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Original Research Article

The concept of "osteoimmunomodulation" and its application in the development of "osteoimmune-smart" bone substitute materials

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ABSTRACT: The traditional biological principle for developing bone biomaterials is to directly stimulate the osteogenic differentiation of osteoblastic lineage cells, the direct effector cells for osteogenesis. This strategy has been successful for the development of bone biomaterials. However, recent progress in bone biology has revealed the vital role of the local bone microenvironment, especially the immune environment, in controlling osteogenesis. Interdisciplinary osteoim-munology has found that the osteoimmune and skeletal systems are closely related, sharing numerous cytokines and regulators. In addition, immune cells play an important role in the physiological and pathological processes of the skeletal system, suggesting that neglecting the importance of the immune response is a major shortcoming of the traditional strategy. Based on this principle, we propose a novel "osteoimmunomodulation"-based strategy to meet the strict requirements of new-generation bone biomaterials: instead of directly.

KEYWORDS: Bone regeneration; Osteogenic differentiation; Bone substitute materials; Immune microenvironment; Osteoimmunomodulation; Marcophage

Bone defects caused by bone tumors, trauma, congenital developmental defects, widespread periodontal disease, and alveolar bone resorption resulting from missing teeth are among the most common clinical conditions in orthopedic and dental clinics and have a very high incidence, seriously affecting patients' normal It has a high incidence and seriously affects the normal oral and skeletal functions of patients[1,2]. Due to the increasing environmental and food pollution, the incidence of tumors and congenital developmental defects is on the rise. With the accelerated aging of the population, there has been a dramatic increase in patients suffering from periodontal disease and the resorption of alveolar bone caused by missing teeth. Systemic diseases such as diabetes and osteoporosis have increased the incidence of fractures, reduced bone quality, and increased the difficulty of treatment for bone regenerative repair. Therefore, how to achieve bone regenerative repair has become a difficult and urgent clinical problem. The application of bone substitution materials for bone defect repair is a common treatment in clinical practice, and the development of bone substitution materials with efficient osteogenic efficacy is of great clinical significance. In this paper, we firstly review the development of bone replacement materials and analyze the concept of bone replacement materials at different stages of development and its shortcomings, and further combine our group's

recent research results on the interaction between bone replacement materials and bone immune system to propose the concept of bone replacement materials based on "bone immune microenvironment regulation" to guide the development of a new generation of bone replacement materials. The research group has proposed a concept of bone replacement materials based on "bone immune microenvironment regulation" to guide the development of a new generation of bone replacement materials based on "bone immune regulation intelligence" in order to improve the effect of bone defect regeneration and repair.

1 Evolution of bone substitute materials and their R&D concepts and shortcomings

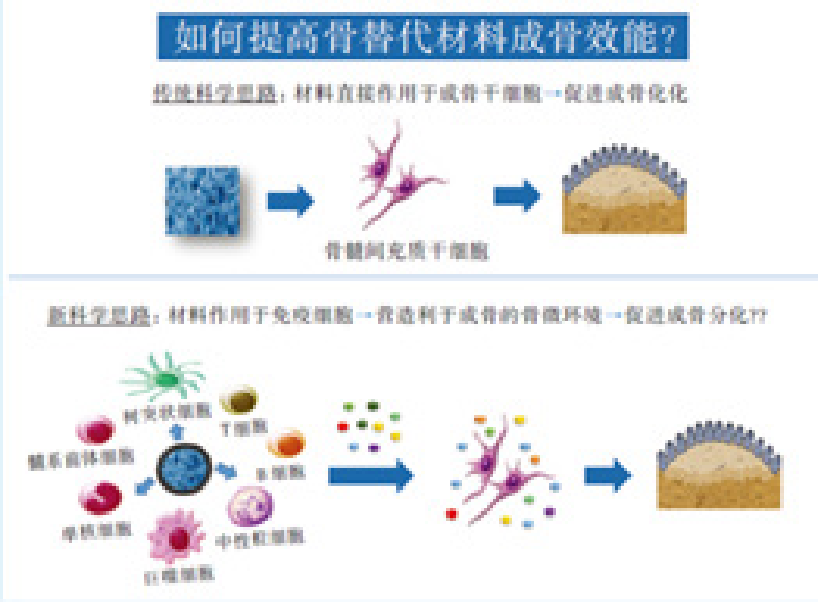
Autologous bone is the "gold standard" for craniomaxillofacial bone defect repair and has been used in clinical practice for nearly a century[3]. However, the limited amount of autologous bone grafting, donor area damage, post-graft resorption, short-term instability, and other problems have limited its clinical application[4–5]. Although the "extended" allograft bone graft solves some of the problems of autologous bone source limitation, its biological and mechanical properties are not good, and it has the risk of spreading diseases, and the clinical failure rate is high[6]. The inadequacy of traditional natural bone replacement materials has led to the development and use of various artificial bone replacement materials. metal materials (cobalt, silver, titanium, etc.) began to be used for bone defect repair in the late 19 th century; after the 20 th century, synthetic materials such as calcium apatite, ceramics, bioglass After the 20 th century, synthetic materials such as calcium apatite, ceramics, bioglass, and polymer compounds began to appear and were used as bone replacement materials in clinical practice, achieving certain bone defect repair results[7–9].

1.1 First generation bone substitute materials

Looking back at the development of bone replacement materials, the first generation of bone replacement materials focused on the direct filling of bone defect areas based on mechanical-physical-chemical principles, i.e., basically restoring the defect in shape, providing good mechanical support, and chemically similar to natural bone tissue. However, this research and development strategy treats bone replacement materials as mechanical restorations without "vitality", ignoring the fact that the repair of bone defects is a dynamic physiological process involving multiple cells and cytokines, and that the physiological response process of the interaction between the material and the body after implantation has a key impact on bone tissue regeneration[10–11]. The development of the first generation of bone replacement materials ignored the physiological nature of the bone tissue repair process, and it was difficult to achieve the clinical demand for bone defect repair.

1.2 Second-generation bone substitute materials

The idea of the development of second-generation bone replacement materials starts from osteoblasts, which are directly related to bone formation, and promotes osteogenic differentiation and bone regeneration and repair by applying bone replacement materials directly to osteogenic stem cells. However, in vivo osteogenic differentiation is accomplished in a local bone microenvironment created by the synergy of cells from multiple systems, including the skeletal system, immune system, and circulatory system. The implantation of bone replacement materials inevitably alters the entire bone microenvironment. It is the new bone microenvironment formed by the interaction of the bone replacement material with the cells of multiple systems that truly regulates osteogenic differentiation, rather than the material acting alone to accomplish it. By ignoring the importance of other systemic cells and their formation of the microenvironment, the bone replacement material developed will likely produce an inappropriate modulation of the microenvironment, leading to the creation of an unfavorable bone regeneration microenvironment and failed in vivo osteogenesis.



How to improve the osteogenic efficacy of bone substitute materials?

Traditional scientific thinking: direct action of materials on osteogenic stem cells → promotes osteogenesis

Bone marrow mesenchymal stem cells

New scientific idea: materials act on immune cells → create an osteogenic bone microenvironment → promote osteogenic differentiation?

Dendritic cells

T cells

B Cells

Macrophages

Mononuclear cells

Myeloid precursor cells

Neutrophils

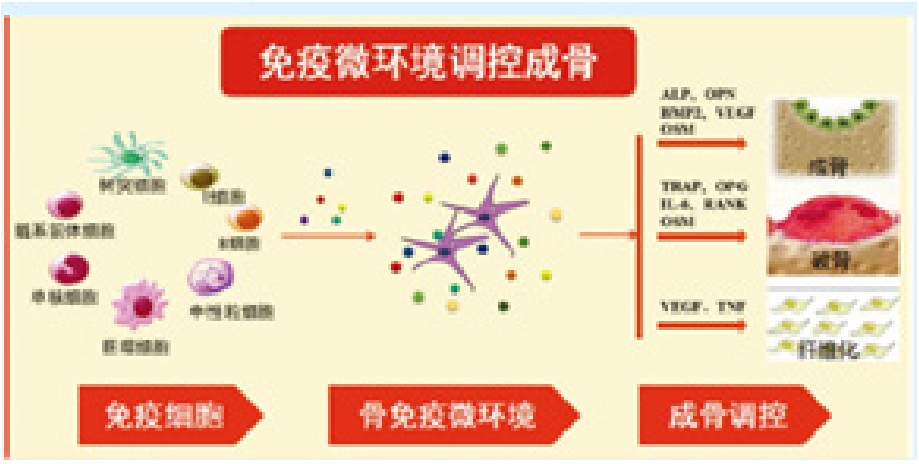
Figure 1 Strategy for developing bone substitute biomaterials

1.3 Third-generation bone replacement material development concept

Therefore, our group proposes the idea of developing the third generation of bone replacement materials (**Figure 1**): to improve the osteogenic efficacy of bone replacement materials, in addition to the direct effect of the materials on the osteogenic differentiation of "stem cells", we should pay more attention to the regulation of the "stem cell differentiation microenvironment" of the materials. In order to avoid the potential "bone microenvironment regulation defects" of bone replacement materials and break through the current R&D bottleneck, we have been working on the development of bone replacement materials.

2 The role of the immune system in bone regeneration

With the introduction of the concept of osteoimmunity and its development in the field of bone regeneration, researchers have gradually discovered that immune cells play a central regulatory role in the formation of the local bone microenvironment: by regulating the expression of various factors such as growth factors, chemokines, and inflammatory factors, they regulate osteogenic differentiation, osteolytic differentiation, fibrosis, vascularization, and other processes closely related to bone regeneration[10, 12] (**Figure 2**). The immune system and the skeletal system are closely related. The immune system and the skeletal system are



Immune cells are the central regulators of the bone immune microenvironment[10] and influence the processes of osteogenesis, osteolysis and fibrosis during bone regeneration by secreting various cytokines into the bone regeneration microenvironment. ALP: alkaline phosphatase; OPN: bone bridging protein; BMP-2: bone forming protein-2; VEGF: vascular endothelial growth factor; OSM: oncoprotein M; TRAP: antitartaric acid acid phosphatase; OPG: osteoprotegerin; IL-6: interleukin-6; RANK: nuclear factor κβ receptor activating factor; TNF: tumor necrosis factor

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Myeloid precursor cells		
Neutrophils		
Immune cells	Bone immune microenvironment	Osteogenic regulation

Figure 2 Effect of immune cells on bone dynamic

closely related and share many commonalities in terms of cytokines, receptors, and signaling[13–14]. The release of regulatory factors by immune cells can influence the osteogenic and osteoclastic processes in bone tissue. The inflammatory cytokines interleukin-1 (IL-1), tumor necrosis factor- α (TNF-α), and interleukin-6 (IL-6) enhance osteoclast differentiation and osteoclastic activity[15].

2.1 B cells and T cells

Studies have shown that nearly two-thirds of bone marrow-derived osteoprotegerin (OPG) is produced by B cells[16], suggesting that B cells are the primary suppressors of osteoclastic activity during normal physiological processes. The surface of activated T cells can express the receptor activator of nuclear factor - κβ li-gand (RANKL) molecule, which promotes osteoclast formation and enhances bone resorption[17]. binding of RANKL to the receptor activator of nuclear factor - κβ (RANK) on the surface of pro-osteoprotegeric cells activates the RANKL/RANK signaling pathway through The RANKL/RANK-OPG response axis directly promotes osteoclast formation and differentiation[18–19]. However, T cells can also release interferon-γ (IFN-γ) to inhibit osteoclastogenesis[20]. IFN-γ can block the activation of the RANKL/RANK signaling pathway by promoting the degradation of tumor necrosis factor receptor - associated factor 6 (TRAF6), a key intermediate in the RANKL/RANK pathway, thereby inhibiting osteoclast formation and preventing physiological inflammation. osteoclast formation and prevent excessive bone destruction during the

physiological inflammatory response[21].

2.2 Macrophages

M1 macrophages are classified into M1 and M2 types and have important effects on both physiological and pathological processes in bone tissue. M1 macrophages mainly regulate osteoclastic processes, but Guihard et al[22] showed that M1 macrophages can also induce osteogenesis of bone marrow mesenchymal stem cells (MSCs) through the oncostatin M (OSM) pathway. OSM is a cytokine in the IL-6 family that shares the same receptor subunit gp130 as IL-6[23–24] and can induce osteoblast differentiation and promote bone regeneration by binding to type II receptors on the surface of MSCs to activate the transcription factor STAT3-related signaling pathway[25–26]. M2-type macrophages are mainly involved in the middle and late tissue repair of bone tissue regeneration process and can induce bone formation by secreting various cytokines such as bone morphogenetic protein 2 (BMP- 2) and vascular endothelial growth factor (VEGF)[16].

The close connection between immune response and bone regeneration process is well illustrated above. Immune cells are the central regulators of the bone regeneration microenvironment, and the immune microenvironment they create has a significant impact on osteogenic and osteolytic activities, playing a key role in the bone regeneration process. Previous studies have achieved successful treatment of inflammatory bone lesions, such as rheumatoid arthritis and ankylosing spondylitis, by modulating the immune microenvironment[27–32], further suggesting the need to manage the bone immune microenvironment. To address the potential "bone microenvironment regulation deficiency" of bone replacement materials, it is necessary to focus on the role of materials in regulating the bone immune microenvironment. By optimizing the properties of the materials, we can guide the immune microenvironment that facilitates the osteogenic differentiation of stem cells and achieve efficient osteogenic effects.

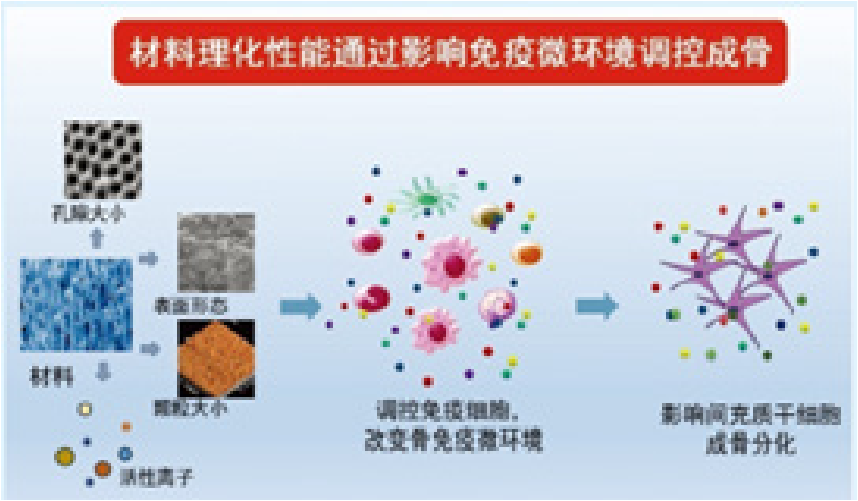
3 Different physicochemical properties of materials and immunomodulatory effects

When a biomaterial is implanted in the body, the body's immune cells will respond most rapidly to recognize the "foreign" biomaterial, causing a "foreign body signaling cascade immune response" and activating host defense mechanisms[33]. An excessive inflammatory response will cause a "foreign body response", resulting in chronic inflammation and fibrous encapsulation, isolating the "foreign body" from the organism or expelling it from the body. In order to avoid this adverse reaction, traditional biomaterial development strategies tend to produce "biologically inert" (non-immune rejection) materials to improve their biocompatibility[34–35].

However, numerous studies have found that in addition to causing "harmful" foreign body reactions, immune cells play an essential "active" role in the effective integration and functional recovery of the material with the surrounding tissue of the host body. Alexander et al[36] found that in a mouse tibial defect model, the removal of macrophages from mice significantly inhibited woven bone deposition and new bone mineralization. It was shown that the deletion of T and B cells in mice caused by gene knockout had some effect in promoting early osteogenic mineralization at the bone defect, but caused an imbalance in the process of pericellular matrix formation and bone mineralization deposition, and the final quality of bone formation was not satisfactory[37–39]. In addition, immune cells are involved in the recruitment process of pro-osteoblasts and have an important regulatory role in osteogenic differentiation[40–41]. Immune cells are the central regulators of the entire regenerative microenvironment and determine the regenerative therapeutic regression of biomaterials[35]. Based on this scientific principle, the development strategy of new generation biomaterials has shifted from the development of "inert (non-immune rejection)" materials to the development of "immunomodulatory" materials, emphasizing the importance of proactive

regulation of immune cells and thus creating an immune microenvironment conducive to tissue regeneration[34–35]. The importance of proactive regulation of immune cells and thus the creation of an immune microenvironment conducive to tissue regeneration has been emphasized[34–35, 42].

Different physicochemical properties of biomaterials, such as surface properties, particle and pore size, and release of bioactive ions, have a significant effect on the local immune response profile they induce[19, 43–46] (**Figure 3**).



After implantation of bone substitute materials as allografts in the body, their physicochemical properties such as surface morphology, pore and particle size, and release of active biological ions can have an impact on the immune response of the organism. By modifying the physicochemical properties of the material, the immune cells and their generated bone immune microenvironment are regulated, affecting the osteogenic differentiation of mesenchymal stem cells and promoting bone regeneration

Material physicochemical properties modulate osteogenesis by affecting the immune microenvironment		
Pore size Surface form Materials Particle size Reactive ions	Modulation of immune cells and alteration of bone immune microenvironment	Affects osteogenic differentiation of mesenchymal stem cells

Figure 3 Osteoimmunomodulatory properties of bone substitute biomaterials

3.1 Material surface properties and immunomodulatory effects

Material surfaces are in direct contact and reaction with the surrounding immune environment, and their wetting and moisture, surface morphology, and charge conditions affect the biological behavior of immune cells in the surrounding environment. In general, hydrophobic surfaces induce stronger local immune responses by increasing the adhesion level of monocytes compared to hydrophilic surfaces[47–48]. Interestingly, it has been found that hydrophilic/neutral copolymer (2-methacryloyloxyethyl phosphorylcholine/alkyl butyl acrylate) surfaces can more significantly inhibit monocyte-macrophage adhesion compared to hydrophilic (butyl butyl acrylate) or hydrophobic (polyurethane) surfaces alone, as well as significantly inhibit inflammatory factors IL-6 compared to control (tissue culture polystyrene plate) surfaces, Il-1β and TNF-α expression[49]. The surface roughness of the material can also affect the adsorption and extension of immune cells, with increased ductility of macrophages on the material surface with increasing roughness[50]. Sandblasting and acid-etching of titanium surfaces to alter their roughness can modulate the release of inflammatory and chemokines from macrophages, which have bone immunomodulatory potential[51]. For the surface charge profile, it is generally believed

that cationic particles promote inflammatory responses more than anionic particles and neutral materials[46, 52].

3.2 Particle size of the material and immunomodulatory effects

In addition to the surface properties, the particle size of the material also has an important impact on the immune response. Biological materials are implanted as foreign bodies and the immune system degrades the material according to the particle size[46]. Macrophages, as immune defense cells, can engulf particles up to 5 μm in diameter, and for larger particles, macrophages will fuse to form foreign material macrophages[53]. For the same mass of material, the smaller the particle, the larger the surface area and chemical activity, thus enabling a greater impact on the biological activity of cells with bone immunomodulatory potential[54], and small diameter hydroxyapatite particles (1–30 μm) stimulate the highest production of pro-inflammatory cytokines by immune cells (TNF-α, IL-1α, IL-6)[55]. However, this does not indicate that the smaller the particle the more intense the immune response it stimulates. Some in vivo studies have shown that the reduction in size of irregular hydroxyapatite particles can relatively suppress the inflammatory response[56].

3.3 Porosity, pore size and immunomodulatory effects of scaffolds

Porosity and pore size are two key parameters in the preparation of bone tissue engineering scaffolds, which determine the type of tissue (inflammatory granulation tissue, vascular tissue or bone tissue) that grows into the scaffold. Too small pores may severely affect the diffusion of nutrients and oxygen, leading to the formation of a local hypoxic microenvironment and a local inflammatory response, and eventually the formation of granulomas blocking the pores preventing osteoblast growth into and bone formation[57–58]. However, at the same time, the hypoxic environment can also promote osteogenesis by stabilizing hypoxia- inducible factors (HIFs) and promoting vascularization[59–60]. It has been shown that a larger porosity and pore size of the material is more conducive to the growth of bone tissue entry while reducing the inflammatory response[61–62]. By adjusting the pore size and porosity to induce an appropriate hypoxic environment, excessive inflammation can be avoided and vascularization and bone regeneration can be promoted.

3.4 Addition of bioactive ions and immunomodulatory effects

The addition of bioactive components to bone replacement materials has become an effective means of enhancing the bone repair capacity of the material. After implantation, bone biomaterials with bioactive components release active biological ions through physicochemical dissolution, hydrolysis, and enzymatic corrosion, which have significant effects on the local biological microenvironment. Numerous studies have shown that calcium ions, magnesium ions, zinc ions, cobalt ions, strontium ions, etc. can act as bioactive ions to regulate the immune microenvironment.

3.4.1 Ca^{2+}

Ca is an important component of calcium phosphate bone bioactive material and is involved in the non-classical Wnt signaling pathway Wnt5A/Ca^{2+}, which promotes inflammatory responses[63]. In addition to this, high concentrations (5 mmol/L) of extracellular Ca ions reduce the expression of TNF - α through activation of the calcium-sensing receptor (CaSR) cascade, thereby attenuating the inflammatory response[64]. Suggesting a high plasticity of Ca in the regulation of immune responses.

3.4.2 Mg^{2+}

Mg has biodegradable and biocompatible properties similar to natural bone and is used clinically as a biodegradable metallic orthopedic material. Mg ions can inhibit the production of inflammatory cytokines by inhibiting the toll-like receptor (TLR) pathway[65]. In vivo studies have shown that the slow release of Mg in the local bone regeneration environment has a role in promoting bone healing[66].

3.4.3 Zn^{2+}

Zn increases the release of the anti-inflammatory cytokine IL-10 and decreases the expression of TNF-α and IL-1β[67].

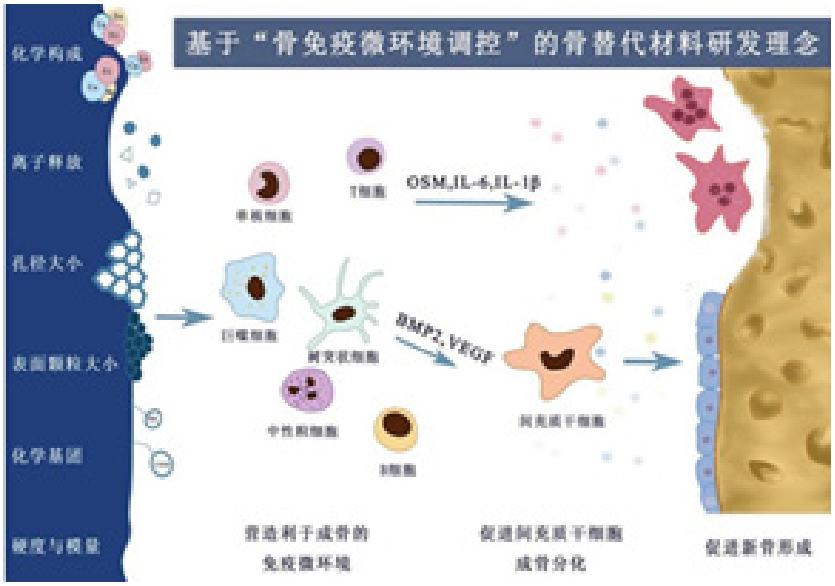
3.4.4 Sr^{2+}

Sr, as a trace element, has a role in promoting osteogenesis and inhibiting osteoclastogenesis[68]. The introduction of Sr into calcium and phosphorus materials has been investigated, and the results showed that it inhibited the release of the pro-inflammatory cytokine TNF-α from monocytes in both high (500 mmol/L) and low (10 mmol/L) ion concentration environments[69]. Many bioactive ions can have a range of effects on the immune response. Modulation of the bone immune microenvironment through the combination and concentration-controlled release of different bioactive elements to promote osteogenesis may become an important development strategy for novel bone bioactive materials.

4 Research and development of bone replacement materials based on the concept of "bone immune microenvironment modulation

4.1 "Bone immune microenvironment regulation" concept

In view of this special relationship between immune cells and bone homeostasis, our group proposed that the "immunomodulatory properties" of bone biomaterials should be optimized as "bone immunomodulatory properties", emphasizing the key role of the bone immune microenvironment created by biomaterials after modulating immune cells on osteogenesis and The key regulatory role of the bone immune microenvironment



The development concept based on the regulation of bone immune microenvironment emphasizes the modification of the physicochemical properties of implant materials, such as chemical composition, surface properties and mechanical properties, in order to regulate immune cells and create an immune microenvironment conducive to osteogenesis, thus promoting the differentiation of mesenchymal stem cells in the direction of osteogenesis and improving the osteogenic performance of bone replacement materials.

<table>
<tr><td rowspan="2">Chemical composition
Ionic Release
Aperture size
Surface particle size
Chemical group
Hardness and Modulus</td><td colspan="3">Bone replacement material development concept based on "bone immune microenvironment regulation
T cells
Mononuclear cells Macrophages Dendritic cells
Mesenchymal stem cells Neutrophils
B-cells</td></tr>
<tr><td>Create a conducive to bone formation Immune microenvironment</td><td>Promote osteogenic differentiation of MSCs</td><td>Promotes new bone formation</td></tr>
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Figure 4 Development of bone substitute materials based on osteoimmunomodulation

created by the regulation of immune cells in biomaterials on the osteogenesis and osteolysis processes[10, 70–71] (**Figure 4**).

To realize the development of "osteoimmunomodulated intelligent" bone substitute materials, we should first elucidate the key role and mechanism of immune cells in the osteogenesis of bone substitute materials, verify the necessity of modulating the immune microenvironment and reveal the key immune cells to provide the target cells for targeting and modulation. To answer this scientific question, our group has analyzed the cases of successful and unsuccessful osteogenesis of bone substitute materials in vivo and found that the bone immune response of macrophages is the key to the successful induction of osteogenesis by bone substitute materials. The immune microenvironment created by tricalcium phosphate, which drives macrophages toward the M2 isoform and upregulates the expression of BMP-2, significantly promotes the osteogenic differentiation of MSCs, confirming the key role of macrophages and their production of BMP-2 in the successful induction of osteogenesis by tricalcium phosphate[70].

In the case of failure, cobalt ion implantation of tricalcium phosphate prompted a subtype shift of macrophages toward M1, leading to an excessive inflammatory response and formation of fibrous inclusions, creating an immune microenvironment that inhibited osteogenic differentiation of MSCs, confirming that abnormal functional response of macrophages leads to failure of bone replacement materials to induce osteogenesis[72]. Thus, it was confirmed that macrophages play a key role in the interaction between the material and the bone regeneration system and that regulation of the bone immune microenvironment must focus on the bone immune response of macrophages.

4.1.1 Altered physicochemical properties of bone replacement materials on macrophage bone free

Regulation of the immune response To further explore the role of modifying the physicochemical property parameters of the bone replacement material on the regulation of the bone immune response of macrophages and its effect on osteogenic differentiation, our group started from the dimension of the chemical composition of the material and used the solid-state reaction method to integrate SrO, MgO and SiO2 to form $Sr_2MgSi_2O_7$, which inhibited the activation of TLR pathway in macrophages by releasing Mg^{2+} that successfully reduced the expression of pro-inflammatory factors and promoted the shift of macrophages toward the M2 subtype[73]. However, this elemental group of bone immune microenvironment failed to promote osteogenic differentiation well. Interestingly, the bone immune microenvironment generated by the novel trace element composite ($Sr_2ZnSi_2O_7$) upon the action of macrophages promotes the osteogenic differentiation of MSCs when the Mg element is replaced by Zn element[74]. The mechanism is related to the release of BMP-2 and the activation of downstream pathways. An important role of chemical element composition in the regulation of the bone immune microenvironment was suggested. Further studies suggested that by altering the composition and ratio of trace elements deposited on the implant surface, such as Ca to Sr, macrophages could be promoted to polarize in the direction of M2, thus promoting bone tissue regeneration and angiogenic processes, an effect that may be associated with increased secretion of BMP-2, VEGF and IL-10, where when Ca:Sr = 2:1, the induction the best osteogenic efficacy of the immune microenvironment[75]. Designing the chemical elemental composition of materials is a feasible strategy when developing bone replacement materials with excellent bone immunomodulatory properties[75–76].

In addition to the chemical composition, the material nanosurface structure can also have a significant modulating effect. Using anodic oxidation method, the author successfully formed highly ordered oxide nanopores or nanotubes on the surface of aluminum sheets. By varying the concentration of electrolyte, electric field voltage, and heat treatment conditions, the group successfully prepared surfaces with different nanopore sizes (15, 50, 100, and 200 nm). Further exploration revealed that macrophages produced significant-

ly different bone immune responses at interfaces with different pore sizes, and the mechanism was to activate the autophagic response by changing the morphology of macrophages and transferring the extracellular physicochemical signals into the cell. Among them, the bone immune microenvironment produced by pore sizes of 50 nm and 100 nm is most favorable for osteogenic differentiation of MSCs[11]. In addition, the porosity and pore size of bone replacement materials also affect the type of cells that grow into them, including those with inflammatory granulation tissue, vascular tissue and bone tissue, where it has been shown that scaffold materials with 80%-88% porosity and >50 nm pore size are more suitable for bone tissue growth[77], and both factors can also have an effect on the polarization of macrophages. For example, in collagen membrane materials, the porosity and pore size of collagen fibers can act on mouse bone marrow-derived macrophages, and with increasing porosity and pore size, the expression of M2-associated markers of macrophages increases, while the expression of M1-associated markers decreases[78]. Meanwhile, it has also been found that macrophages can be regulated by changing the surface roughness of the implant material, and in the range of submicron titanium surface roughness (100 ~ 400 nm), the differentiation of osteoblasts was enhanced with increasing titanium surface roughness, and the cytoskeleton of macrophages changed with the change of titanium surface roughness, and TNF-α, IL-6, IL-4 and IL-10 cytokine secretion can also be regulated by the titanium surface roughness[47].

In addition to the effect of pore size, this group further explored the effect of nanosurface chemical composition and particle size. The plasma polymerization nano-engineering technology uses electrical discharge to plasma gasify volatile organic-like gaseous monomers to form polymeric films on the material surface, forming nano-thick coatings with different functional group surfaces. Due to the ultra-thin nano-thickness, ultrastructures such as substrate nanoparticles can be retained. By combining plasma polymerization and electrostatic self-assembly nano-engineering techniques, the group precisely prepared nanosurface structures with different nanoparticle sizes (16, 38, 68 nm) and different surface chemistries (amine-rich acrylamide and carboxylate-rich acrylic acid). It was further found that both chemical interfaces inhibited the inflammatory response of macrophages, while the inhibitory effect of amine-rich acrylamide was more effective. The addition of nanoparticles enhanced the anti-inflammatory effect of the chemical interface by a mechanism related to the regulation of macrophage morphology and intracellular autophagic response. Among them, the bone immune microenvironment generated by this nanosurface of 68 nm composite acrylic acid was the most favorable for osteogenic differentiation of MSCs[79].

In addition, the wettability of the material chemical interface can also have an effect on macrophages and associated cytokines, and it has been shown that macrophages cultured on material surfaces with high surface wettability can produce an anti-inflammatory microenvironment[43].

4.1.2 Altered mechanical properties of bone substitute materials on macrophage bone free

The regulation of the immune response on the other hand, the mechanical properties of the implanted material can also modulate the activation state of macrophages. It has been shown that the macrophage phenotype can be regulated by changing the modulus of polyurethane scaffolds implanted in subcutaneous tissues in rats, and this experiment prepared scaffolds of polyurethane with matrix modulus ranging from 5 to 266 MPa, and the results showed that the effect of promoting the regenerative response of the organism was strongest when the modulus of the scaffold was closest to that of collagen fibers, i.e., when the modulus was 24 MPa, at which time the regenerative response of the fibroblasts was Wnt/β-linked protein signaling pathway is downregulated in fibroblasts, while promoting the polarization of macrophages toward the M2 type[80]. In addition, it has been shown that the stiffness of the material has no significant effect on macrophage attachment, but can affect macrophage morphology.

When mouse macrophages were stimulated with lipopolysaccharide, stiffer hydrogels promoted the expression of macrophage pro-inflammatory-related genes, such as TNF-α, IL-1β and IL-6, which triggered a stronger foreign body response, suggesting that lower stiffness hydrogels triggered a milder foreign body response and therefore may be more suitable for application in tissue engineering[81].

4.2 Application of "Bone Immunomodulating Intelligence" novel bone replacement material

Research and development results from practical exploration show that by precisely modulating the physicochemical properties of the material surface (chemical component composition, nano-surface pore size, particle size, mechanical properties, etc.) to create a material with a particular physicochemical parameter, the bone immune response of the targeted cellular macrophages can be correspondingly In addition, the group has been able to create a specific bone immune microenvironment with specific physicochemical parameters. Based on this research result, our group further applied the concept of "bone immune microenvironment regulation" to magnesium metal, implants, barrier membranes and other branches, and successfully developed a new bone immune regulation "intelligent The group has successfully developed new bone biomaterials with bone immunomodulatory "intelligence" to create an osteogenic immune microenvironment and effectively promote the formation of new bone, and confirmed that targeting and regulating the macrophage-mediated bone immune microenvironment can improve the osteogenic repair effect mediated by bone replacement materials.

4.2.1 New magnesium metal material magnesium metal material has excellent

Biomechanical properties, with mechanical properties similar to cancellous bone, and as a degradable material that can eventually be replaced by new bone tissue, have made it the "star" metallic material in the field of bone tissue engineering[62,82]. However, the undesirable immune microenvironment resulting from inappropriate degradation rates and excessive inflammatory responses has limited the widespread use of these materials. By modifying magnesium scaffold materials with tricalcium phosphate, we successfully reduced the rate of macrophage-mediated material degradation, down-regulated the inflammatory response of macrophages and the expression of fibrogenic factors, inhibited osteoclastic differentiation, up-regulated the expression of angiogenic and osteogenic factors, and created a bone immune microenvironment that significantly promoted osteogenic differentiation, and successfully developed magnesium scaffold materials with both appropriate degradation properties and excellent bone immune modulation properties[83].

4.2.2 New implant coating materials to improve the bone integrity of the implant

Integration is a difficult problem in oral implantology research. Implant coatings have been considered as an effective strategy to improve the osseointegration of implants, however, the introduction of coatings has brought about key problems such as delamination of the implant from the coating and poor integration of the coating with the bone tissue, which have limited the application of coatings. By integrating micronutrients ($MgSiO_3$), we developed an implant coating with "osteoimmunomodulatory intelligence", and combined with the plasma spraying method of coating preparation, we greatly improved the bonding strength of the coating to the implant and formed a coating material with excellent osteoimmunomodulatory properties, which effectively improved the osseointegration effect of the implant. The scientific problem of "delamination" and "poor osseointegration" of the coating was successfully solved[84].

4.2.3 The novel barrier collagen membrane guided bone tissue regeneration technique is

It is an important technique for bone regeneration in the dental clinic, which guarantees the successful completion of bone regeneration by

first filling the bone defect area with bone repair material and then covering it with a barrier membrane to prevent the surrounding soft tissues from growing in and separating the hard and soft tissue regeneration environment. Barrier membrane materials play an important role in guiding bone tissue regeneration, separating the hard and soft tissue regeneration environment and directly affecting the final treatment outcome. Traditional barrier membrane development strategies have focused on its physical barrier function, degradation properties and how to circumvent immunogenicity to improve biocompatibility. However, the implantation of barrier membranes, in addition to producing a basic physical barrier effect, also has an impact on the local microenvironment, which directly affects the tissue regeneration outcome, a regulatory role that has been overlooked. Neglecting the regulatory role of the barrier membrane on the local microenvironment will likely produce a microenvironment that is detrimental to bone tissue regeneration, thus adversely affecting the regeneration process. Our group found that the BioGide collagen membrane, which is commonly used clinically, produced a significant immune response after implantation in vivo, with the smooth and rough surfaces showing different response effects, and the rough surface forming a distinct band of mononuclear cell infiltration, and histochemical analysis confirmed that this cell band was dominated by macrophages[79]. In vitro experiments further confirmed that collagen membranes promote the secretion of pro-inflammatory factors such as TNFα, IL-1β, IL-6 and IL-18 by macrophages and effectively promote the osteogenic differentiation of MSCs through the release of osteogenic factors such as BMP-2 and OSM, confirming the effective bone immunomodulatory effects[85]. Recent advances in materials science suggest that the development of immune-responsive collagen membranes that confer good properties in regulating the polarization of macrophages and modulating the balance of pro- and anti-inflammatory immune microenvironment may be a novel strategy to enhance the therapeutic efficacy of guided bone tissue regeneration techniques[86].

In order to achieve optimization of the bone immunomodulatory properties of collagen membranes, our group successfully coated $Ca2ZnSi_2O_7$ uniformly on the surface of collagen membranes by using pulsed laser deposition technique, forming uniformly sized nanoparticles on collagen fibers, which endowed collagen membranes with excellent bone immunomodulatory properties and effectively promoted osteogenic differentiation[85]. Related studies have also shown that collagen membranes loaded with immune-related factors, such as IL-4, can promote the expression of anti-inflammatory-related factors through the release of IL-4, thus promoting the elimination of inflammation. In addition, changing the porosity and pore size of collagen membranes, loading-related growth factors, and surface particle size may also affect the activation state and polarization direction of macrophages, which is also a feasible direction to optimize the osteoimmunomodulatory properties of collagen membranes[86].

4.2.4 New nano bone replacement material mesoporous silica nano

Particles are a commonly used drug or growth factor carrier with the advantages of large specific surface area and controllable particle size. For application in bone regeneration, they are often used as carriers of osteogenic and angiogenic factors such as BMP-2 and VEGF to promote the formation of vascularized new bone through slow release of osteogenic and angiogenic factors[87]. However, this method has disadvantages such as expensive and unstable release of growth factors. The author used a simple "in si-tu one-pot" synthesis method to load copper into mesoporous silica nanoparticles to achieve the slow release of copper. Further acting on macrophages, we found that it could induce macrophages to secrete osteogenic factor OSM and vascularizing factor VEGF, thus promoting osteogenic differentiation and vascular regeneration, realizing the development of multifunctional nanomaterials with immunomodulation, vascularizing and osteogenic properties[88]. The development of this novel material is based on the regulation of the bone immune response of

macrophages, creating an immune microenvironment favorable to osteogenesis and vascularization, avoiding the use of expensive growth factors, and avoiding the use of high-value medical materials by loading inexpensive copper elements into mesoporous silica through an easy preparation method.

5 Summary

Bone defects are a major clinical problem with high morbidity and high risk. The development of bone replacement materials with excellent osteogenic efficacy to achieve regenerative repair of bone defects has important scientific and translational medical significance. In addition to the direct regulation of osteogenic differentiation of stem cells, the development of bone replacement materials should also focus on the management of the microenvironment of stem cell differentiation, especially the immune microenvironment, so as to regulate the local microenvironment favorable to osteogenic differentiation and induce the formation of new bone. Based on this scientific principle, this paper proposes a new research and development idea of "regulation of immune cells to create a microenvironment conducive to osteogenesis, thus improving osteogenic efficiency", and condenses the concept of "bone immune regulation performance", and elucidates the multidirectional role of bone immune microenvironment, assessment content, and assessment method. The concept of "bone immunomodulation performance" was developed, and the multi-directional role of the bone immune microenvironment, the assessment contents, assessment methods and regulation strategies were elucidated, providing a scientific basis for the construction of a new interdisciplinary branch of "bone immunomodulation of biomaterials", guiding the development of a new generation of advanced multifunctional bone replacement materials with targeted regulation of the immune microenvironment, thus improving the osteogenic efficacy of bone replacement materials. In order to improve the osteogenic efficacy of bone substitution materials and meet the demand for regenerative repair of bone defects.

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