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Contents

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REVIEW

- 527 Potential of transposon-mediated cellular reprogramming towards cell-based therapies
Kumar D, Anand T, Talluri TR, Kues WA
- 545 Approaches to promoting bone marrow mesenchymal stem cell osteogenesis on orthopedic implant surface
Huo SC, Yue B
- 562 Photodynamic therapy regulates fate of cancer stem cells through reactive oxygen species
Zhang ZJ, Wang KP, Mo JG, Xiong L, Wen Y
- 585 Decellularized adipose matrix provides an inductive microenvironment for stem cells in tissue regeneration
Yang JZ, Qiu LH, Xiong SH, Dang JL, Rong XK, Hou MM, Wang K, Yu Z, Yi CG

MINIREVIEWS

- 604 Vitamin D and calcium signaling in epidermal stem cells and their regeneration
Oda Y, Bikle DD
- 612 Adipose-derived stem cell therapy shows promising results for secondary lymphedema
Hu LR, Pan J

ORIGINAL ARTICLE

Basic Study

- 621 Involvement of glycated albumin in adipose-derived-stem cell-mediated interleukin 17 secreting T helper cell activation
Pestel J, Robert M, Corbin S, Vidal H, Eljaafari A
- 633 Bone marrow mesenchymal stem cells induce M2 microglia polarization through PDGF-AA/MANF signaling
Yang F, Li WB, Qu YW, Gao JX, Tang YS, Wang DJ, Pan YJ

SYSTEMATIC REVIEWS

- 659 Role of stem cell therapies in treating chronic wounds: A systematic review
Raghuram AC, Yu RP, Lo AY, Sung CJ, Bircan M, Thompson HJ, Wong AK
- 676 Application and prospect of adipose stem cell transplantation in treating lymphedema
Li ZJ, Yang E, Li YZ, Liang ZY, Huang JZ, Yu NZ, Long X

- 688** Mesenchymal stem cells and mesenchymal stem cell-derived extracellular vesicles: Potential roles in rheumatic diseases

Yang JH, Liu FX, Wang JH, Cheng M, Wang SF, Xu DH

ABOUT COVER

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Approaches to promoting bone marrow mesenchymal stem cell osteogenesis on orthopedic implant surface

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Abstract

Bone marrow-derived mesenchymal stem cells (BMSCs) play a critical role in the osseointegration of bone and orthopedic implant. However, osseointegration between the Ti-based implants and the surrounding bone tissue must be improved due to titanium's inherent defects. Surface modification stands out as a versatile technique to create instructive biomaterials that can actively direct stem cell fate. Here, we summarize the current approaches to promoting BMSC osteogenesis on the surface of titanium and its alloys. We will highlight the utilization of the unique properties of titanium and its alloys in promoting tissue regeneration, and discuss recent advances in understanding their role in regenerative medicine. We aim to provide a systematic and comprehensive review of approaches to promoting BMSC osteogenesis on the orthopedic implant surface.

Key words: Bone marrow mesenchymal stem cells; Osseointegration; Orthopedic implant; Biofunctionalization

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Core tip: Bone marrow-derived mesenchymal stem cells (BMSCs) play a key role in tissue repair after bone and joint injuries. The effects of the surface treatment of the orthopedic implants on the osteogenic differentiation of BMSCs are worthy of attention. In this paper, we review recent advances in approaches that promote osseointegration of BMSCs on the surface of orthopedic implants.

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INTRODUCTION

Since Friedenstein *et al*^[1] isolated bone marrow mesenchymal stromal cells from for the first time and regarded them as bone tissue progenitor cells, they have played an increasingly important role in orthopedics. Bone marrow-derived mesenchymal stem cells (BMSCs) are ideal candidates for tissue repair after traumatic injury because they are relatively easy to harvest *in vitro* and can undergo self-renewal and multi-directional differentiation into several mesodermal and non-mesodermal cell lineages including osteoblasts, chondrocytes, and adipocytes^[2-6]. Degenerative diseases of bone such as osteoarthritis can lead to bone fractures and immobility, compromising quality of life. In the treatment of osteomyelitis, after effectively controlling the symptoms of infection using local or systemic antibacterial drugs, BMSCs differentiate into osteoblasts and lipoblasts, and finally differentiate into mature bone adipose tissue for repair local injury^[7]. However, although much attention has been paid to the engineering of biomaterials that regulate BMSC commitment to specific lineages, like the chondrogenic and osteoblastic lineages, harnessing BMSC fate remains a major challenge^[8,9]. Therefore, overcoming these challenges would be very significant in the field of orthopedics, where the ability to stimulate osteogenic BMSC differentiation on biomaterials like titanium and its alloys would translate into higher rates of implant osseointegration and improved long-term functionality. In addition, it is necessary to stimulate the *in vivo* environment using BMSCs to study the cellular response at the bone-implant interface since BMSCs are in direct contact with the implant after surgery^[10].

The term “osteointegration” has been used since Professor Branemark first reported the phenomenon of “osteointegration” to describe the stable combination of biomaterials and bone tissue. Osseointegration refers to the direct contact of the bone with the implant without an intermediate layer of connective tissue. This biological fixation is a prerequisite for implantable prostheses and their long-term success.

Titanium and its alloys have been widely used in biomedical areas in recent decades for cardiovascular, orthopedic, and dental applications due to their resistance to fatigue, superior mechanical properties, and load-bearing capabilities^[11,12]. For example, the elastic modulus of nitinol is 40 GPa, compared to 30 GPa for bone^[13]. However, there are major disadvantages to using Ti-based implants, including inert biomaterials and poor biological activity^[14,15]. In addition, they fail to achieve sufficient osseointegration, leading to increased aseptic loosening and premature implant failure^[16,17]. Therefore, these problems with Ti-based implant materials have hindered to some extent their development as orthopedic implants. Campoccia *et al*^[18] believed that the surface of an ideal osteo-compatible biomaterial should possess the following characteristics *in vitro*: (1) Allow good and tight initial adhesion; (2) Support cell attachment and viability; and (3) Have a positive influence on the osteogenic differentiation process. Given that the interaction between the implant materials and bone tissue first occurs on the implant surface, it is necessary to modify the implant surface to solve the problems in titanium and its alloys. BMSCs have the critical role to achieve bone and implant osseointegration. Surface composition, hydrophilicity, and roughness of the orthopedic implant can affect BMSC differentiation and affect osseointegration. Thus, the surface of the implant must be biomodified to create a bioactive surface that is helpful to promote cell-material interactions and improve osseointegration of titanium and its alloys^[19-21].

Many surface modification techniques like physical vapor deposition, sol-gel, ion implantation, anodization, and micro-arc oxidation have been investigated to improve the surface properties of titanium and its alloys^[22-25]. Although many researchers pay attention to the effect of titanium surface modification on its biological activity, there are still few studies on the effect of modification of titanium and its alloys on the behavior of mesenchymal stem cells. The main aim of this review study is to report the state of art on the technological advancements of titanium implant surfaces to promote osteogenic differentiation of BMSCs on orthopedic implants. This review article deals with the titanium properties, innovative physicochemical procedures to modify titanium surfaces, biomimetic functionalization, promotion of BMSC osteogenesis, and inhibition of biofilm accumulation. We hope that it can provide some ideas for better methods to improve osseointegration efficiency.

BIOFUNCTIONALIZATION OF ORTHOPEDIC IMPLANT WITH BIOACTIVE CERAMIC TO REGULATE BONE MARROW MESENCHYMAL STEM CELL BEHAVIOR

Bioactive ceramic materials have a certain degree of solubility in the body, releasing certain ions that are not harmful to the body, participating in organic metabolism, stimulating or inducing bone hyperplasia, promoting defective bone tissue repair, and showing other good biological properties. This type of material may contain hydroxyapatite, or it can produce hydroxyapatite after reacting with body fluids, which can be integrated with bone tissue to form a bone binding interface. This method belongs to chemical combination with high strength and good stability. In this section, we will review the effects of different methods of bioactive ceramic coating on the behavior of BMSCs. The overall situation is shown in [Table 1](#).

Plasma spraying

Plasma spraying technology is a method in which a plasma electric arc driven by a direct current is used as a heat source to heat materials like ceramics, alloys, and metals to a molten or semi-fused state before spraying the surface of a pretreated workpiece at a high speed to form a firmly adhered surface layer. Plasma spraying is an effective method to prepare bioactive ceramic coatings. Hydroxyapatite [$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, HA] is a calcium hydroxide and tricalcium phosphate compound salt with a chemical composition and crystalline structure similar to the main minerals in human bones and teeth. It is also the main inorganic component of human bone tissue, and a typical bioactive material with good biocompatibility and chemical stability. It has been reported that spraying a hydroxyapatite ceramic coating on the surface of titanium-based implants leads to good cellular compatibility, promotes adhesion, proliferation, and osteogenic differentiation of BMSCs, and improves the implant's bond to surrounding bone tissue. In one study, Dimitrievska *et al.*^[26] fabricated a new type of titanium alloy that possesses a layer of hydroxyapatite on titanium dioxide by plasma spraying. They studied the behavior of BMSCs on this titanium-based material. The results show that cells have stronger initial adhesion (improved by 20% after 2 h) and higher metabolic activity (improved by 20% after 2 h) on TiO_2 -HA compared to the titanium dioxide group. Furthermore, the differentiation of BMSCs is evidenced by alkaline phosphatase (ALP) and osteocalcin (OCN), early indicators of osteogenic differentiation, which are significantly increased on TiO_2 -HA. However, the pure HA coating also has some serious defects: High brittleness, poor fatigue resistance, and weak bonding strength with metal substrates. Porous tantalum has attracted much attention for its good biocompatibility and microstructure similar to cancellous bone^[27]. In a recent study, Ta-incorporated HA coatings were developed by Lu *et al.*^[28] using the plasma spray technique on a titanium substrate. The result demonstrated that Ta-incorporated HA coating could promote initial adhesion and faster cell proliferation after incubation for 3 and 5 days, but it also promotes osteogenic differentiation of BMSCs compared to HA coatings. Akermanite ceramics can induce apatite mineralization. They also have moderate stability in simulated body fluid (SBF) and generally good mechanical properties, and support BMSC attachment^[29,30]. The researchers found that the bonding strength between the plasma-sprayed akermanite bioactive coatings and Ti substrates is higher than hydroxyapatite (HA) coatings, and BMSC attachment and proliferation were more significant on akermanite coatings than on HA coatings^[31].

Sol-gel method

Sol-gel process first described 150 years ago is still receiving great attention as one of the easiest ways to develop modified materials which possess required properties and are characterized by durability and stability^[32]. Hence, sol-gel process is another method for preparing bioactive ceramic coatings. The sol-gel technology has some advantages compared to plasma spraying methods, including chemical uniformity, fine grain structure, and lower processing temperature^[33]. In a study, a micro/nano-layered structure was prepared on a micro-structured titanium (Micro-Ti) substrate using a sol-gel method with a spin coating technique. The results confirmed that the micro/nano-level structure of large particles (80 nm) significantly promoted MSC proliferation and differentiation compared to other small particles (20 nm and 40 nm)^[23]. Inzunza *et al.*^[34] prepared nanoporous silica coatings on Ti using the sol-gel method and evaporation-induced self-assembly method. The silica coatings with highly ordered sub-10 nm porosity accelerate the adhesive response of early BMSCs and promote BMSC osteogenic differentiation.

Table 1 Biofunctionalization of orthopaedic implant with bioactive ceramic to regulate bone marrow mesenchymal stem cell behavior

Method	Preparation of bioactive ceramic	Cell response	Ref.
Plasma spraying	TiO ₂ -HA nanocomposite powders were thermally sprayed <i>via</i> the HVOF (high-velocity oxy-fuel) technique.	HBMSCs have stronger initial adhesion and favor osteogenic differentiation.	Dimitrievska <i>et al</i> ^[26]
	Ta-incorporated HA coatings were fabricated using the plasma spray technique on a titanium substrate.	Ta-incorporated HA coating could promote initial adhesion, faster proliferation, and osteogenic differentiation of BMSCs.	Lu <i>et al</i> ^[28]
	An atmosphere plasma spray system was applied to spray the synthesized 40-80 µm powders onto the treated substrates.	The attachment and proliferation of BMSCs were more significantly on akermanite coatings than on HA coatings.	Yi <i>et al</i> ^[31]
Sol-gel method	Ti disks were etched with the mixed solution of HF and H ₂ SO ₄ . Next, EtOH solutions containing tetrabutyl titanate (TBT) were spin-coated onto samples.	The micro/nano-level structure of large particles (80 nm) significantly promoted MSC proliferation and differentiation.	Shen <i>et al</i> ^[23]
	Pre-hydrolyzed silica solution was added to a solution containing the pores structure-directing agents dissolved in ethanol.	The silica coatings accelerate the adhesive response of early BMSCs and promote BMSC osteogenic differentiation.	Inzunza <i>et al</i> ^[34]

HVOF: High-velocity oxy-fuel; HBMSCs: Human bone marrow-derived mesenchymal stem cells; HA: Hydroxyapatite; BMSCs: Bone marrow-derived mesenchymal stem cells; HF: Hydrofluoric acid; H₂SO₄: Sulfuric acid; TBT: Tetrabutyl titanate; MSC: Mesenchymal stem cell.

SURFACE TOPOGRAPHY TO REGULATE BONE MARROW MESENCHYMAL STEM CELL BEHAVIOR

A bioactive ceramic layer is coated on the surface of porous titanium, and its osteoconduction supports the new bone to grow into the pore along the pore wall, which can effectively improve biological fixation of the porous titanium coating. However, this method also has some shortcomings: (1) After applying the bioactive ceramic coating, the pores of bone tissue are reduced, so the contact area with bone tissue is reduced; and (2) Bioactive ceramic coating still has degradation, poor combination with titanium, and other problems^[35]. A variety of surface modification methods have been developed to improve titanium bioactivity. In this section, we will review the different surface modification methods to provide a reference for clinical use (Table 2).

Chemical treatments

Chemical methods can be used to increase the thickness of the oxide film to improve the biocompatibility and bioactivity of titanium and its alloys. The surface chemical treatment of titanium and titanium alloys mainly includes alkali treatment, acid treatment, and acid-base two-step treatment. Alkali solution is used to modify the titanium surface to obtain sodium titanate gel with rich Ti-OH groups on the surface, endowing it with biological activity^[36,37]. For this purpose, Cai and his team employed potassium hydroxide to modify the surfaces of titanium substrates; the formed potassium titanate layer enhances titanium's corrosion resistance. The proliferation and differentiation levels of alkaline phosphatase and osteocalcin were significantly increased in MSCs cultured on alkaline-treated titanium after 7 and 14 d of culture, respectively^[38].

Acid treatment is often used to remove the oxide layer and contaminants on the surface of the medical titanium material to obtain a clean and uniform surface. The acid treatment results in a 10-nm thick oxide layer, while the titanium oxide in the air is only 3-6 nm thick^[39]. Maekawa *et al*^[40] treated titanium with polyphosphoric acid solution for 24 h at 37 °C. Surface texture measurement results show that the maximum surface roughness of the treated titanium surface significantly increased. Significantly higher cell attachment and proliferation were also found on titanium treated with polyphosphoric acid in contrast to untreated titanium (control). By comparing the effects of acid-treated titanium and pure titanium on osteogenic differentiation of bone MSCs, Perrotti *et al*^[41] concluded that 1 wk of treatment was more than enough for osteoblast differentiation on acid-treated titanium. Silva and his group suggested that rough surfaces submitted to acid-etching favor undifferentiated mesenchymal cell differentiation into osteogenic lineage cells compared to smooth titanium surfaces without acid treatment^[42]. Although many studies have shown that surface acidification can increase the degree of roughening and improve the biological activity of titanium implants, acid treatment may cause hydrogen to penetrate below

Table 2 Surface topography to regulate bone marrow mesenchymal stem cell behavior

Method	Treatment process	Cell response	Ref.
Chemical treatments	Commercial pure Ti was immersed into KOH solutions.	The differentiation levels of ALP and OCN were significantly increased.	Cai <i>et al</i> ^[38]
	The Ti disks were immersed into solutions of polyphosphoric acid.	Significantly higher cell attachment and proliferation were also found on Ti treated with polyphosphoric acid.	Maekawa <i>et al</i> ^[40]
	Surfaces submitted to polishing plus etching with 0.8% HF, 13% HNO ₃ solution.	Rough surfaces submitted to acid-etching favor undifferentiated BMSCs into osteogenic lineage cells.	Silva <i>et al</i> ^[42]
	The Ti disks were pickled in oxalic acid solution and NaOH, respectively.	Although BMSC adhesion and osteogenesis were promoted, proliferation was significantly inhibited on treated surfaces.	Li <i>et al</i> ^[47]
	The titanium was treated with H ₂ O ₂ .	H ₂ O ₂ -treated surfaces were beneficial for promoting BMSC attachment, proliferation, and osteogenic differentiation.	Daw <i>et al</i> ^[52]
	The anodic oxidation was carried out to prepare nanotube on titanium surface.	NT30 supported adhesion, stretching, proliferation, and osteogenic differentiation of BMSCs.	Xu <i>et al</i> ^[24]
Electrochemical anodization	Nanonets on titanium surfaces were prepared.	BMSC cultured on nanonets structured Ti surfaces present a high frequency of alignment.	Grimalt <i>et al</i> ^[53]
	The Ti disks were micro-arc oxidized in an electrolyte solution.	The MAO-coating significantly promoted adhesion and osteogenic differentiation of BMSCs by mediating the integrin β 1 signaling pathway.	Li <i>et al</i> ^[57]
	O-PIII treatment was performed in a high-vacuum chamber with a radio frequency plasma source.	O-PIII treatment could enhance the adhesion of BMSCs.	Yang <i>et al</i> ^[59]
Plasma ion implantation and deposition	O-PIII treatment was performed in a high-vacuum chamber with a radio frequency plasma source.	The group treated with the highest concentration of oxygen ions has the best effect on adhesion, migration, proliferation, and differentiation of BMSCs.	Yang <i>et al</i> ^[60]
	The Ti-based alloy was modified by electropolishing and plasma electrolytic oxidation process.	The calcium-ion-implanted titanium remarkably improved BMSC adhesion and proliferation compared to the untreated sample.	Michalska <i>et al</i> ^[61]
	Highly ionized Ca and Mg plasmas were generated from a filtered vacuum arc source and accelerated within the electric field between a sheath and the substrates.	Initial cell attachment on a titanium surface can be improved by Ca and Mg ion implantation. In addition, the expression of osteogenic-related genes like RUNX ₂ and type I collagen was higher in the Mg ion-implanted surface.	Won <i>et al</i> ^[62]
	The Ti discs were polished with abrasive grit (grades 240–600), and then treated with laser radiation at various fluences (132, 210, or 235 J/cm ²).	Laser-modified titanium surfaces could enhance upregulation of expression of the osteogenic markers and enhance alkaline phosphatase activity of BMSCs.	Bressel <i>et al</i> ^[66]
Laser beam treatment	DMLS discs were fabricated in an argon atmosphere with Yb fibre laser system.	Topographical cues of DMLS surfaces could enhance BMSC adhesion, as well as osteogenesis.	Zheng <i>et al</i> ^[67]
	The laser system was a Ti: Sa laser chain, which delivers 120 fs, 800 nm pulses at a repetition rate of 5 kHz.	BMSCs exhibited a more elongated, spindle-like morphology and higher spreading speeds on FS laser-modified surfaces.	Dumas <i>et al</i> ^[68]

Ti: Titanium; KOH: Potassium hydroxide; ALP: Alkaline phosphatase; OCN: Osteocalcin; HF: Hydrofluoric acid; HNO₃: Nitric acid; BMSC: Bone marrow-derived mesenchymal stem cell; NaOH: Sodium hydroxide; H₂O₂: Hydrogen peroxide; MAO: Micro-arc oxidation; O-PIII: Oxygen plasma immersion ion implantation; Ca: Calcium; Mg: Magnesium; RUNX₂: Runt-related transcription factor 2; DMLS: Direct metal laser sintering; Yb: Ytterbium; FS: Femtosecond.

the oxide layer, thereby triggering hydrogen embrittlement^[43].

The acid-alkali two-step method is also used for titanium surface modification. Strong acid erosion could cause micropores on the surface of titanium and titanium

alloys to increase surface area. Meanwhile, alkaline solution can form a thicker microporous titanium oxide layer on the titanium surface, improving the titanium implant's biological activity^[44-46]. Li *et al.*^[47] first placed titanium in oxalic acid solution (5 wt%) at 100 °C for 2 h to remove the oxide layer and acquire a homogeneous micropit surface. Each pretreated titanium plate was treated in 5 mmol/L NaOH solution at 80 °C for 24 h. An *in vitro* cell experiment demonstrated that BMSC adhesion and osteogenesis can be better promoted on a micro/nanoporous surface than on an acid etched titanium surface. However, BMSC proliferation was significantly inhibited on treated surfaces after culturing for 4 and 7 days, which may be due to the high pH around the implant. The high pH at the cell/material interface may cause alkalosis and inhibit BMSC proliferation and viability^[48].

Hydrogen peroxide can also be used for activation treatment of titanium. Hydrogen peroxide treatment of titanium is a chemical dissolution and oxidation process, which could alter surface roughness, thickness, and hydrophilicity, with improvements in titanium osteoconductivity^[49-51]. In one study, titanium was treated with 30% volume (v/v) of H₂O₂ (5 mL H₂O₂/g disc) for different times in an unsealed covered container under darkness at room temperature. The modifications induced by 6-24 h H₂O₂-treated surfaces are most beneficial for maintaining or promoting the attachment, proliferation, and osteogenic differentiation of BMSCs^[52].

Electrochemical anodization

Anodization refers to the use of an electric field and various dilute acids as electrolyte solutions. A series of REDOX chemical reactions take place on the anode surface to form an oxidation layer. Due to anodization's simplicity, versatility, and low cost, it has gained widespread attention in the surface treatment of titanium implants. In a study, Xu *et al.*^[24] found that tube diameter had a significant effect on adhesion, proliferation, and differentiation of MSCs. Titanium was used as the working electrode, platinum sheet was used as the cathode, and 0.50 wt% NH₄F + 10 vol% H₂O mixture was used as the electrolyte. The anodic oxidation was carried out at 10, 30, and 60 V, which were designated as NT10, NT30, and NT60, respectively. Finally, NT10, NT30, and NT60 were obtained with pore diameters of 30, 100, and 200 nm, respectively. By comparison, although NT60 can promote osteogenic differentiation to the greatest extent, it significantly inhibits cell adhesion and proliferation. NT10 can promote cell proliferation and adhesion, but it is useless for osteogenic differentiation of cells. NT30 supported adhesion and proliferation of BMSCs, and the cells on NT30 became increasingly elongated with increased diameter and showed a large number of prominent filamentous pseudopods. Moreover, it showed better osteogenesis-inducing ability. In another study, Grimalt *et al.*^[53] produced a nanonet structure on titanium discs. BMSCs cultured on nanonet structured titanium surfaces present a high frequency of alignment and promote osteogenic differentiation of the cells, while cells on untreated titanium surfaces exhibited a random orientation.

Micro-arc oxidation (MAO) is a new type of anodic oxidation technology that deposits a ceramic coating on the metal surface, and it has been widely applied in the surface modification of titanium and its alloys to enhance biological activity and osteogenic capacity. Based on ordinary anodization, arc discharge is used to enhance and activate the reaction occurring on the anode, thereby forming a ceramic film *in situ* on the surface of titanium^[54-56]. Zhou *et al.*^[25] reported that porous coatings prepared by MAO promote BMSC adhesion and osteogenic differentiation. In addition, the larger the pore size, the more conducive to BMSC adhesion and osteogenic differentiation when the pore size is in the range of 3-10 µm. A similar phenomenon was observed in BMSCs in another study. Li *et al.*^[57] developed two kinds of coatings (MAO and MAO-Alkali coatings) with similar micro-morphologies, both of which significantly promote BMSC adhesion and osteogenic differentiation by mediating the integrin β1 signaling pathway.

Plasma ion implantation and deposition

Plasma ion implantation (PIII) is known to modify the surface and near surface regions of materials, and it has many advantages for surface modification of materials, including the following: (1) Changing the surface characteristics of the material alone without affecting the properties of the material; (2) The modified layer will not fall off or fail in combination; and (3) PIII is a low-temperature process (approximately 100 °C), and there is no change in the size of the workpiece due to thermal distortion.

PIII surface modification mainly uses plasma generated after Ar, N₂, O₂, and other gases or metal gasification to treat the material surface. Under the action of plasma, the surface of the material is bombarded with high-energy particles in the plasma. Chemical bond breakage occurs, and large molecular radicals are generated. At the

same time, the material is etched to change the surface properties. PIII of metal materials can effectively improve the mechanical properties, wear resistance, and corrosion resistance of orthopedic implants, thus enhancing their biocompatibility^[58]. Yang *et al*^[59] explored the effect of titanium treated with oxygen plasma immersion ion implantation (O-PIII) on the behavior of BMSCs with different oxygen doses. The results showed that O-PIII treatment could enhance BMSC adhesion, and there was no significant difference in the titanium surface treated with O-PIII when the oxygen ion dose differed. In their later study, Yang *et al*^[60] compared the effects of three doses of oxygen ion implantation into titanium on BMSC behavior. Among these treated titanium disks, the group treated with the highest concentration of oxygen ions has the best effect on cell adhesion, migration, proliferation, mineralization, and differentiation of BMSCs. It has been reported that calcium-ion-implanted titanium also remarkably improved BMSC adhesion and proliferation compared to the untreated sample^[61]. Similarly, other studies have evaluated the response of BMSCs to titanium surfaces that had been implanted with Ca and Mg ions using the PIIID technique. The results showed that initial cell attachment on a titanium surface can be improved by Ca and Mg ion implantation. Cells on the Mg ion-implanted surface showed more extended filopodia after 4 and 24 h of cultivation. In addition, the expression of genes associated with osteogenic differentiation like RUNX₂ and type I collagen was higher in the Mg ion-implanted surface^[62]. These results are consistent with previous studies showing that significant cytotoxicity was not observed after Mg ion implantation into a titanium implant, and initial BMSC adhesion was improved with resulting osteoblast differentiation enhancement^[63].

Laser beam treatment

Laser beam treatment is a controllable and flexible approach to modifying surfaces, which results in surfaces with increased surface area and enhanced wettability, and it displays negligible corrosion and high removal torques of established implants in preclinical bone models^[64,65]. Laser-modified titanium surfaces could enhance upregulation of expression of the osteogenic markers and enhance alkaline phosphatase activity of BMSCs^[66]. A recent investigation on the direct metal laser sintering (DMLS) titanium surface found that topographical cues of DMLS surfaces could enhance both protein adsorption ability and BMSC adhesion performance. Moreover, DMLS titanium surface could efficiently induce osteogenesis-associated gene expression in BMSCs *via* H3K27 demethylation and increases in H3K4me3 levels at gene promoters after osteogenic differentiation^[67]. In another study, dynamic analyses of early cellular events showed that BMSCs exhibited a more elongated, spindle-like morphology and higher spreading speeds on femtosecond laser-modified surfaces compared to commercially pure titanium^[68].

COVALENT IMMOBILIZATION BIOACTIVE MOLECULES TO PROMOTE BONE MARROW MESENCHYMAL STEM CELL ADHESION, PROLIFERATION, AND OSTEOGENIC DIFFERENTIATION

The basic principle of the above physical and chemical methods is to change the physical and chemical characteristics of the metal matrix surface to improve the biocompatibility of the material and BMSC growth inductivity, which is an indirect surface modification method. However, the application of biochemical technology proposed by David A Puleo to improve the surface activity of implants provides a different approach to surface modification from the traditional physical and chemical methods^[69]. Contrary to topography-based approaches, biochemical surface modification utilizes macromolecules like extracellular matrix components, peptides, cell growth factors, and others to be fixed on the surface of biomaterials to act as receptors for adjacent cells, matrices, and soluble factors, which form a transition layer suitable for living organisms to control the tissue-implant interface^[70]. In this section, we list different types of titanium-implant-bound macromolecules that have been shown to influence BMSC behavior. The overall data are listed in [Table 3](#).

Extracellular matrix components

The extracellular matrix (ECM) is composed of several molecules secreted by cells. In addition to providing structural and mechanical support for tissues to interact with cells, these molecules can also bind to soluble molecules like growth factors that are present in extracellular fluid and regulate the occurrence of tissues and physiological

Table 3 Covalent immobilization bioactive molecules to promote bone marrow mesenchymal stem cell adhesion, proliferation, and osteogenic differentiation

Bioactive molecules	Treatment process	Cell response	Ref.
Type I collagen	Titanium fiber meshes were treated with NaOH, followed by p-nitrophenyl chloroformate, and coated with collagen type I.	The modification of titanium fiber meshes can promote BMSC osteogenic differentiation.	van den Dolder <i>et al</i> ^[72]
	Covalent immobilization of collagen on titanium.	Greater regulation effect on BMSC osteogenesis compared to adsorptive immobilization.	Ao <i>et al</i> ^[74]
	Hyaluronic acid was immobilized on titanium surface by layer-by-layer technique.	BMSCs had more lamellipodia and adhered more closely to the covalently immobilized HyA surface.	Ao <i>et al</i> ^[78]
HyA	Covalent immobilization of RGD peptide on titanium surface.	RGD-functionalized titanium can improve early bone growth and matrix mineralization.	Elmengaard <i>et al</i> ^[87] , Karaman <i>et al</i> ^[88]
RGD peptide	HBII-RGD was immobilized on the Ti surface.	HBII-RGD-functionalized Ti surfaces could stimulate BMSC differentiation and mineralization.	Guillem-Marti <i>et al</i> ^[90]
Growth factors	Covalently graft EGF and BMP-2 onto the oxide surfaces.	BMSC adhesion and proliferation were dramatically increased by covalently grafting EGF, but covalently grafted BMP-2 did not.	Bauer <i>et al</i> ^[92]
	PDGF-BB loading on titanium nanotube.	PDGF-BB functionalized surfaces significantly enhanced BMSC attachment and osteogenesis-related functions	Ma <i>et al</i> ^[98]

NaOH: Sodium hydroxide; BMSC: Bone marrow-derived mesenchymal stem cell; HyA: Hyaluronic acid; RGD: Arg-Gly-Asp; HBII-RGD: Heparin binding II-Arg-Gly-Asp; Ti: Titanium; EGF: Epidermal growth factor; BMP-2: Bone morphogenetic protein-2; PDGF-BB: Platelet-derived growth factor BB.

activities of cells. The ECM provides a framework for tissue construction and plays an important role in regulating the survival, migration, proliferation, morphology, and other functions of cells in contact with it. Therefore, ECM components are the first choice for the biochemical surface modification of titanium-based bone implant materials.

TYPE I COLLAGEN

Collagen type I, one of the main organic components of bone ECM, is known to play an important role during adhesion, proliferation, and mineralization processes and osteogenic differentiation of cells, and it is an intriguing candidate for surface immobilization^[71]. Dolder *et al*^[72] showed that the modification of titanium alloy by type I collagen can promote BMSC osteogenic differentiation.

Morra *et al*^[73] fixed collagen I to the surface of titanium (denoted as Col-Ti), finding that enhanced BMSC adhesion and cell density on Col-Ti, together with increased cell spreading areas on the microscopic surface morphology. RT-PCR analysis of several osteogenic related genes showed that the titanium surface immobilized on type I collagen could significantly promote BMSC osteogenic differentiation.

In another study, Ao and his team also found that immobilizing type I collagen on a titanium coating could enhance interactions between cells and materials and improve BMSC functions like adhesion, proliferation, and osteogenic differentiation. Furthermore, they compared the effects of different type I collagen fixation methods on BMSC behavior. They concluded that covalent immobilized collagen on titanium coating has a greater regulation effect on BMSC osteogenesis in contrast to adsorptive immobilization, which can be explained from the perspective of increasing the amount of covalently connected collagen and improving stability^[74].

HYALURONIC ACID

Hyaluronic acid (HyA) is rich in carboxyl groups, and it is another major ECM component that possesses good biocompatibility, degradability, and low antigenicity. In addition, HyA could enhance cell migration and proliferation^[75-77]. Based on HyA's excellent properties, Ao *et al*^[78] fabricated a titanium coating modified with HyA by covalent immobilization. They confirmed that BMSCs had more lamellipodia and

adhered more closely to the covalent immobilized HyA surface than untreated samples. Other *in vitro* cell experiments have also shown that HyA immobilization on titanium coatings could significantly enhance BMSC attachment, proliferation, and differentiation. Furthermore, Ao *et al*^[79] prepared a stable collagen/HyA (Col/HyA) polyelectrolyte multilayer (PEM) film on a titanium coating using a combination of the layer-by-layer self-assembly technique and covalent immobilization. The results showed that BMSCs displayed a polygonal and fusiform-shaped morphology, and cell adhesion and proliferation on the material were also improved. In other words, the construction of Col/HyA PEMs on TCs improved the cell-material interaction. The induction of osteogenic differentiation was further determined using qPCR, and the results confirmed that stable Col/HyA PEM could significantly enhance BMSC osteogenic differentiation.

Peptide sequence

It has been found that some short peptides in ECM proteins play important roles in cell behavior regulation^[80,81]. Among different ECM proteins, fibronectin (FN), a multifunctional cell adhesive glycoprotein, is one of the most well-known and commonly used to functionalize biological materials. It contains several domains that mediate many cellular processes like cell adhesion, migration, growth, and differentiation. The use of FN-functionalized titanium implants has been shown to improve bone conduction capacity for its ability to attach cells to ECM components *via* integrin receptor interactions^[82]. Chen *et al*^[83] fixed FN on the surface of titanium, and BMSCs exhibited substantial actin polymerization, in the form of lamellipodia, pseudopodia, and actin stress fiber. However, the cells retained a rounded morphology on untreated surface. Besides, FN-functionalized titanium had a significant positive effect on BMSC proliferation compared to the control. However, its use for clinical applications is hampered due to poor stability, high production costs, and poor ECM protein immunogenicity, which have reduced their biomedical potential^[84]. The use of ECM-derived synthetic peptides containing the functional domains of ECM proteins is an effective method to overcome these problems. Therefore, the synthesis of short peptide fragments representing ECM proteins and the modification of titanium-based implants have been gradually developed^[85,86]. The most commonly used peptide sequence for surface modification is the arginine-glycine-aspartic acid (RGD) motif. RGD-functionalized titanium can improve early bone growth and matrix mineralization, and it can enhance the combination of materials and new bone^[87]. There have been several reports on the effects of RGD on BMSCs. In a study, Karaman *et al*^[88] covalently attached RGD peptide to titanium discs. The results indicated that RGD peptide treatment significantly enhanced BMSC adhesion and proliferation. Furthermore, this effect was enhanced by combining cold temperature plasma treatment and RGD peptide coating. Consistent with this, Herranz *et al*^[89] concluded that the RGD motif was more favorable for BMSC adhesion, proliferation, and osteogenic differentiation in contrast to fibronectin. In another study, Jordi and his group covalently attached a novel molecule on the titanium surface. The novel molecule possesses adhesion capacity by an RGD gain-of function DNA mutation installed to the heparin binding II (HBII) fragment. The presence of RGD in the HBII domain stimulated focal adhesion formation at BMSC edges where filopodia were spikier compared to bare titanium samples with completely round cells. In addition, HBII-RGD-functionalized titanium surfaces could also stimulate BMSC differentiation and mineralization^[90].

Growth factors

Growth factors are a class of proteins secreted by cells that act as signaling mediators for the relevant target cells to perform specific behaviors. Growth factors can promote cell proliferation, differentiation, protein synthesis, and migration of specific cells. Growth factors released from the implant surface can increase osteoblast activity and facilitate bone tissue regeneration^[91]. Many researchers have been depositing growth factors on biomaterials to affect cell behavior. In one study, Bauer *et al*^[92] showed the covalent immobilization of two growth factors, epidermal growth factor (EGF) and bone morphogenetic protein-2 (BMP-2), on the surface of TiO₂ nanotubes and their effects on BMSC behavior. Cell adhesion and proliferation were dramatically increased by covalently grafting EGF on a surface of a 100 nm nanotube, but covalently grafted BMP-2 did not. The result was consistent with the finding of previous studies that BMP-2 promotes BMSC differentiation into osteoblast lineages but does not contribute to the cell attachment, adhesion, or proliferation like EGF^[93]. Studies on BMP-2's effect on BMSC differentiation have shown that BMP-2 has a significant effect on osteoblast differentiation potential^[94].

Platelet derived growth factor (PDGF) has been shown to play critical roles in bone regeneration after injury, and it significantly contributes to all stages of bone regeneration after trauma^[95,96]. Among three types of dimerism, PDGF-AA, -BB, and -AB, PDGF-BB exerts the most potent chemotactic effects on BMSCs^[97]. Ma *et al.*^[98] fabricated a nano-micro hierarchical TiO₂ clustered nanotubular structure using anodization, and PDGF-BB was functionalized with PhoA (11-hydroxyphosphonic acid)/CDI (carbonyldiimidazole). The resulting new material had almost no cytotoxicity to host cells, and it significantly enhanced BMSC attachment and osteogenesis-related functions (early proliferation, extracellular matrix synthesis, and mineralization).

LOCAL CONTROL RELEASE OF BIOACTIVE MOLECULES TO PROMOTE BONE MARROW MESENCHYMAL STEM CELL ADHESION, PROLIFERATION, AND OSTEOGENIC DIFFERENTIATION

Recently, many researchers have focused on biomolecule-controlled release. This controlled release system overcomes the limitation of rapid degeneration and diffusion of biomolecules in the body, which may decrease biomolecule doses, reduce costs, and more importantly, minimize side effects of high-dose biomolecules. An effective controlled-release system can encapsulate bioactive cues in biocompatible and biodegradable microparticles. As the microparticles gradually degrade, biological molecules are released with predesigned dose kinetics over time^[99-101]. The key to making bioactive molecules work is their release so that they can induce the required biological response. Many bioactive molecules can be used in this kind of sustained-release system, including growth factors, short peptides, clinical drugs, and others. By sustained release on the implant surface, cell adhesion, proliferation, differentiation, and other behaviors can be regulated, thus improving the implant's biocompatibility. Table 4 lists the commonly used bioactive molecules and their cellular responses reported in the recent literature.

Coating biodegradable polymers is an effective method to control the drug release kinetics from titanium. In a study, Kim *et al.*^[102] prepared a new dopamine coating that enhances the initial cell adhesion, mitochondrial activity, and proliferation of BMSCs on the titanium surface. Son *et al.*^[103] successfully developed hydroxyapatite (HA)-titanium disc surfaces immobilized with dexamethasone (DEX)-loaded poly(lactic-co-glycolic acid) (PLGA) particles using a low-temperature high-speed collision method. The evaluation of HA-titanium surfaces with a particle carrier system potently induced BMSC differentiation *in vitro*. This showed that the gene expression levels of ALP, OPN, BSP, and OC were enhanced, and these functional surfaces showed greater osteoinductivity than pure-Ti and HA-Ti surfaces. Cheng *et al.*^[104] used catechol as a template to modify a photo-crosslinked gel-based hydrogel to enhance its adhesion to the titanium surface, thereby improving the coating's stability. Synthetic silicate nanoparticles (SNs) were introduced into the hydrogel formulation. The results showed that the addition of SNs to the hydrogel formulation can promote bone formation when co-cultured with BMSCs, suggesting the potential to promote new bone formation in surrounding tissues.

APPROACH TO INDIRECTLY AFFECT BONE MARROW MESENCHYMAL STEM CELL ADHESION, PROLIFERATION, AND OSTEOGENIC DIFFERENTIATION

In fact, once implanted, metallic implants would adsorb various proteins, elicit a clotting reaction, trigger an innate inflammatory response, and induce the bone regeneration process^[105-107]. Intrinsic inflammation is undesirable but inevitable, and the result of the inflammatory response plays a vital role in the formation of new bone in and material around after implantation^[108]. Therefore, it is important to take into account the immunomodulatory effects of biological materials^[109]. Specifically, macrophages are involved in almost all-natural wound healing processes. Macrophage polarization has an important effect on wound healing and the biological properties of biological materials^[110]. As the key participants of innate host immunity, classically (M1) and alternatively (M2) activated macrophages, the two main phenotypes, are pro-inflammatory and anti-inflammatory, respectively^[111]. M1 macrophages express

Table 4 Local control release of bioactive molecules to promote bone marrow mesenchymal stem cell adhesion, proliferation, and osteogenic differentiation

Bioactive molecule	Cell response	Ref.
L-DOPA	The new L-DOPA coating enhances the initial cell adhesion, mitochondrial activity, and proliferation of BMSCs on the titanium surface.	Kim <i>et al</i> ^[102]
DEX	The HA-Ti surfaces with DEX carrier system potently induce BMSC osteogenic differentiation <i>in vitro</i> .	Son <i>et al</i> ^[103]
SNs	The addition of SNs to the hydrogel formulation can promote bone formation when co-cultured with BMSCs.	Cheng <i>et al</i> ^[104]

L-DOPA: L-3,4-dihydroxyphenylalanine; BMSCs: Bone marrow-derived mesenchymal stem cells; HA: Hydroxyapatite; Ti: Titanium; DEX: Dexamethasone; SNs: Silicate nanoparticles.

high levels of interleukin (IL)-1 β , IL-6, tumor necrosis factor alpha (TNF- α), monocyte chemoattractant protein-1, inducible nitric oxide synthase, and others. M2 macrophages synthesize IL-10, arginase-1, vascular endothelial growth factor A, and platelet-derived growth factor-BB (PDGF-BB), which support the homing, proliferation, and osteogenic differentiation of BMSCs^[112].

Successful biomaterial implantation can be achieved by controlling immune system activation. Hence, many researchers have focused on indirectly regulating the behavior of BMSCs by regulating macrophage polarization. In a study, patterned titanium coatings were prepared by combining grit-blasting, ultrasonic washing, and atmosphere plasma spray which copper meshes were applied to block the molten titanium droplet when spraying. Macrophages tend to polarize to M2 on a patterned titanium surface, while macrophages on traditional titanium coatings exhibit higher M1 polarization.

Up-regulation of osteoinductive cytokines was detected, suggesting that macrophages provide a favorable osteogenic microenvironment^[113]. In our previous study, a multi-biofunctional titanium implant was fabricated by covalently immobilizing titanium with the bacitracin. *In vitro* cell biology experiments showed that bacitracin-immobilized titanium could inhibit the secretion of inflammatory factors like TNF- α , IL-6, IL-8, and others, which represent M1 polarization of macrophages, and significantly promote the adhesion, proliferation, and osteogenic differentiation of BMSCs^[114]. In another study, Ma *et al*^[115] evaluated the osteogenic behavior of BMSCs on TiO₂ nanotubular (NT) surfaces in conditioned medium (CM) generated by macrophages. BMSC morphology in CM from macrophages cultured on the NT surfaces was aligned in a consistent direction, while an unordered distribution was observed on the pure titanium surface. In addition, the modified titanium dioxide surface and CM in monocytes cultured on the surface jointly promoted the proliferation, migration, and osteogenic differentiation of BMSCs. The transition of macrophages from M1 to M2 at specific time points is very important for wound healing and tissue regeneration. In a recent study, a dual system hydrogel layer (chitosan/ β -glycerophosphate disodium and carboxymethyl chitosan/genipin) of titanium dioxide nanotubes was fabricated to regulate the release of IL-4 and interferon- γ (IFN- γ). In the culture with BMSCs and macrophages, the system showed good cell compatibility and significantly promoted cell proliferation^[116].

PERSPECTIVE OF OSTEOGENESIS ON TITANIUM SURFACE

BMSCs are used as core cells for the renewal and repair of local bone, cartilage, and medullary adipose tissue^[117]. BMSCs perceive the titanium surface and become activated during the osteogenesis and osteointegration phases. BMSCs then establish contact with the titanium surface and maintain this relationship until they differentiate into osteoblasts and osteocytes, subsequently embedding in the mineralized matrix^[118]. At present, many researchers are mainly focused on the effect of different modification methods on the behavior of BMSCs and have made great progress. However, problems also exist in the modified implants such as poor biological safety and poor stability^[119].

In addition, it is important to note that there are great limitations to the existing methods of judging osteogenesis on titanium surface, and the current means of skeletal muscles mainly rely on magnetic resonance imaging (MRI), X-ray computed

tomography, and X-rays^[120,121]. Nevertheless, there is still no effective method for the bone integration evaluation on metal implants, which can only rely on pathological biopsy examination. Therefore, the evaluation of osteogenesis on the surface of titanium and its alloys *in vivo* may be an important research target in the future. And more in depth basic and clinical research is necessary to develop more products.

CONCLUSION

In this article, we have summarized recent advances in the approaches for surface modification of titanium and its alloys, and systematically elaborated these modification methods and their effects on cell behavior. The methods like sol-gel, ion implantation, anodization, and micro-arc oxidation can promote osteogenic differentiation of BMSCs and improve the rate of osseointegration by changing surface roughness and hydrophilicity, or regulate the microenvironment of the bone-implant interface. We recommend that the application of modern surfaces in the clinical practice of orthopedics be encouraged to increase and accelerate the osseointegration of the implant and its alloys. To the best of our knowledge, few researchers have done similar work, so we hope that our work might develop some ideas for better methods to improve osseointegration efficiency.

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