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Research Progress on Mechanism and Application of Zinc in Osteogenesis

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Abstract: *As the second most abundant trace metal element in the human body, zinc plays an important role in bone homeostasis and bone disease treatment. Adequate amounts of zinc not only mediates osteogenesis-related pathways through zinc dependent enzymes and zinc finger proteins to induce the differentiation of mesenchymal stem cells into osteoblasts and promote osteogenesis, but also inhibits osteoclast resorption activity, reducing bone resorption and thus promoting osteogenesis. In recent years, the importance of zinc in bone development, regeneration and homeostasis has been gradually discovered. The mechanism and application of zinc's osteogenic effect have been extensively studied. The aim of this paper is to summarize the research on zinc osteogenic mechanism and review its application research in bone tissue engineering in recent years.*

Keywords: *zinc, osteogenic effect, osteoblasts, bone tissue engineering*

1. Introduction

Zinc is element number 30 in the periodic table and is often found widely in nature in the form of divalent ions. At the same time, zinc is also one of the 14 essential trace elements in the human body, distributed in various tissues and organs throughout the body, and is the most widely metabolized element in the human body[1]. Zinc is involved in a large number of cellular processes [2], and deficiency of zinc can affect cell growth, division and differentiation, It is closely related to growth and development, immune function , skin and nervous system diseases [3] . In recent years, domestic and foreign scholars have conducted in-depth studies on the role of zinc in osteogenesis, and it has been found that zinc can promote osteogenesis of osteoblasts by stimulating cell proliferation, alkaline phosphatase activity, collagen synthesis and protein synthesis [4- 7], Its enhanced expression of osteoblast marker genes has also been demonstrated [2]. Zinc has been used in clinical studies for the construction of tissue-engineered scaffold materials and the treatment of bone metabolic diseases and bone tumors. In this paper, we review the research progress on the osteogenic effect of zinc and its related applications.

2. Osteogenic effect and mechanism of zinc

Zinc, as one of the essential trace elements in the human body, is involved in a large number of cellular processes and plays a crucial role in the proliferation and differentiation of osteoblasts and new bone formation. Zinc not only preserves bone mass by promoting osteogenesis, but also inhibits osteoclastic bone resorption. Combined with its role in the immune system, it has very promising applications in bone regeneration research[8].

2.1 Promotion of osteoblast proliferation and differentiation by zinc

Zinc is an important regulator of bone formation, involved in the regulation of osteoblast proliferation, differentiation and apoptosis, thereby maintaining a constant number of cells in vivo. Zinc is thought to promote osteogenesis in osteoblasts by stimulating cell proliferation, alkaline phosphatase activity, collagen synthesis, and protein synthesis [9].

Zinc is a cofactor of alkaline phosphatase (ALP), collagenase, DNA polymerase and other bone metabolism-related enzymes and participates in bone metabolism as a component of bone matrix; it is also an important cofactor of zinc finger that are widespread in the body at the same time. The primary

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function of ALP in bone metabolism is to participate in the synthesis of bone calcium phosphate and provide mineral molecules for bone mineralization. Zinc has been shown to enhance osteoblast adsorption and ALP activity in bone to promote osteoblast expression and to promote preosteoblast differentiation and mineralization. The presence of zinc is necessary to maintain ALP activity and function. Zinc deficiency leads to decreased alkaline phosphatase activity in osteoblasts and triggered down-regulation of extracellular matrix mineralization. A study by Westhauser [10] et al showed that 5Zn-MBGNs exhibited good cytocompatibility due to sustained release of zinc, while genes encoding extracellular matrix-associated members were up-regulated in late culture [11-12] . Therefore, studies assessing later stages of osteogenic differentiation may be able to reveal the osteogenic effect of zinc in this regard in more detail. In Suzuki [13] et al analysis of the expression and activity of ALP related proteins in zinc-deficient osteocytes revealed that ALP gene expression was not significantly different between zinc-deficient cells and normal cells interphalangeal, but ALP activity was significantly reduced, and its degree was positively correlated with zinc deficiency. In the relationship between ALP and zinc in mammalian cells, ALP activity was also found to be related to zinc concentration, and the enzyme activity increases with increasing zinc concentration within a certain range [14].

Zinc finger are structures formed by short fragments of peptides that play an important role in gene regulation, while proteins containing such structures are called zinc finger proteins (ZFP) [15]. Zinc is the key to the regulation of zinc finger proteins, which regulates gene expression by specifically binding activator proteins to enhancer sequences through zinc finger, and zinc finger proteins do not form stable fold structures in zinc deficiency [16]. Currently, there are two main zinc finger proteins found in vertebrates, vitamin D receptor (VDR) and Osterix [15]. The relationship between zinc and VDR is mainly reflected in that some studies found [17] When 1 mol VDR binds to 2 mol zinc ion, the DNA-binding region (VDR DBD) in VDR binds best to the DNA sequence; while when zinc ion decreases, the VDR DBD does not bind to DNA. Osterix is an essential transcription factor and the most direct osteoblast transcription factor in the process of bone formation. It can regulate the expression of functional proteins such as osteopontin, type I collagen, bone sialoprotein and osteocalcin, synthesize matrix, undergo mineralization reaction, and achieve bone formation.

2.2 Effect of Zinc on Osteoclast Resorptive Activity

Since it was discovered that zinc is an essential nutrient for normal osteogenesis, a succession of studies have been conducted to provide additional evidence on the need for zinc for osteogenesis in various ways. For example, decreased volume of trabeculae was found in bone formation of zinc deficient animals and was characterized by retarded growth plate movement. A low zinc diet is associated with defects in hypertrophic chondrocyte proliferation, with biophysical consequences and also including reduced longitudinal and radial expansion of long bones, increasing fracture sensitivity. Specific inhibition of osteoclast-mediated bone resorption in vitro and promotion of osteogenesis by zinc provide important evidence for their role in bone tissue accumulation and maintenance. When zinc is sufficient, the osteoclast phenotype is characterized by decreased resorptive activity and increased TRAP expression. Kevin [18] et al. found that femoral osteoclast resorption potential decreased with increasing zinc content in the diet within a certain range, as evidenced by a decrease in matrix metalloproteinase (MMP2 and MMP9) and carbonic anhydrase-2 activities, by separately feeding 30 male weanling rats randomly divided into six groups with different zinc contents. This study suggests that up-regulation of extracellular matrix mimicry index and decrease of osteoclast resorptive activity provide physiological evidence of a relevant role for zinc in regulating the balance between bone formation and resorption when dietary zinc content increases from 2.5 to 30 μ g/g.

2.3 Immunomodulatory effects of Zinc in Osteogenesis

The principle of osseointegration has long been known as direct contact between bone and biomaterial without any fibrous capsule. This criterion is clinically feasible, but it needs to be recognized that there are differences between in vitro culture and in vivo biological responses. These differences are thought to be caused by the complexity of environmental conditions in vivo, one reason being immune regulation in vivo. It is well-known that the immune system is also involved in the process of osteogenesis and osteoclastogenesis. Abnormalities in immune cell function often create an imbalance between bone and osteoclasts [19]. In recent years, it has been gradually realized that several cytokines, receptors, signaling molecules and transcription factors in the immune system play an important role in bone regeneration. Immune cells such as macrophages and T cells actively participate in osteoclastic and osteogenic processes by regulating the release of immune cells and osteocyte-binding molecules. Insufficient

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macrophage activation may lead to failure of bone regeneration. Therefore, consideration of immune cells is necessary when evaluating osteogenic induction ability.

Interactions between cells, signaling pathways, cytokines, and extracellular matrix are considered critical factors in determining the prognosis of bone healing. Macrophages (Mϕs) and BMSCs are important parts of functional cells in bone healing. By source, macrophages are divided into two parts, resident macrophages from the embryonic yolk sac and macrophages from the hematopoietic lineage of the bone marrow [20]. Macrophages possess the ability to clear cellular debris to maintain a stable microenvironment by activating the appropriate inflammatory cascade [21, 22]. It has been shown that macrophages differentiate into two phenotypes, pro-inflammatory and anti-inflammatory [23, 24] , both as inflammatory cells to remove necrotic components and as functional cells to promote tissue regeneration in specific microenvironments. Zinc is considered a promising bone immunomodulator that acts on macrophage polarization and regulates osteoblast differentiation. Zhang [19] et al. prepared micron or nanostructured titanium dioxide with a zinc oxide coating and observed the osteogenic activity of osteoblast-like cells SAOS-2 in conditioned cultures in combination with the inflammatory response of macrophages on the coating to evaluate the in vitro osteogenic ability of this zinc oxide coating. The results showed that the expression of osteoblast differentiation markers was enhanced in conditioned cultures and that titanium dioxide as well as zinc oxide coating modulated the polarization of macrophages to M1 and M2 phenotypes and enhanced osteogenesis compared to the control group.

3. Application and research progress of zinc in bone tissue engineering

According to the important role of zinc in osteogenesis, researchers have found considerable research and development potential by further exploring its effect on promoting osteoblast proliferation, inhibiting osteoclast activity, antibacterial effect in a certain concentration range, and effects on the immune system. It is embodied in zinc-doped biomimetic membrane, zinc-containing coating, zinc-containing bone tissue engineering scaffold and the use of zinc regulation in the treatment of bone metabolism and bone tumor-related diseases.

3.1 Application of Zinc Containing Films

Zinc-doped films are often used to guide bone regeneration (GBR). Zinc-containing membranes not only have good biocompatibility, but also promote angiogenesis, osteogenic activity, and also act as local bacteriostatic agents to achieve healing effects. Zinc-doped membranes differ in their minimum inhibitory concentrations for different bacteria, and studies have demonstrated that different concentrations of zinc oxide have antibacterial effects on bacteria [25], but it should be noted that excessive concentrations of zinc can also produce cytotoxicity.

Guo [26] et al. designed different types of pure zinc membranes according to pore size and tested the effect of membranes on the viability of MC3T3-E1 cells using non-porous pure titanium membranes as controls, and established a rat calvarial bone defect model to evaluate the in vivo behavior of three pure zinc membranes, and the results showed that pure zinc membranes with pore size of 300 μm had the best osteogenic potential and were comparable to non-porous titanium membranes. Toledano[27] et al. separately incorporated zinc or doxycycline into a novel nanostructured silicon dioxide-loaded membrane to fabricate bone defects on the New Zealand rabbit skull, which was then covered with the membrane, and the nonmembrane sham defect area was used as the control, to quantify bone regeneration using histometry. After 6 weeks, histological analysis showed higher values of new bone area in the center of the defect area and under the membrane when membranes were present, and the results showed that zinc-doped nanostructured silica loaded membranes had direct osteoinductive effects with doxycycline-doped nanostructured silica loaded membranes.

3.2 Zinc-doped bone tissue engineering scaffolds

In the repair of bone defects, bone tissue engineering (BTE) is a promising direction of research and can compensate for many limitations of traditional bone grafting. And bone scaffolds made of various biomaterials are very important components in bone group engineering. Researchers have increasingly extensively and intensively investigated novel scaffolds with multiple functions that can be used as bone substitutes. Li [28] et al prepared a scaffold with porous properties and containing organic and inorganic components similar to natural bone tissue. The scaffold was mainly composed of three-dimensional graphene oxide foam, polydimethylsiloxane or zinc silicate (GF/PDMS/ZS) , which was verified by in

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vivo and in vitro experiments to not only have good biocompatibility, but also induce proliferation and directed osteogenic differentiation of mouse bone marrow mesenchymal stem cells (m BMSCs) without significant inflammatory response at the defect. The scaffold was also found to promote activation of key genes ALP, RUNX2, VEGFA and OPN. Qian [29] et al synthesized zinc-doped mesoporous silica using a one-pot hydrothermal method, whose nanoparticles had a uniform mesoporous structure and exhibited sustained release of zinc ions over a low concentration range, which not only reduced the potential toxicity of metal ions to cells, but also up-regulated the expression of m BMSC s osteogenesis-related genes and promoted osteogenic differentiation. Bone tissue engineering scaffolds are a large range, including the research and application of many materials, of which the two widely used are hydroxyapatite and bioactive glass. The following will focus on the application of two commonly used materials after zinc doping.

3.2.1 Zinc-doped hydroxyapatite

Hydroxyapatite (Hap) is a common bone repair material due to its good biocompatibility, non-toxicity, non-irritation and easy to bind to adjacent bone tissues, rarely causing rejection and inflammatory reactions. However, hydroxyapatite also has the disadvantages of unsatisfactory mechanical strength and low osteoinductive activity, so researchers often make up for its shortcomings by combining with other materials. Chopra [30] et al optimized a zinc-doped hydroxyapatite (HapZ) nanocomposite and confirmed its antibacterial activity, and showed osteoinductive potential by in vitro mineralization (alizarin red staining) and expression of osteogenic markers including alkaline phosphatase (ALP), short stature-related transcription factor - 2 (RUNX-2), type 1 collagen (COL1), bone morphogenetic protein-2 (BMP-2), osteocalcin (OCN), and osteopontin (OPN). Yu et al [31] investigated a zinc-doped mesoporous hydroxyapatite microsphere/collagen scaffold (zinc-MHMS/Coll) with a hollow mesoporous structure and uniform zinc distribution, which showed sustained release of zinc ions in the range of 100 – 300μm. The results showed that Zinc-MHMS/Coll scaffolds could promote osteogenic differentiation of rat MSCs. It demonstrated a role in promoting bone regeneration.

3.2.2 Zinc-doped bioactive glass

There are many other popular materials for bone repair besides hydroxyapatite, and bioactive glass is one of them. Sun et al [32] used zinc-containing mesoporous bioactive glass nanoparticles (Zn-MBGS), prepared by sol-gel method, with concentration-dependent osteogenic and anti-inflammatory activities, and found that 0.1 mg/mL Zn-MBGS extract not only promoted in vitro mineralization and osteogenic-related gene expression in rat bone marrow stromal cells (BMSCs), but also inhibited lipopolysaccharide- and interferon-γ-induced pro-inflammatory M1 polarization in RAW264.7 cells was also inhibited. Some investigators have added gelatin microspheres to bioactive glass to compensate for the high variability in B AG uptake rate and solubility, while zinc is incorporated to be responsible for biological activity and regenerative potential, while the protective gelatin layer better controls the release rate of ions and each structure complements each other. It was shown that this synthetic construct ZBGs had a positive effect on wound healing. It not only accelerates recovery from hemostasis and reduces local inflammation, but also stimulates anabolic activity of epithelial cells and osteoblastic lineage cells in soft and hard tissues [33]. Heras et al [34] designed a multifunctional scaffold loaded with levofloxacin (LEVO), vancomycin (VANCO) rifampicin (RIFAM), or gentamicin (Genta) at saturating inhibitory concentrations and minimum inhibitory concentrations before gelatin coating (BL-Ge) and after doping 4% zinc oxide (4ZN-Ge) using bioactive glass as a carrier, and performed inorganic ion and antibiotic release studies from the scaffold , Staphylococcus aureus and Escherichia coli were found to be the model strains for infection, and zinc ions released from the scaffold had good inhibitory effect and synergistic effect with antibiotics. The results showed that with the inclusion of zinc oxide inclusions in the scaffold, bacterial infection could be resisted at a low antibiotic dosage.

3.3 Role of zinc in the treatment of bone-related diseases

Most of the zinc in the human body is stored in bone and zinc plays an important role in bone homeostasis. Zinc is also an important cofactor for many proteins which are involved in microstructural stabilization and bone remodeling. Abnormal function of certain zinc transporters contributes to imbalances in bone homeostasis, which may be one of the causes of bone disease in humans. It has been shown that the content of bone zinc decreases as aging progresses particularly in postmenopausal women, which also demonstrates its role in bone disease. Clinical observations have demonstrated that supplementation of menopausal women with trace element zinc increases bone mineral density in both the calcium deficiency group and the group without calcium deficiency, and supplementation of zinc along with calcium supplementation is more effective than calcium supplementation alone in

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postmenopausal osteoporotic patients. Zinc deficiency affects the normal physiological function of the human body. Some studies have found that zinc in trace elements is closely related to the occurrence and development of various malignant tumors including gastrointestinal cancer, breast cancer, prostate cancer and osteosarcoma. Gao et al [35] found that zinc levels were significantly lower in blood and tumor tissues of osteosarcoma patients. Analysis of the experimental results suggests that zinc can inhibit the proliferation and invasion of osteosarcoma cells by inducing the Wnt/β-Catenin signaling pathway , promote apoptosis, and inhibit tumor growth. He et al [36] prepared zinc oxide nanoparticles with good dispersion, and RNA-Seqs analysis revealed that zinc ions released from zinc oxide nanoparticles induced down-regulation of HIF-1 catenin expression through β-1α/BNIP3/LC3B-mediated mitotic phagocytic pathway , confirming that zinc oxide nanoparticles degrade β-catenin through degradation, Inhibition of pulmonary metastasis of osteosarcoma in the HIF-1α/BNIP3/LC3B-mediated mitophagocytic pathway.

4. Conclusion

In summary, the importance of zinc in the process of bone regeneration is indelible. With more and more extensive research on zinc in promoting osteogenesis and bone-related diseases, researchers have become more and more deeply aware of the application of zinc in related biomaterials and its role in bone metabolism. It is believed that there will be more evidence in the future to determine the best treatment for zinc to promote bone regeneration, and through the mechanism of action of zinc and the application of further research, to explore better methods that can promote bone defect healing, inhibit bone tumor development, and maintain bone metabolism stability.

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