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Vascularization in the Bone Repair

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1. Introduction

The repair of critical-size bone defects resulted from severe traumatic injury, infection, surgery for bone cancer or congenital malformation remains a continuous challenge for orthopedists. Currently, autogenous bone grafting is a clinical gold standard for bone repair, and provides excellent osteoconduction, osteoinduction, high-healing rate and absence of immunogenic reaction after surgery. However, autogenous bone grafts are associated with the morbidity of donors, additional surgical procedures for harvest, and limitations in the quantity and available bone size. Bone tissue engineering has become a new and promising alternative approach for the repair of bone defects. Moreover, the clinical application of these advanced technologies in the field of tissue engineering seldom leads to satisfactory results. Increasing evidences have demonstrated that the key factor for the poor repair with tissue-engineered bone is poor vascularization (Nakasa et al. 2005; Kawamura et al. 2006). Bone is a highly vascularized tissue that relies on the supply of essential nutrients and oxygen from blood vessels for maintaining skeletal integrity (Kanczler and Oreffo 2008). Under the circumstance of a well-developed vascular network, the osteoblasts can produce osteoid tissues, differentiate to osteocytes, and form healthy bone. In order to provide sufficient oxygen for survival, osteoblasts must reside within 150-200 mm of a capillary lumen and no cells are greater than 0.2 mm from a blood vessel (Kannan et al. 2005). Without the perfusion of blood supply, the osteoblasts in the middle of tissue-engineered constructs will be necrosis due to ineffective transportation of oxygen, nutrients and metabolites (Smith et al. 2004; Rouwkema et al. 2008). Insufficient vascularization can often restrain the formation of new bones and delay the healing of bones. Therefore, vascularization plays a key role in bone regeneration. The rate and range of vascular growth are the determinants of the efficiency and consequence of new bone formation.

2. The role of angiogenesis in bone development

Besides providing nutrients and removing waste products, intraosseous vasculature also can accomplish other important functions including bone development and remodeling. Bone formation and development occurs through two distinct processes: intramembraneous and endochondral ossification. The vascularization is the prerequisite of two different processes of ossification (Clarkin et al. 2008). In intramembranous bone formation, mesenchymal stem cells (MSCs) can be transported through capillaries and differentiate

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directly into mature osteoblasts. These osteoblasts then deposit bone matrix and lead to bone formation. On the other hand, during the endochondral ossification, the chondrocytes secret angiogenic growth factors promoting the invasion of blood vessels, which then bring along a number of highly specialized cells and replace the cartilage mold with bone and bone marrow (Chung et al. 2004). Vasculature also plays a key role in bone formation by the production of growth factors that control the recruitment, proliferation, differentiation and function of various cells including osteoblasts and osteoclasts. These growth factors are secreted by endothelial cells (ECs) (Red-Horse et al. 2007).

During the bone remodeling, the osteoblasts play an important role in the balance of resorption and bone deposition by secreting osteoprotegerin that is an inhibitor of osteoclast activity. However, the mature osteocytes lose the capability to produce this molecule (Marx et al. 2007). Blood vessels transport osteoprogenitor cells for the deposition of new bones (Barou et al. 2002). The invading vasculature, thus, serves as both a reservoir and a conduit for the recruitment of essential cells involved in bone remodeling, and provides critical signals necessary for bone morphogenesis (Brandi et al. 2006).

3. Interaction between osteoblasts and endothelial cells

The intercellular signaling between vessel-forming cells and bone-forming cells plays a critical role in bone integrity. The cell-to-cell communication is crucial to coordinate cell behavior, which is necessary for the development and remodeling of bones (Rivron et al. 2008). Several models have been established for studying cellular interactions between osteoblasts (OBs) and ECs in two-dimensional culture dishes (Guillotin et al. 2008 and Grellier et al. 2009), three-dimensional (3D) scaffolds (Choong et al. 2006 and Unger et al. 2007), or 3D spheroids (Wenger et al. 2004 and Stahl et al. 2005). The OBs and ECs can communicate through a couple of mechanisms such as indirect cell contact (Guillotin et al. 2004) through the secretion of diffusible factors with paracrine and autocrine action, and gap junction communication mediating direct cytoplasmic connections between adjacent cells (Villars et al. 2002).

Many diffusible factors released from ECs and OBs that affect the growth and differentiation of both cell types has been identified. Some diffusible factors secreted by ECs include platelet-derived growth factor AB (PDGF-AB), transforming growth factor β_1 (TGF-β_1), transforming growth factor β_2 (TGF-β_2), fibroblast growth factors-2 (FGF-2), epidermal growth factor (EGF), osteoprotegerin (OPG), and bone morphogenetic protein 2 (BMP-2) (Bouletreau et al. 2002), which can affect the migration and proliferation of OBs and the differentiation of osteoprogenitor cells. In contrast, vascular endothelial growth factor (VEGF) secreted by OBs can promote the proliferation of ECs, and stimulate the differentiation and angiogenesis through the activation of specific receptors (Clarkin et al. 2008 and Clarkin et al 2008).

Gap junction is another mechanism for direct cell-to-cell communications. Some special membrane domains composed of aqueous intracellular channels provide direct cytoplasmic connections between cells, and allow for the passage of ions or small molecules between adjacent cells, thus ECs and OBs can communicate and exchange information (Dbouk et al. 2009). Several predominant gap junction proteins including Cx43, Cx37 and Cx40 have been identified to express in ECs and OBs (Yeh et al. 2006). Similarly, the communication via Cx43 gap junctions can promote the expression of osteoblastic differentiation markers such as alkaline phosphatase (ALP), osteocalcin (OC) and bone sialoprotein in OBs (Guillotin et al. 2008).

4. Strategies for improving vascularization

Several strategies for improving vascularization have been proposed. These strategies include the modification of scaffold design, the delivery of angiogenic factors, cell-based techniques, and microsurgery strategies (Rouwkema et al. 2008; Phelps et al. 2010).

4.1 Modification of scaffold design

Biomaterial scaffold, a key component in the bone tissue engineering, serves as a template for cell interactions and the formation of extracellular matrix in bones. The scaffolds should match certain criteria including biocompatibility, biodegradability and mechanical properties similar to the bone repair site. However, the scaffold itself should also be engineered to promote rapid and effective vascularization, and the architecture and design of a scaffold is the key factor for controlling the rate of vascularization after implantation. Currently, the effect of pore size and interpore distance on the scaffolds during the growth of endothelial cells has been evaluated (Narayan and Venkatraman 2008). The growth of endothelial cells can be improved by a smaller pore size (5-20 μm) and lower interpore distance. However, the growth of blood vessels is more extensive in scaffolds with larger pore size (> 250 μm) than those with smaller pore size (Druecke et al. 2004). Other *in vivo* studies have also confirmed that a higher porosity and pore size can result in extensive osteogenesis and sufficient vascularization (Bonfield, 2006), which can be explained by the fact that large pores facilitate vascular ingrowth and osteoblastic cell migration into the scaffold and promote the vascularization and osteogenesis. Porosity also plays an important role in the vascularization of scaffolds. The high porosity allows for the maximum space of vascularization, osteoblast migration and bone deposition (Karageorgiou and Kaplan 2005). In addition, high porosity has a beneficial effect on the diffusion of nutrients and oxygen, transportation and vascularization (Park et al. 2009). The scaffold for bone tissue engineering must possess interconnecting open pores for the maximum potential of vascularization; otherwise, it will be inhibited (Karageorgiou and Kaplan 2005). The interconnected pores facilitate cell migration and vascularization (Jovanovic et al. 2010). This strategy for promoting vascularization still relies on the vessel ingrowth from the host. Limited benefits can be achieved due to the single use. Therefore, it is strongly recommended to combine the scaffold design with other strategies.

4.2 Delivery of angiogenic factors

It is well understood that the local and controlled release of growth factors from a tissue-engineered scaffold can effectively enhance the vascularization of engineered tissues (De Laporte et al. 2010; Zhu et al. 2008). Many angiogenic factors such as vascular endothelial growth factor (VEGF) (des Rieux et al. 2011; Anderson et al. 2011), fibroblast growth factor (FGF) (Kim et al. 2010; Zhu et al. 2008), TGF-β (Lee et al. 2006) and angiopoietin 1 (Ang1) (Chiu and Radisic 2010) have been used for promoting the vascularization of scaffolds. VEGF has gained considerable attention due to its central role in physiology and neovascularization of endothelial cells. The VEGF diffused from the scaffolds or released as the scaffold degrades can stimulate local vessels to sprout towards the implanted tissue-engineered constructs. Current reports have demonstrated that the controlled release of FGF-1 from alginate microbeads can result in an increase of initial vessel invasion into the collagen scaffolds and a longer persistence of vascular network formation (Moya et al. 2010; Uriel et al. 2006). However, the dosage must be tightly controlled because excessive amounts

of VEGF and FGF can cause high permeability and poor long-term stability (Ozawa et al. 2004; Zisch et al. 2003). Growth factors including TGF-β and Ang1 for the stabilization of new vessels are also important because subsequent stabilization of newly-formed vessels is critical for the generation of functional vascular networks within tissue-engineered constructs. TGF-β can stimulate the mobilization and recruitment of endothelial cells, and thus accelerating vascularization. Ang 1 plays a key role in regulating vessel homeostasis and stabilization of newly-generated capillaries (Fiedler et al. 2006; Zisch et al. 2003). The neovascularization requires the temporal and spatial expression of multiple angiogenic growth factors, which stimulates different stages of blood-vessel formation to enhance the vascularization of tissue-engineered bones. More and more researchers are investigating the delivery of two sets of factors to mimics under *in vivo* conditions (Tengood et al. 2010; Sun et al. 2011). The combinatorial application of angiogenic factors for stimulating new blood-vessel formation and maturation is highly necessary for the optimal vascularization of tissue-engineered constructs.

4.3 Cell-based techniques

Regardless of the approach adopted to improve vascularization, all of these strategies include endothelia cells. Previous studies have shown that the addition of endothelial cells to tissue cultures can result in the formation of vascular structures *in vitro* and can anastomose to the vessels of the host after implantation (Tremblay et al. 2005; Levenberg et al. 2005). Another approach to accelerate the vascularization of tissue-engineered graft is the co-culture with endothelial cells based on the principle that the transplanted ECs will interact with host ECs and vasculature to establish faster blood supply. The sources of ECs used in the promotion of vascularization in bone tissue engineering included mature ECs, endothelial progenitor cells (EPCs) and MSCs-derived ECs.

Mature ECs can be isolated from a wide variety of sources such as umbilical cords, kidney vasculars, fat tissues and saphenous veins. Previous studies have revealed the 3D pre-vascular network formation when the human umbilical vein endothelia cells are co-cultured with human mesenchymal stem cells in a spheroid co-culture model. After implantation, the pre-vascular network can be developed further and the structures containing lumen can be observed regularly (Rouwkema et al. 2006). The co-culture of rat bone marrow MSCs with kidney vascular ECs on 3D scaffolds exhibits a pre-vascular network-like structure after *in vivo* implantation and results in the increased amount and size of new bone formation when compared with the control group (Sun et al. 2007). These results suggest that mature ECs can efficiently enhance the vascularization of the tissue-engineered grafts. However, the low availability and proliferation capability will severely restrict its large-scale applications (Kim and Von Recum, 2008).

An alternative source of ECs to promote vascularization in tissue engineering is endothelial progenitor cells. The EPCs are enriched in bone marrow, peripheral blood and umbilical cord blood. EPCs have greater proliferation capability than mature ECs (Lin et al. 2000) and can differentiate into ECs *in vitro*, thus contributing to the formation of vascular networks (Rafii and Lyden 2003). Physical and biochemical interactions between EPCs derived from bone marrow and MSCs in a co-culture system *in vitro*. These studies suggest the co-culture of EPCs derived from bone marrow and MSCs can induce endothelial phenotype and angiogenesis without the addition of exogenous growth factors (Aguirre et al. 2010). The co-culture of MSCs and peripheral blood EPCs in Matrigel with 2-3 mm of biphasic calcium

phosphate particles for the analysis of bone formation at 6 weeks after implantation in nude mice has demonstrated that co-implantation of EPCs isolated from peripheral blood can significantly enhance osteogenic differentiation *in vitro* and support bone formation *in vivo* (Fedorovich et al. 2010). The influence of EPCs combined with mesenchymal stem cells on early vascularization and bone healing in critical-size defect *in vivo* has also been evaluated to reveal an improvement of early vascularization in the combinatorial group of EPCs and MSCs. Meanwhile, more bony bridges also can be observed in the combinatorial group between EPCs and MSCs at 8 weeks after implantation. These studies suggest that the combinatorial delivery of MSCs and EPCs can support early vascularization and accelerate bone healing.

Similarly, previous studies have been proved that MSCs can be induced to differentiate into ECs and these ECs have more proliferation potential than the terminally-differentiated ECs (Oswald et al. 2004). The MSCs-derived ECS should be ideal for pre-vascularized bone tissue engineering and the pre-vascularized bone tissue engineering construct can be prepared by a single, easily accessible, bone marrow biopsy. ECs and osteogenic cells derived from bone marrow have been seeded in an apatite-coated poly(lactide-co-glycolide)/hydroxyapatite composite scaffolds and then transplanted into critical-size calvarial defects in mmunodeficient mice (Kim et al. 2010). The bone regeneration reveals a significant enhancement due to the addition of ECs derived from bone marrow. Critical-size ulnar defects in the rabbits have also been repaired through vascularized tissue-engineered bone (Zhou et al. 2010). The vascularized tissue-engineered bone is constructed with MSCs and MSC-derived ECs and then co-cultured in porous β-tricalcium phosphate ceramic. The rabbits treated with vascularized tissue-engineered bone exhibit more extensive osteogenesis and better vascularization. Therefore, the ECs derived from bone marrow can be used as a source for pre-vascularized bone tissue engineering with multiple advantages. First, bone marrow aspiration is less invasive. Second, the use of autologous bone marrow cell grafts can avoid immune rejection.

4.4 Microsurgery strategies

Another promising approach for enhancing vascularization in tissue engineering is the hybrid strategy coupled with microsurgery approaches with bone tissue-engineered constructs such as flap fabrication and arteriovenous (AV) loop (Kneser et al. 2006). The vascularization of tissue-engineered grafts basically consists of a two-stage surgical procedure. In the first stage, the scaffolds loaded with cells and/or growth factors are implanted into a site of rich vascularization, usually a muscle or the forearm. Then the capillaries are grown into the scaffold to form a microvascular network in the engineered graft at the initial implantation site after several weeks (Kneser et al. 2006). In the second stage, the tissue-engineered construct with microvascular network is harvested and then re-implanted at the defect site. The microvascular network in the tissue-engineered grafts will anastomose with the host vessels and result in instantaneous perfusion of the entire construct (Kneser et al. 2006). For example, the studies have been conducted the in situ implantation of prefabricated tissue-engineered bone flaps and recombinant human bone morphogenetic protein-2 (rhBMP-2) to accomplish the mandible reconstruction (Zhou et al. 2010). The AV-loop model provides a new approach for the fabrication of axially vascularized tissue so that the vascularization of tissue-engineered grafts can be emanated from internal vascular pedicle independent of local conditions. This AV-loop approach has

applied to induce axial vascularization in a bovine cancellous bone matrix (Beier et al. 2011). The micro-CT scans and histomorphometry have showed a significant increase of axial vascularization in bovine cancellous bone matrix constructs, and immunohistochemistry has confirmed the endothelial linking of newly-formed vessels. Similarly, a vascularized tissue-engineered bone graft composed of implanted MSCs and a vascular bundle into the xenogeneic deproteinized cancellous bone (XDCB) scaffold has also constructed (Zhao et al. 2011). The histological and biomechanical examinations have showed that the combination of MSCs and a vascular bundle implantation can result in the promotion of vascularization and osteogenesis in the XDCB graft, and the improvement of new bone formation and mechanical properties during the repair of radius defects. These studies suggest that the vascular bundle implantation is a promising strategy for promoting vascularization in the tissue-engineered grafts.

5. Conclusion and future directions

Insufficient vascularization remains one of the major problems in bone tissue engineering. The critical factor for the limitation of clinical application of tissue-engineered bone is poor vascularization. Multiple approaches such as scaffold design, angiogenic factor delivery, cell-based technique and microsurgery strategy have been explored to promote the vascularization in the field of tissue engineering. These approaches may generate capillary-like structures within the tissue-engineered graft, however, the best method for successful application *in vivo* is still uncertain because there is no convincing evidence. Therefore, the integration of several strategies for enhancing the repair of bone defects is highly desired in the future.

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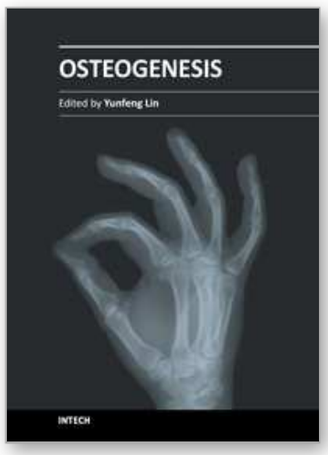
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This book provides an in-depth overview of current knowledge about Osteogenesis, including molecular mechanisms, transcriptional regulators, scaffolds, cell biology, mechanical stimuli, vascularization and osteogenesis related diseases. Hopefully, the publication of this book will help researchers in this field to decide where to focus their future efforts, and provide an overview for surgeons and clinicians who wish to be directed in the developments related to this fascinating subject.

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