Research progress on the angiogenic-osteogenic coupling signaling molecules of bone tissue engineering

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Abstract: Angiogenesis and osteogenesis are integral to the process of bone growth, development, and repair and reconstruction. The close spatial and temporal association between osteogenesis and angiogenesis is known as "angiogenesis-osteogenesis coupling". Vascular invasion is a prerequisite for bone formation, and their mutual coupling is a key factor in bone formation. Vessels not only provide nutrients, transport oxygen, growth factors and metabolic wastes to bone tissue, but also regulate the various stages of angiogenesis and bone formation through vascular endothelial growth factor and angiopoietin. With the extensive research on tissue engineering in recent years, the role of signaling molecules related to angiogenesis-osteogenesis coupling in bone tissue engineering has been broadened. In this paper, we intend to review the relevant research results in order to provide ideas for tissue engineering bone vascularization.

Keywords: growth factors; angiogenesis; osteogenesis; bone tissue engineering

1. Introduction

Bone tissue is a vascular-rich tissue, and the oxygen and various nutrients needed by bone tissue cells come from the vascular system, which provides a transport channel for metabolites [1-2]. A clinically rich vascular system ensures the nutritional supply of the transplanted bone mass and improves its survival rate [3]. Recent studies have shown [4] that bone formation and vascular formation have a synergistic effect. The role of the vascular system in bone formation is twofold: on the one hand, the rapid perfusion of the vascular system provides the supply of oxygen and nutrients to bone tissue, and on the other hand, it coordinates the secretion of signaling factors by bone progenitor cells to promote bone growth. Thus, bone repair under physiological conditions is a rapid, coordinated and efficient process involving a tight coupling of osteogenesis and angiogenesis. Bone regeneration is accompanied by the orderly generation of blood vessels in space and time [5], and therefore, the promotion of osteogenic-angiogenic coupling is crucial for the healing of bone defects. Extensive research has been conducted on tissue-engineered bone vascularization, with studies focusing on vascularization factors, biomaterials, cells, and surgical adjuncts. With the development of biomaterials technology, growth factors can be combined with tissue-engineered bone scaffold materials to promote vascularization of tissue-engineered bone through slow-release effects. Growth factors used in supraphysiological doses when applied locally or systemically inevitably bring side effects. Insufficient vascularization of biological scaffold materials after implantation has become a huge bottleneck in current bone tissue engineering research. How to ensure rapid vascularization of scaffold materials after transplantation into the body and establish a vascular network to provide sufficient nutrients for subsequent new bone production is an urgent problem. Angiogenesis activity is dependent on the balance between many stimulating and inhibiting factors. The key aspects of angiogenesis are migration, proliferation and aggregation of endothelial cells. Angiogenesis is a complex, dynamic and multi-stage process involving multiple cells and cytokines [6]. This article will review the recent research results related to angiogenic-osteogenic coupling-related signaling molecules that can promote angiogenesis in bone tissue engineering.

2. Angiogenic-osteogenic coupling signaling molecules

Signal molecules are mainly used to transmit information between and within cells, such as

hormones, neurotransmitters, growth factors, Micro RNA, etc. Collectively, their only function is to bind to cellular receptors and transmit cellular information.

2.1 Vascular endothelial growth factor

The vascular endothelial growth factor (VEGF) family consists of VEGF-A, B, C, D, E and placental growth factor (PLGF). VEGF, as one of the most important growth factors regulating angiogenesis and postnatal angiogenesis [7-8], can promote bone growth and development by acting directly or indirectly on osteoblasts, which in turn can secrete VEGF and other factors to regulate angiogenesis in turn, and is essential for the mechanism of angiogenic-osteogenic coupling. Modern studies have shown that the bone repair process can be influenced by VEGF levels, and blocking VEGF receptors VEGFR1 and VEGFR2 with neutralizing antibodies reduces angiogenesis and bone regeneration [9], while administration of exogenous VEGF promotes the formation of mineralized bone within bone defects. However, the addition of exogenous VEGF may not stimulate bone regeneration when endogenous VEGF levels are normal, and the addition of excessive VEGF may even inhibit osteoblast function. Hu et al [10] found that osteoblast production of appropriate levels of VEGF has a key role in angiogenesis and osteogenesis coupling in small bone defect experiments in mice, and delivered recombinant VEGF to the defect site to demonstrate that The effect of extracellular VEGF is dose-dependent, with high levels of VEGF inhibiting infiltration of regenerative cells and osteoinduction of mesenchymal progenitor cells in the case of small bone defects and leading to reduced bone formation, thus demonstrating that the requirement for VEGF depends on the size of the bone defect. In order to control the dose and spatial distribution of VEGF, Burger et al [11] found that the uniform dose of VEGF delivered to the graft material is crucial for the success of transplantation, and that uniform distribution of matrix-associated factors in the microenvironment enables effective coupling of angiogenesis and bone formation, and found that non-uniformly distributed VEGF in human bone marrow MSCs failed to expand at 1-4 weeks and largely disappeared at 8. It was found that non-homogeneously distributed VEGF failed to expand at 1-4 weeks and largely disappeared at 8 weeks, while homogeneously distributed VEGF had no negative impact. To address the short half-life of VEGF, Poldervaart et al [12] introduced gelatin granular scaffold material to make it release VEGF continuously and slowly, prolonging VEGF activity and increasing scaffold vascularization. Rapid vascularization of critical bone defects for tissue-engineered bone implantation is one of the current challenges in tissue-engineered bone, and Largo et al [13] demonstrated that exogenous VEGF accelerates early blood perfusion and tissue growth in critical bone defect grafts.Schumacher et al [14] found that bioactive glass nanoparticles decorated with peptides that bind biologically active VEGF165 ensuring the high efficiency and specificity of VEGF, which stimulates angiogenesis with a smaller dose of VEGF compared to exogenous VEGF, providing an idea for the lack of neovascularization in critical bone defect tissues.

2.2 Platelet-derived growth factor

Platelet-derived growth factor (PDGF) [15] is a serum growth factor that is mainly synthesized by megakaryocytes, stored in platelets and released into the blood upon external stimulation, and has the ability to promote the proliferation and angiogenesis of fibroblasts, smooth muscle cells and glial cells. PDGF-BB can also stimulate osteogenic differentiation of bone progenitor cells or mesenchymal stem cells (MSCs) to promote bone regeneration. PDGF consists of two polypeptide chains, A and B, linked by disulfide bonds to form a dimer, including PDGF-A, PDGF-B, PDGF-C and PDGF-D. In addition to the four homodimers of PDGF, there are also Gao et al [16] found that monocytes differentiated into anti-periosteal tartrate acid phosphatase-positive monocytes and released PDGF-BB to induce transcription and expression of periostin and recruit periosteal cells to the periosteal surface, and to promote H-type angiogenesis and osteoblast differentiation. Lee et al [17] found that transfection of platelet-derived growth factor (PDGF)-transfected human adipose-derived stem cells (hADSC) were complexed to biomineral assembled into spheroids, and PDGF enhanced not only osteogenic differentiation but also endothelial differentiation of hADSCs. Stem cell spheroids combining PDGF and biominerals resulted in increased bone regeneration and neovascularization.Wu et al [18] found that polydopamine nanoparticles (PDA-PEGNPs) synthetically modified by methoxypolyethylene glycolamine (mPEG-NH2) inhibited osteoclast-associated angiogenesis by downregulating platelet-derived growth factor-BB (PDGF-BB); In vivo, PDA-PEGNPs inhibited subchondral bone resorption and angiogenesis.Li et al [19] showed that a specific bone vascular subtype of H-type endothelial cells (EC) surrounded by platelet-derived growth factor receptor β (PDGFRβ) perivascular cells (PVC), after radiation H-type EC and PDGFRβ PVC between HIF-1α / PDGF-BB / Cao et al [20]

found that PDGF-BB could mediate MSC self-renewal and maintain its osteogenic potency through steroid-activated PDGFR/Akt/GSK3β/CERB signaling. And PDGF-BB also stabilizes newly formed vessels by recruiting MSCs to improve intraosseous vascular integration.Gao et al [21] showed that a potential mechanism for bisphosphonate-associated osteonecrosis of the jaw is inhibition of PDGF-BB secretion to inhibit angiogenesis and osteogenesis during the early stages of bone healing. Topical PDGF-BB treatment after debridement may promote healing of bisphosphonate-associated osteonecrosis of the jaw by increasing angiogenesis and osteogenesis.

2.3 Transforming growth factor-β

Transforming growth factor-β (TGF-β), TGF-β regulates the growth and differentiation of a variety of cells and is involved in bone development and angiogenesis through various signaling pathways. Kang et al [22] found that loss of SERPINF1, which encodes pigment epithelium-derived factor (PEDF), delayed osteoblast maturation and extracellular matrix (ECM) mineralization, and that PEDF attenuated TGF-β-induced pro-angiogenic factor expression, controlling osteogenesis and bone angiogenesis through functional antagonism between the PEDF and TGF-β pathways. Tang et al [23] demonstrated that mononuclear macrophages (MKs) deficiency significantly reduced bone formation, that MKs promote osteoblast proliferation and differentiation, and that they promote blood vessel formation through secretion of high levels of TGF-β1 by CD31 and Emcn, and that MKs promote bone formation by coupling osteogenesis to angiogenesis through secretion of TGF-β1. Elimelech et al [24] found that inoculation of MSCs transfected with the TGF-β gene onto β-tricalcium phosphate promoted bone defect repair in rat skull, with significantly higher vascular density and scaffold degradation in the TGF-β group, and increased bone formation.

2.4 Angiopoietin

Angiopoietin (Ang) is a secreted pro-angiogenic factor expressed in osteoblasts, osteoclasts and some bone marrow interstitial cells, which is involved in vascular growth and development, remodeling; it plays a key role in regulating and maintaining vascular growth and maturation; the Ang family is composed of two receptors Tie-1, Tie-2 and four ligands Ang1, Ang2, Ang3, and Ang4; Tie-1 is an orphan receptor does not bind to Ang, Tie-2 is an Ang receptor, Ang1 is an agonist of Tie-2 receptor, and Ang2 antagonizes Ang1 and Tie-2 [25].Ang2 weak agonist/antagonist is environment-dependent, and Ang2 can also act as an agonist to bind to Tie2 [26].Shen et al [27] found that inhibition of vascular endothelial-tyrosine phosphatase (VE-PTP) gave Ang2 agonist properties. sanchez et al [28] found that Ang-1 induction of angiogenesis presupposes downregulation of six miRNAs (miR-103b, miR-330-5p, miR-557, miR-575, miR-1287 -Jeong et al [29] demonstrated that the chimeric form of Ang1, cartilage oligomeric matrix protein (COMP)-Ang1, is a potent stimulator of BMP2-induced osteoblast differentiation and bone formation, synergistically enhancing BMP2 expression and promoting osteoblast differentiation proliferation and angiogenesis.Suzuki et al [30]found that Ang1 overexpression can lead to increased bone mass in vivo, and Ang1 expression in osteoblasts induces angiogenesis and osteogenesis in a coupled manner. Wang Zhen et al [31] found that Ang-1 gene transfection of BMSCs with composite PLGA/HA scaffolds promoted the repair of radial bone defects in rabbits and promoted new bone formation and angiogenesis. Liu Xudong et al [32] demonstrated that inoculation of Ang-1 gene-transfected BMSCs onto β-tricalcium phosphate compounded with platelet-rich plasma promoted the repair of segmental bone defects in rabbit radius, and neovascularization could be formed in tissue-engineered bone to promote bone healing.

2.5 Fibroblast growth factor

FGF is a potent mitogenic and pro-vascular regenerative factor, which can promote the proliferation and differentiation of various cells including mesenchymal cells and preosteoblasts, stimulate the migration and proliferation of capillary endothelial cells, and promote the expression and release of bone morphogenetic proteins, vascular endothelial growth factor and other osteogenic factors. The FGFs can stimulate the migration and proliferation of capillary endothelial cells, promote the expression and release of osteogenic factors such as bone morphogenetic protein and vascular endothelial growth factor, and thus exert osteogenic effects. Human and mouse FGFs include 22 ligand members and 4 FGFRs receptors (Fgfrs) [33], and phylogenetic analysis has shown that they can be divided into 7 subfamilies.Kuttappan et al [34] found no difference in induced angiogenesis and bone formation between these two growth factors by loading VEGF + BMP2 or FGF2 + BMP2 composite fiber scaffolds and transplanting them into extreme bone defects. FGF2 mainly promoted stem cell

migration, while VEGF enhanced neointima formation at the defect site. Yang et al [35] demonstrated that FGF-21 treatment upregulated the expression of HGF, PI3K and AKT in BMSCs, and knockdown of HGF eliminated the PI3K/AKT signaling pathway reduced by FGF-21, and FGF-21 promoted bone defect repair. lai et al [36] found that gelatin-coated magnesium-doped calcium silicate (MgCS) scaffolds with FGF-2 showed a trend towards better bone healing.

2.6 MicroRNA

There are a large number of noncoding RNAs (nc RNAs) that do not encode proteins in cells. Micro RNAs (miRNAs) are nc RNAs of approximately 22 nt in length that have been discovered in recent years. miRNAs are regulated mainly by binding to the 3'untranslated region (3'-UTR) of target gene mRNA through base complementation after transcription [37], degrading the target gene mRNA or inhibiting mRNA translation, and exerting post-transcriptional gene expression regulation. 'Untranslated region, 3'-UTR), which degrades the target mRNA or inhibits mRNA translation to play a post-transcriptional role in gene expression regulation. Since bases 2-8 of miRNAs are often not fully complementary to the 3'-UTR sequence of target gene mRNAs, their effects are mainly achieved through mechanisms such as inhibition of translation initiation and elongation of target gene mRNA proteins, degradation of co-translated proteins, and early suspension of translation [38]. Recent studies have reported some, microRNAs involvement in angiogenesis [39] and osteogenesis [40]. It has also been shown that overexpression of miR-137 alkaline phosphatase (ALP) activity is elevated [41] and blocking endogenous miR-137 increases the growth and migration of human umbilical vein endothelial cells (HUVECs) [42]. Yang et al [43] demonstrated that overexpression of MiR-100-5p can inhibit hBMSCs by targeting BMPR2 and inhibiting the BMPR2/SMAD1/5/ 9 signaling pathway to inhibit osteogenesis in hBMSC and angiogenesis in HUVEC. Zhang et al [44] demonstrated that miRNA-378 is an ideal target for osteogenic-angiogenic coupling in bone regeneration. Nan et al [45] showed that miR-378-ASCs-Exos enhances osteogenesis and angiogenesis by targeting the Sufu upregulation Shh signaling pathway. NOTCH2 is a miR-205 target gene, and knockdown of NOTCH2 inhibited angiogenesis and inhibition of miR-205 enhanced osteogenesis and remodeling in vivo [46].

3. Conclusions

In summary, osteogenic-osteogenic coupled growth signaling molecules used in bone tissue engineering promote vascularization of tissue-engineered bone. The osteogenic-osteogenic coupling factor composite scaffold implanted in extreme bone defects can improve the problem of insufficient early vascularization and increase the graft success rate, and the osteogenic-osteogenic coupling growth factor composite in tissue-engineered bone has significant efficacy in the treatment of bone defects and has a good application prospect in bone tissue engineering.

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