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MICRORNAS' CONTRIBUTION TO AUGMENTED ANGIOGENESIS IN BONE REGENERATION

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Abstract

In the field of bone tissue engineering, ensuring adequate blood supply post-transplantation is critical for successful outcomes. Recent advances in microRNAs (miRNAs) provide new opportunities for improving bone regeneration by precisely regulating target genes and promoting angiogenesis. miRNAs, known for their sequence conservation, temporal expression patterns, and tissue specificity, play a pivotal role in angiogenic processes. Addressing the challenge of insufficient blood supply is essential to bridge the gap between laboratory research and clinical application in bone tissue engineering. This article explores the potential of miRNAs as a tool to enhance angiogenesis in bone regeneration therapy.

1. Introduction

Over the past three decades, the field of bone tissue engineering has made important advances in the development of new materials and methods to enable cell-based therapies in orthopedics [1]. However, bone tissue engineering after transplantation often results in inflammation and poor survival environment due to inadequate blood supply in the early stages affecting the final treatment outcome. The emergence of microRNAs (miRNAs) has opened new avenues for gene therapy modalities for bone regeneration, which can inhibit post-transcriptional messenger RNA (mRNA) translation or promote mRNA degradation through precise regulation of target genes and negative feedback mechanisms.[2] Most of these miRNAs are highly sequence conserved, time-sensitive in expression and tissue specific [3]. miRNAs can act on angiogenic factors associated with angiogenesis to promote the majority of these miRNAs are highly conserved in sequence, expressed in a time-series and tissue-specific manner. It was found that the successful transition of bone tissue engineering bone from the laboratory to the clinic can only be achieved if the problem of insufficient blood supply formation is addressed at the root.

2. Overview of angiogenesis

Angiogenesis is the process of forming new blood vessels from existing vessels and involves cell proliferation, narrow migration, differentiation, tube formation and regulation of angiogenic factors [4]. Seed cells are the most fundamental aspect of tissue engineering [5]. Mesenchymal stem cells, vascular endothelial cells and endothelial progenitor cells are the most promising seed cells for tissue engineering vascularization gene therapy, which not only have good vascular induction, but also facilitate the introduction of a variety of viral and non-viral vectors and the expression of genes targeted for vascularization. Vascularization target genes, such as vascular endothelial growth factor, angiopoietin 1, basic fibroblast growth factor, bone morphogenetic protein 2, and hypoxia-inducible factor 1α, are mainly used to construct an efficient and stable vascular network inside the engineered grafts through double/multiple gene association, osteogenic and angiogenic coupling and upstream gene regulation.

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Vascular endothelial growth factor (VEGF) is an endothelial cell-specific mitogen and chemokine, which is an important factor for promoting neovascularization and promoting neovascularization [6]. VEGF, as the most precise factor with pro-angiogenic ability, has been widely and intensively studied by researchers in the last three decades [7]. The VEGF family is the most crucial factor in the process of angiogenesis, and studies have found that its main role is in the formation of blood vessels However, a large number of experiments have confirmed that VEGF alone forms naive and immature blood vessels.

Bone marrow mesenchymal stem cells (BMSCs), the most popular seed cells in the field of tissue engineering because of their multidirectional differentiation ability, wide source and low technical sensitivity, have the potential to differentiate into vascular endothelial cells. PDGF-BB plays a huge role in vascular neogenesis and stabilization of neovascularization, promoting peritubular motility by stimulating the production of collagen fibers from cells in a quiescent state [9].

3. The importance of angiogenesis in bone tissue engineering

Vascularization is essential for bone growth, development, healing and remodeling and is therefore a prerequisite for bone tissue engineering. In bone tissue engineering reliance on vascularization solely through the growth of neighboring angiogenic cells is very slow. Studies have shown that a distance of 200μm from the vasculature is critical for cell survival, and in order to obtain vascularized bone structures with full function, the field of bone tissue engineering includes two main strategies: first, prevascularization of the construct, which can significantly reduce the time required for implant vascularization compared to methods that rely on scaffold design and angiogenic factor-controlled release; second, in bone forming cell culture Introduction of angiogenic cells to improve angiogenesis and thus promote bone formation in cell-based constructs[10]. In addition, impaired vascularization or altered interactions between the vascular system and osteoblasts can disrupt bone growth and may lead to a variety of clinical manifestations. Establishing a functional vascular system is a key bottleneck in the clinical translation of tissue engineering strategies, including bone tissue engineering[11]. Therefore, further standardized protocols and innovative measures are needed to overcome these shortcomings and to facilitate the clinical application of techniques to enhance bone regeneration[12] .

Biomaterial scaffolds in bone tissue engineering serve as templates for the establishment of vascular systems and the growth of osteogenic precursor cells. The early vascular network established after scaffold material implantation is able to provide adequate nutrition and transport metabolic substances [13-14], if the local vascular network formation is slow resulting in lack of blood supply, it will lead to delayed osteogenesis or even failure to form new bone. Modification of scaffold materials by changing their physicochemical properties, loading growth factor retardation systems or simulating periosteal structures can facilitate early angiogenesis during the induction of bone regeneration and facilitate the whole bone regeneration process [15].

4. Characteristics and biological functions of miRNAs

miRNAs are a class of small non-coding RNAs consisting of 21-25 nucleotides, synthesized in the cytoplasm, released outside the cell as ribosomal protein complexes, lipid vesicles, exosomes, etc. They are not digested by ribonucleases (RNases) and are stable in some body fluids[16], by binding to the 3'-untranslated region (3'UTR) of specific target mRNAs, they regulate gene expression at the post-transcriptional level regulates gene expression, leads to decreased protein expression by blocking translation, and promotes degradation of mRNA targets[17]. miRNAs are closely associated with the survival of bone marrow mesenchymal stem cells and angiogenesis [18-19]. In recent years, several scientific studies have demonstrated that miRNAs are important regulators of cell growth, differentiation and apoptosis. Each miRNA has been shown to have hundreds of target mRNAs, and a complex regulatory network between miRNAs and target mRNAs is involved in a wide variety of regulatory pathways, including development, viral defense, hematopoietic processes, organ formation, cell proliferation and apoptosis, and lipid metabolism, etc., with important roles in the regulation of gene expression[20].

5. Role of miRNA in angiogenesis

The importance of miRNAs in the regulation of angiogenesis and arteriogenesis has been recognized in the last decade. The fact that DICER (microRNA processing enzyme) knockout mice die during embryogenesis due to vascular malformations emphasizes this phenomenon[21]. Furthermore, adaptive neovascularization during

ischemia is associated with multiple growth factors, such as VEGF, fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), each of which has its own unique effect on vascular development. Regulation of a single growth factor after ischemia does not yield any significant clinical benefit[22-23]. miRNAs are abundant in the vascular system, play an important regulatory role in the vascularization of stem cells toward differentiation, and may be important mediators of vascular system disease[24] microRNAs can regulate the expression and stability of multiple proteins, so altering a single microRNA has the potential to activate multiple growth factors simultaneously mediated signaling pathways[25].

In addition to acting on VEGF to regulate angiogenesis in various diseases, miRNAs can also act on other angiogenic factors associated with angiogenesis to promote or inhibit angiogenesis.

5.1 Pro-angiogenic miRNAs

Past strategies based on the presentation of vascular endothelial growth factor or micro-RNA (miR-26a) [26], combining calcium phosphate cement with osteoconductive properties with gel scaffolds loaded with vascular endothelial growth factor, were found to provide a combination of angiogenic and osteogenic effects [27].

Zuo Xinhui et al. [28] Different expression levels of relevant osteogenic and angiogenic genes were identified by overexpression versus underexpression of hypoxia-inducible factors in BMSCs. Li Jun et al.[29] delivered miRNA-378a to SD rat bone marrow stem cells (BoneMarrowMesenchymalStemCells (BMSCs) by lentiviral transfection in an in vitro experiment for long-term stable expression. The results showed that miRNA-378a was successfully delivered to the cells without significant morphological changes in BMSCs, which provided an experimental basis for the application of miRNA-378a in tissue-engineered bone stabilization at a later stage. It was also found that osteogenesis-related genes were significantly up-regulated in BMSCs, and ALP and collagen secretion were increased. MiRNA-378a was suggested to be a more ideal target for coupling bone regeneration and angiogenesis, which could induce both osteogenesis and angiogenesis through Wnt signaling pathway and mitogen-activated protein kinase (MAPK) signaling pathway, while the polarization of macrophage M2 phenotype promoted bone defect repair.

Bo et al.[30] found that BMSCs modified with miRNA-378a have more pronounced osteogenic and angiogenic coupling and have validated miRNA-378a at the cellular level as a potential tool for bone regeneration gene therapy. Recent studies have identified microRNA-378a as a positive regulator of osteogenesis and angiogenesis, promoting osteogenic-angiogenic coupling in BMSCs for potential bone regeneration.

GENG et al. [32] loaded miR-21 nanocapsules onto acid-treated titanium surface and inoculated MSCs on the treated titanium surface. miR-21 nanocapsule-treated titanium surface more significantly promoted MSC osteogenesis and angiogenesis, in addition to enhancing MSC osteolytic activity, compared to unloaded miR-21 nanocapsules. miR-29a can regulate angiogenesis [33], LU et al. [34] found that bone marrow MSC-derived exosomes can be taken up by human umbilical vein endothelial cells and promote human umbilical vein endothelial cell proliferation, migration and tube formation. MiR-29a is highly expressed in bone marrow MSC exosomes and can regulate angiogenesis through VASH1-dependent translocation to human umbilical vein endothelial cells. More importantly, bone marrow MSC-derived exosomes carrying miR- 29a have a strong ability to promote angiogenesis and osteogenesis in mice.

5.2 miRNAs that inhibit angiogenesis

Studies have shown that miR-195 inhibits bone marrow MSC survival and angiogenesis. Previously, miR-195 has been found to reduce the resistance of bone marrow MSCs to ischemic injury by downregulating the expression of anti-apoptotic genes[35]. Another study showed that miR-195 expression was increased in aged MSCs, and that it accelerated the senescence and inhibited the regenerative capacity of MSCs by inactivating telomerase reverse transcriptase [36], whereas downregulation of miR-195 expression reversed the senescence of MSCs. The same study found that knockdown of miR-195 in aged bone marrow MSCs after transplantation could more significantly reduce myocardial infarct size and improve cardiac function[35]. On the other hand, miR-195 has been shown to be an important inhibitor of angiogenesis by targeting downregulation of pro-angiogenic gene expression and thus inhibiting angiogenesis[37-38]. It has been reported that miR-195 can impair the survival and angiogenesis of bone marrow mesenchymal stem cells by directly inhibiting vascular endothelial growth factor[37-38]. In this study, the authors found that the survival and pro-angiogenic capacity of bone marrow MSCs were

significantly increased after hypoxic pretreatment, and that hypoxic pretreatment with mimics transfected with upregulated miR-195 resulted in a decrease in the proliferation rate, an increase in apoptosis, and a significant decrease in the number of vascular lumen-like structures. qRT-PCR showed that the mRNA levels of miR-195 in the hypoxic group were higher than those in the normoxic group. 195 mRNA levels in the hypoxic group showed a significant decrease compared with the normoxic group. The above indicates that miR-195 expression was inhibited after hypoxic pretreatment, which had a certain effect on the survival and pro-angiogenic ability of bone marrow MSCs[39].

6. Conclusions

In summary, rapid early vasculogenesis is crucial for subsequent osteogenic differentiation during bone tissue regeneration. The establishment of a vascular network to provide adequate nutrition for subsequent new bone production is an urgent issue to be addressed.

Going forward, understanding the mechanisms of miRNAs in angiogenesis will help explore the process of angiogenesis and may contribute to the development of miRNA-based therapies to enhance vascular defenses and slow the progression of clinically relevant diseases associated with angiogenesis.

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