our hypothesis.

Conflicts of interest statement

The authors indicate no potential conflicts of interest.

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