Heliyon 9 (2023) e16309

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Potential application of inorganic nano-materials in modulation of macrophage function: Possible application in bone tissue engineering

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ARTICLE INFO

Keywords:
Bone regeneration
Inorganic nano-structure
Osteo-immunomodulation
Osteo-inductive biomolecules
Macrophage polarization

ABSTRACT

Nanomaterials indicate unique physicochemical properties for drug delivery in osteogenesis. Benefiting from high surface area grades, high volume ratio, ease of functionalization by biological targeting moieties, and small size empower nanomaterials to pass through biological barriers for efficient targeting. Inorganic nanomaterials for bone regeneration include inorganic synthetic polymers, ceramic nanoparticles, metallic nanoparticles, and magnetic nanoparticles. These nanoparticles can effectively modulate macrophage polarization and function, as one of the leading players in osteogenesis. Bone healing procedures in close cooperation with the immune system. Inflammation is one of the leading triggers of the bone fracture healing barrier. Macrophages commence anti-inflammatory signaling along with revascularization in the damaged site to promote the formation of a soft callus, bone mineralization, and bone remodeling. In this review, we will discuss the role of macrophages in bone hemostasis and regeneration. Furthermore, we will summarize the influence of the various inorganic nanoparticles on macrophage polarization and function in the benefit of osteogenesis.

1. Introduction

Bone is considered as a mechanical supporter and shield of the most important tissue [1,2]. Bone fractures are majorly occurring as a result of inappropriate or incompetent bone regeneration [3]. Bone and bone-associated diseases are challenging clinical conditions that are considered to account for more than 50% of the chronic diseases in the aged population (over 50 years). Bone healing/-regeneration is not able to instinctively repair large segmental fractures, which are serious orthopaedics problems in clinics [4,5]. Application of autologous bone grafting, as the gold standard approach, is a current treatment for large bone defects that is mostly limited in clinics under the influence of bone grafting secondary damages (post-surgery nerve injuries and infections), high levels of donor site morbidity or chronic pain, special shape limitation and the low availability of autogenous bones [5,6]. Bone allografts are alternative strategies that apply donor tissues for implantations which are majorly potent for sharing of diseases; infections and induction of inciting immune responses. Therefore, there are numerous attempts to overcome complications of bone grafting by the

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https://doi.org/10.1016/j.heliyon.2023.e16309
Received 30 December 2022; Received in revised form 11 May 2023; Accepted 12 May 2023
Available online 27 May 2023

application of natural or synthetic biomaterials for bone tissue regeneration (BTR) [6,7].

Tissue engineering combines multidisciplinary approaches to develop or substitute biologically damaged tissues. The bone scaffold structure consists of porous biodegradable materials which provide mechanical support for the repair and regeneration of injured or diseased bone tissues. Most bone tissue engineering experiments are focused on providing the scaffold of different materials for structural support as appropriate angiogenesis and osteogenesis option [8,9]. To better mimic and support the nanostructure in the bone's natural extracellular matrix (ECM), various scaffolds are produced to provide effective resembling of the bone ECM and replacement of damaged bone tissues [10].

Macrophages are a subset of innate immune cells which are finable almost nearby of all tissues, these cells play a crucial role in preserving normal tissue homeostasis [11]. Macrophages population have a great tendency to be in the damaged sites which are resulted from infection and inflammation, the regional and circulating monocyte support this increase in the affected area [12]. The main role of the macrophages in damaged sites is the restoration of tissue homeostasis by modulating inflammation responses through phagocytosing invading microorganisms (in infection) and recruitment of the other immune cells [13]. Following clearance of the tissue-damaging factors by macrophages, these cells commit to supporting tissue regeneration by producing anti-inflammatory and growth factors and recruiting progenitor cells in damaged sites. The released growth factors can regulate the differentiation of progenitor cells, precisely toward angiogenesis [11,13,14]. Polarization is a concept to define the functional plasticity of the macrophages; M1 macrophages are activated immune cells that participate in modulation of the inflammation in damaged sites and M2 macrophages are alternatively activated immune cells that provide tissue regeneration, remarkably macrophages are able to switch between M1 and M2 classes [15,16]. Macrophages are one of the first cells that arrive to the bone fracture sites, these cells can contribute to the regulation of bone regeneration within normal bone homeostasis and fracture healing [1,17].

Inorganic materials (bioceramics and bioglasses) are extensively applied in bone tissue engineering because of their great bioactivity and osteo-integration in comparison to metals and polymers. Components and crystallinity of inorganic materials are crucial factors for determining their Physico-chemical and biological characteristics which can alter the in vivo bone formation capability [18,19]. The line of evidence confirms that nano-biomaterials provide greater options for osteo-conductivity and multifunction. The morphology and size of the nano-biomaterials and surface nanostructure of the scaffolds are crucial factors for modulating target stem cell attachment, proliferation, and differentiation for bone formation [10,20–22]. In this review, we briefly explained the bone structure, matrix, and associated cells in bone repair and regeneration. Also, we discussed the role of the macrophages inflammatory role and dependent polarization in bone hemostasis and regeneration. Finally, we summarized the influence of the various inorganic nanoparticles in bone healing with the main focus on macrophage polarization.

2. Bone structure, matrix, cells and repair mechanism

Bone structure is not homogeneously solid; it is consisted of the outsider supportive solid structure to provide the toughening of the bone but the insider medium is abundant in living bone cells that establish a scaffold-like structure (bio-mineral medium) to provide hemostasis of the bone [23].

The bio-mineral medium of the bone mainly consists of the organic (30%) and inorganic (70%) segments [24]. Collagen is the major compound of the organic segment (90%) and non-collagenous proteins, lipids, proteoglycans, osteopontin, and other bone matrix proteins comprise a small fraction of this segment (10%) [25]. The matrix proteins in the bio-mineral medium support the mechanical strength and tissue adhesive of the bone cells. Mainly, the mineral segment of the bone is rich in hexagonal hydroxyapatite (HA) crystals which are organized parallel to the long axes of collagen fibers [26,27].

Bone contains four main cells including osteogenic, osteoblasts, osteocytes, and osteoclasts which contribute to bone function, regeneration, and structure [28]. Osteoblasts (or MSC or osteo-progenitor cells) can differentiate and proliferate toward osteoblasts prior to bone formation; these cells are affected by bone morphogenetic proteins (BMPs). Osteoblasts control the growth or remodeling of bone by modulating the synthesis, deposition, and mineralization of the bone matrix through the production of the osteoid [29–32]. The only cells with the ability to division in bone are osteogenic cells that can differentiate and develop toward osteoblasts which, in turn, form new bones [33]. Osteocytes are star-shaped cells and are the most abundant cells in bone tissue [34]. These cells provide the crucial connections between osteocytes and osteoblasts to support communications within bone tissue. Also, osteocytes can regulate calcium and phosphate homeostasis in bone, therefore any possible malfunction leads to osteoporosis [35,36]. Osteoclasts are responsible for resorption by releasing dissolving enzymes and acids to break down and digest minerals in bone. These cells support the remodeling of the damaged bones and facilitate the creation of channels for nerves and blood vessels. Excessive activity of the osteoclasts can lead to osteoporosis [28,36].

Bone fracture repair is comprised of three main steps: inflammation, bone production, and bone remodeling which includes the participation of progenitor cells accompanied by inflammatory, endothelial and hematopoietic cells at the damage site [37]. Hematoma formation at the broken sites of the bone causes inflammation as the primary response to bone damage which lasts for several days [30,38]. Substitution of the coagulated blood in the damaged site by fibro-cartilaginous callus triggers the bone repair mechanism. During bone regeneration, the soft callus gradually switches to a bony callus (hard bone). Bone remodeling is the final step in bone regeneration [6,39].

3. Role of macrophages in bone hemostasis and regeneration

For the bone healing process, the skeletal system directly cooperates with the immune system.

Several studies demonstrated immune microenvironment has a crucial role in the regulation of growth, differentiation, rebuilding

of bone tissue, and surrounding soft tissue.

Hence, control of immune components and microenvironment can be helpful in bone regeneration and fracture healing process [40,41]. Hematoma and inflammation are the main triggers for commencing the bone fracture healing procedures, also initiate anti-inflammatory signaling and revascularization in the damaged site to promote the formation of a soft callus, bone mineralization, and remodeling [42].

The initial immune response to bone fracture consists mainly of the innate immune system including neutrophils, mast cells, monocytes, and macrophages, and the later immune response usually consists of an adaptive immune system including T and B cells. These systems release several inflammatory cytokines and chemokines that can influence the bone remodeling process [43,44]. Neutrophils, as the most abundant leukocytes in the blood of mammals, play an important role in the innate immune system and are usually the first cells to be recruited to inflammatory sites after injury and play a vital role in regulating bone homeostasis in the early stages of bone Repair [45].

Neutrophils can release a variety of cytokines that alter monocyte and macrophage recruitment and polarization in the bone repair process. In addition, as shown in some studies in mouse bone fracture models, neutrophil depletion leads to impaired bone healing after fracture [46].

Regarding the complexity of bone fracture healing, macrophages are the dominant phagocytic cells that are continuously present in all healing phases [47] Macrophages are heterogeneous groups of cells that are not able to divide easily into further subsets. There are various macrophage subsets that indicate unique functions depending on their anatomical location [48]. Macrophages can affect the process of inflammation or bone remodeling by being polarized to either M1 or M2 types, and the M1/M2 ratio modulates the results of bone repair [1].

Bone tissue comprises a set of residential macrophages known as osteomacs which are located through bone lining cells in both endosteum and periosteum structures [49]. Osteomacs are closely linked to the bone formation regions and form a canopy-like structure over active cuboidal osteoblasts. Lack of macrophages in the macrophage-fas-induced apoptosis model leads to suppression of the active bone-forming surface of osteoblasts and demonstrates a key role for the macrophages in osteoblast-mediated bone formation [49,50]. Also, there is a report that genetically modified mouse models that lack Lysozyme-M-expressing cells (especially macrophages) indicate comprised post-natal bone growth. Furthermore, in some in vivo studies, macrophage-deficient mice have a reduced ability to regenerate bone after fracture, suggesting M2 macrophages can stimulate osteoblast differentiation [51,52].

Macrophages are crucial cells in both intramembranous and endochondral routes of the bones for fracture healing. Macrophages are tightly linked to osteoblast depositing in the murine model of intramembranous bone formation and continuously regenerate bone at the fracture site during all stages of the healing, also remove of the macrophages from fracture sites leads to the defective bone healing process [53–55]. During bone fracture and hematoma formation, pro-inflammatory factors (i.e., IL-1, IL-6, TNF-α, and IFN-γ) recruit and differentiate monocytes into type 1 (M1) macrophages. M1 cells are associated with the main acute inflammatory stages of bone regeneration, removing the area of dead cells and debris and releasing some cytokines to initiate the first phase of the bone healing process [56].

In addition, several studies have shown that M1 macrophages stimulate the osteogenic differentiation of BMSCs by synthesizing cytokines including OSM, TNF-α, and IL-6, which positively affects bone regeneration [57–59]. In 2021, Hong Lei et al. showed that M1 macrophages modulated by methyltransferase 3 (METTL3) play an important role in the osteogenic differentiation of BMSCs, and

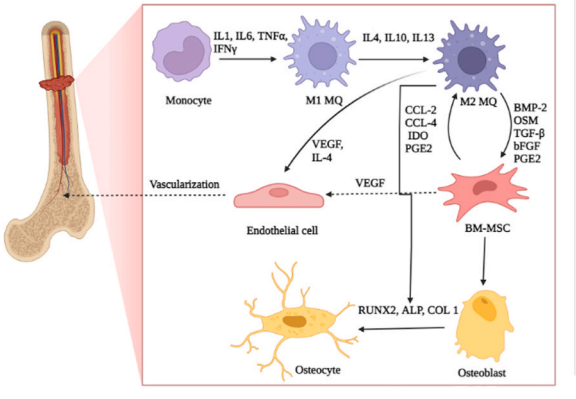

Fig. 1. Involving of macrophages in bone healing. Upon bone fracture and hematoma formation, the pro-inflammatory factors (i.e., IL-1, IL-6, TNF-α, and IFN-γ) recruit and differentiate monocytes into macrophages type 1 (M1 MQ) to clear the area of dead cells and debris. After that, anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 polarized M1 to M2 phenotype. Activated M2 phenotypes stimulate MSCs to induce initiate osteogenesis and angiogenesis by TGFβ, PGE2, bFGF, BMP-2, and OSM. Vice versa, activated MSCs-derived factors including CCL2/4, IDO and PGE2 mediate more M2 type infiltration and activation to accelerate bone healing. M2 type also upregulates RUNX2, COL 1 and ALP in osteoblast toward osteocyte differentiation. **Abbreviations**: MSCs, mesenchymal stem cells; TGFβ, transforming growth factor β; BMP-2, bone morphogenetic proteins −2; OSM, Oncostatin M; CCL2/4, C–C motif chemokine ligand 2/4; bFGF, basic fibroblast growth factor; IDO, indoleamine-2,3-dioxygenase; PGE-2, prostaglandin E2; RUNX2, RUNX, Family Transcription Factor 2; COL1, collagen type I; ALP, alkaline phosphatase; VEGF, vascular endothelial growth factor.

the expression of METTL3 was positively associated with the polarization of M1 macrophages [60]. Furthermore, M1 signaling by IL-12 and IFN-γ has been confirmed to inhibit osteoclast differentiation [61,62].

In another study, Laura Y. Lu et al. showed that pro-inflammatory macrophages (M1) can stimulate osteogenesis and bone mineralization of MSCs early in co-culture by the COX-2-PGE2-pathway [63]. Moreover, anti-inflammatory cytokines such as IL-4, IL-10, IL-13, and TGFβ polarized M1 to M2 phenotypes have a key role in osteogenesis and activated M2 phenotypes, stimulating MSCs to induce initiate osteogenesis, and angiogenesis by releasing TGFβ, PGE2, bFGF, BMP-2, BMP-4, and OSM [64,65].

Conversely, activated MSC-derived factors, including CCL2/4, IDO, and PGE2, mediate further M2-type infiltration and activation to accelerate bone healing. The M2 variant also regulates RUNX2, COL 1, and ALP in osteoblasts towards osteocyte differentiation (Fig. 1) [66].

Also, macrophages contribute to endochondral bone formation, it is reported that these cells were tightly linked to the formation of cartilage in the soft callus in the murine model of endochondral fracture healing [67]. Removing the macrophages from the early phases of the inflammation suppresses the production of the cartilagenous soft callus, also elimination of these cells in later stages leads to smaller callus in murine models. These data indicate that the size of the callus is in direct correlation with the number of the macrophages in callus [51]. Contrary to the crucial role of macrophages in inflammation and bone production, these cells are largely absent in the remodeling of bone [42,67]. The M2 macrophage population has different subsets, including M2a, M2b, and M2c which have their own distinct markers and functions and play a key role in the latest phases of bone healing and remodeling stage, for example, M2c macrophages are induced by IL-10 and have a key role in the tissue remodeling stage by releasing IL-10 and TGF-β, furthermore in the remodeling phase several pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α are highly express and make a balance between osteoclastic and osteoblastic activity to restore the bones original shape, structure, and mechanical properties which named bone remodeling [1,68]. Therefore, macrophages are important cells for intramembranous and endochondral fracture healing besides maintaining normal bone tissue homeostasis.

However, macrophages take slightly different roles in intramembranous and endochondral fracture healing. These cells contribute to the deposition of woven bone in intramembranous bone formation mode but promote formation of the soft callus in endochondral bone formation mode [42,49,51,53,55,67].

Nevertheless, the roles and functions of M1 and M2 macrophages in bone regeneration remain controversial, but it revealed they have complementary work and complete each other in the osteogenesis process and further studies need to reveal unsaid issues in this field.

4. Nano-structured materials and macrophages cross-talk for bone regeneration

Unique physical and chemical properties of nanomaterials candidates for drug delivery systems, these materials benefit from high surface area grades, high volume ratio that enables them for effective drug loading, ease of functionalization by biological targeting moieties, and small size that enables them to pass through biological barriers for efficient targeting [69]. Inorganic materials indicate great bio-activity and osteo-integration in comparison to polymers and metals, therefore these materials are extensively applied for bone repair [18,19]. The bone is mostly composed of inorganic materials including hydroxyapatite [HA: Ca10(PO4)6(OH)2] and whitlockite [Ca18Mg2(HPO4)2(PO4)12], inorganic nanomaterials are highly similar to these materials in structural and mechanical proprieties [69,70]. Also, nano-materials have greater osteo-conductivity and are multifunctional materials in contrast to inorganic materials [10,20]. Nanomaterials are able to provide novel strategies in bone regeneration; the nanostructured scaffolds indicate closer structural support approximation to native bone architecture for attachment of the cells and modulate the regulation of cell proliferation, differentiation, and migration. Various nanomaterials are reported to be used for nano-scaffolds for bone tissue engineering which are between 1 and 100 nm, these nanomaterials include Nano-patterns, Nano-fibers, Nano-tubes, Nano-pores, Nano-spheres, and Nano-composites [8,71]. Ideal scaffolds offer temporary mechanical support for target sites, also they can represent 3-dimensional (3D) shapes and are porous, bio-conductive, biocompatible, and bio-resorb able. Therefore, scaffolds should mimic native cell arrangements and diffusion features properly to avoid tissue necrosis and appropriately facilitates cell attachment, proliferation, differentiation, and cell-cell communication [72]. Various nanomaterials are studied as scaffold fillers to investigate their effect on target cells; in the following, we summarized the effect of the different nanomaterials on macrophages during bone regeneration.

Various biomaterials are applied as implantable medical devices in bone regeneration which can trigger an inflammatory response that is crucial for activation of macrophages. These cells can act as pro-inflammatory (M1) and anti-inflammatory macrophages (M2), the balance between M1 and M2 is critical for initiation of the healing and remodeling of the injured tissues [73]. Embedded biomaterials in implantations strongly provoke the recruitment of the macrophages and their pro-inflammatory and pro-wound healing responses. Polarization of the macrophages can be affected by diverse properties of the materials such as topography, and surface chemistry [73,74]. The surface properties of the biomaterial can influence the concentrations and kinds of the adsorbed proteins. These features are key players in the inflammatory and wound healing responses towards implantable biomaterials [75]. Consequently, the presence of the newly taught layer of proteins dictates the activation of the extrinsic and intrinsic coagulation systems, the complement system, platelets, and immune cells and directs their interactions toward the formation of an initial thrombus at the interface between tissue and material surface, also known as the transient provisional matrix [68]. The presence of nanomaterials in biological environments is accompanied by the formation of protein corona at the outer layer. This corona protein pattern can play a crucial role in macrophage behavior [76].

In general, when biomaterials are implanted into the body, the host response is stimulated and the immune system triggers a variety of biochemical signals and stimulates the recruitment of different immune cells to the area of the implanted biomaterials, and secretion of these signaling molecules has a key role in the regeneration process [77]. Activated immune cells and macrophages can adhere to the

implanted biomaterials, and some properties of these materials play an important role in macrophage vascularity, plasticity, and polarization, which affect the bone healing process [78]. Some of these important features are below.

4.1. Physical properties of biomaterials for osteogenesis

The physical properties of NMs such as roughness, topography, porosity, and pore size can affect macrophage polarization and related cellular function in the bone formation process [79,80].

The surface of biomaterials roughness has been reported to improve the adhesion, proliferation, and differentiation of osteoblasts via a modifying immune response. In a case, Ma et al. modified the surface of titanium (TiO2) with UV irradiation to provide different roughness (6–12 nm) and implanted these materials in rats to investigate the effects of different nanoroughness groups on immunomodulation. They observed these materials with higher roughness implanted in rats have a higher secretion of pro-inflammatory immune elements and demonstrated rougher surfaces tend to resemble the activity of M2 macrophages [81].

In another study, Hotchkiss et al. prepared Ti surfaces with microroughness and indicated more secretion of IL-4 and IL-10 which related to M2-like macrophage polarization and osteoblasts differentiation compared to culture on a smoother surface [80]. In addition, the surface topography of biomaterials can modify immune cells' behavior and responses also macrophages polarization and function by transforming the cell shape and elasticity [82].

Recently in a case, Chen et al. made up surfaces with controlled nano topography and modified surface chemistry to investigate the interactions of these surfaces with macrophages and the osteogenic effects of bone marrow stromal cells (MSCs). They demonstrated that the adjusted surface chemistry and nano topography (16, 38, and 68 nm) efficiently modulate the cell shapes, expression of inflammatory cytokines, osteoclastic activities, attachment, osteogenic, fibrogenic, and angiogenic factor expression of macrophages [83].

Another physical property of biomaterials that can change immunomodulation and macrophages polarization is scaffold structure porosity and pore sizes [84]. Because it determines the infiltration of biological molecules, such as proteins or oxygen, nutrient transport, vascularization, and cell migration which can also affect osteogenesis [85]. There are several studies about porosity and Pore sizes; In a case Chen et al. made-up anodic alumina with nanoporous structures with pores in diameters of 100 and 200 nm in its surfaces and demonstrated this surfaces induced macrophages with round shape and increased expression of M2 phenotype markers [86].

In another study, Garg et al. reported biomaterials porosity and Pore sizes can affect macrophage polarity and their results demonstrated increasing the pore size of scaffolds stimulate the expression of the M2 markers (Arg1 VEGF, TGFβ), along with decreasing the expression of the M1 markers [87].

4.2. Chemical properties of biomaterials for osteogenesis

There are several studies that revealed the surface chemistry of biomaterials has a significant role in immune system modulation, macrophage vascularization, and polarization and can be an important approach to designing bone tissue engineering scaffolds based on these properties [88]. Both important chemical features that can affect immune system modulation and macrophage responses are surface charge and surface hydrophilicity [89]. An increase in the surface hydrophilicity of biomaterials has been demonstrated to enhance the monocyte adhesion and activation of immune cells and affect osseointegration and osteoblasts function, on the other hand, surface hydrophobicity can lead to apoptosis signaling [90].

Vlacic-Zischke and colleagues revealed that surface-modified hydrophilic titanium (Ti) enhanced signals associated with osteoblast cytokine production compared to unmodified hydrophobic surfaces [91]. They demonstrated surface hydrophilicity has a positive effect on osteogenesis by upregulation of TGF-β, BMP, IL-10, IL-4, and downregulation of TNF-α, IL-1α, IL-1β, Ccl-2and IL-6, cytokines which have an important role in macrophages polarization [80]. Furthermore, we can change biomaterials' hydrophilicity by plasma modification or hydrolysis in order to modulate the osteogenesis process.

Another chemical property of biomaterials that can affect the immune response and osteogenesis is the surface charge. Hunt et al. revealed surface charge has an important role in neutrophils penetration, macrophage stimulation, and related cytokines secretion in the initial phase of acute inflammatory response [92]. In another experiment, Brodbeck and co-workers prepared biomaterials based on acrylamide with the anionic functional of poly (acrylic acid) and cationic functional groups of poly (acrylic acid) and poly (dimethylaminopropyacrylamide), then demonstrated the anionic substrates upregulate and increase the secretion an anti-inflammatory cytokine IL-10, which has a positive effect in osteogenesis and downregulate the secretion of a pro-inflammatory cytokine IL-8 that has an inflammatory role. In contrast, the cationic substrate downregulates the secretion of IL-10 and IL-1RA, which positively affect osteoblasts regeneration [93].

Macrophages are very potent cells and under particular conditions can form multinucleated giant cells (MGCs) which have three major subtypes: osteoclasts, foreign body giant cells (FBGCs), and Langhans giant cells (LGCs) [94]. Among these subtypes, FBGCs are formed on the surface of foreign bodies, including implants, prostheses, and inorganic particles that make an inflammatory reaction against these materials and contribute to the degradation of these foreign particles by different mechanisms such as phagocytosis or secretion of ROS (Reactive Oxygen Species), MMPs (Matrix Metallo Proteases), and hydrogen protons and subsequently inhibit new bone formation [95]. FBGCs are hypothesized to form when macrophages are unable to remove foreign body material individually, therefore, in this condition, macrophages combine to form FBGCs to remove foreign particles [96,97].

Initially, FBGCs produce pro-inflammatory cytokines such as IL-1 and TNF-α, and stimulate inflammation, then the pro-inflammatory cytokines decrease, and the expression of anti-inflammatory mediator (TGF-β) increases. They play an important role

in tissue repair, fibrosis, and bone formation [98]. The physicochemical properties of biomaterials such as surface chemistry, topography, stiffness, and other parameters can influence the composition and severity of the FBGCs reaction [99].

4.3. Inorganic nanomaterials effect on macrophage in osteogenesis

One of the promising nanotechnology-based approaches in bone regeneration is the modulation of macrophages in the benefit of osteogenesis. Recently, it has been demonstrated that mimetic nano-hydroxyapatite particles (BMnP) can polarize the macrophages toward the M2 phenotype which increases bone formation and improves mesenchymal stem cells (MSCs) osteogenesis capability, BMnP regulates this phenomenon through modulation of IL-10 activity [100]. Also, biomaterial topography can effectively regulate the osteoimmune environment in the osteogenesis process. Micro/nano hierarchical structures can efficiently provoke M2 macrophage polarization which subsequently promotes osteogenic differentiation of human bone marrow stromal cells during osteogenesis [101].

Hydroxyapatite (HA) is one of the bioceramics family and contains only calcium and phosphate ions whit very special and unique properties such as high chemical similarities with the natural bone, biocompatibility, bioactivity, bio-affinity, osteoconduction, osteointegration, and osteoinduction, which makes it suitable for bone substitute or regeneration process [102]. There are different factors that can affect ontogenesis by Hydroxyapatite such as microporosity, geometry topography, and surface area [103].

Micro/nano hierarchical structures on titanium which are coated by Ag^{+} and Sr^{2+} can effectively overcome infection and poor osteogenesis as the main reasons of inappropriate bone formation. Also, this strategy partially induces M2 phenotype in macrophages [104]. Moreover, fullerenol nanoparticles (a polyhydroxy derivative of fullerene) can prevent osteoclastic differentiation and block pre-osteoclast fusion which results in osteoclast maturation and function. Also, fullerenol nanoparticles can regulate the differentiation of bone marrow macrophage cells in the benefit of osteoclastogenesis following treatment by macrophage colony-stimulating factor which stimulates receptor activator of nuclear factor (NF)-κB and mitogen activating protein kinase signaling pathways in a dose-dependent manner [105]. All these data support the possibility of macrophage modulation by certain nanoparticles in the benefit of osteogenesis, in the following we will discuss the role of different nanoparticles in macrophage polarization and bone formation.

4.4. Inorganic synthetic polymers

Inorganic synthetic polymers lack carbon atoms in their skeletal backbone, these polymers indicate certain advantages in contrast to further polymers including adequate supplementation, easy fabrication and adaptation, great biosafety profile, and low costs. Moreover, these polymers possess adjustable physiochemical and morphological characteristics which support wide-scale production and application [106–108]. The most commonly applied inorganic synthetic polymers in biomedical include poly-α-hydroxy esters (poly-glycolic acid (PGA), poly-lactic acid (PLA), poly-lactic-glycolic acid (PLGA), and poly-caprolactone (PCL) polymers [107].

PGA is a biodegradable, thermoplastic polymer and aliphatic polyester which is widely used in biomedicine studies. There is a report on the application of PGA in the induction of osteogenesis [109]. The effect of PGA is studied in osteogenesis, PGA indicates relatively rapid degradation which results in rapid clearance of inflammation in macrophages that can lead to induction of rapid osteogenesis in contrast to other similar polymers such as PLA [110,111]. PGA hydrolysis can increase the osmosis pressure at the site of osteogenesis and an increase in the concentration of acidic monomers is a potential reason to suppress bone formation [112].

PLGA is a common synthetic polymer with a wide application in drug and therapeutic biomolecule delivery systems, cancer treatment, and in tissue engineering [113–117]. It is previously reported that macrophages are able to biodegrade PLGA in vitro [118–121]. It is indicated that biodegradation of PLGA is a cell-mediated procedure under low pH (~5.5) and in the presence of phagosome hydrolytic enzymes that hydrolysis ester bonds specially related to glycolic acid blocks in PLGA [122–124]. CD200, also known as OX-2, is an endogenous protein which is expressed on the surface of host tissues that suppresses spurious immune activation. Alternation of CD200 function can influence the activation of macrophages to PLGA microspheres [125]. PLGA supports osteogenesis, in a study PLGA microspheres in combination with zinc silicate were used to promote calcium phosphate cement-associated bone regeneration which is due to macropores formation in situ after the fast hydrolysis of PLGA microspheres that improves osteogenic differentiation and reduces macrophage inflammatory reaction [126].

One of the main obstacles in the way of PCL application in biomedicine was low optimal mechanical strength and biocompatibility. Therefore, blending of PCL with natural or synthetic polymer or ceramic is a promising attitude for overcoming these limitations. Blend of PCL with +1% Sr2+ releases a low amount of cation and is not cytotoxic for cultured macrophages. This blend indicates promising in vivo osteo-compatibility and increases bone tissue regeneration without inducing any local inflammation [24].

4.5. Dendrimers

Dendrimers have branching treelike structures with uniform morphology which are biocompatible and biodegradable. The high number of surface functional groups on dendrimers suggests them as appropriate carriers for drug delivery [127,128]. However, dendrimers indicate relatively high cytotoxicity and poor drug retention [127]. The anti-inflammatory role of the dendrimers in vivo and in vitro is reported previously [129]. Poly (amidoamine) also known as PAMAM is a class of dendrimers comprised of repetitively branched subunits of amide and amine functionalities. PAMAM-DG (3.5 PAMAM ended by 64 carboxylic acid groups whit nine conjugated branches to glucosamine residues) indicates anti-inflammatory effects on bacterial lipopolysaccharides (LPS) stimulated human monocyte-derived macrophages and immature monocyte-derived dendritic cells by suppressing release of pro-inflammatory cytokines [130]. Regarding the numerous advantages of dendrimers, it is a promising tool for further studies, the biological effects of inorganic nanomaterials on bone-related events and macrophages polarization are summarized in Table 1.

4.6. Silica nanoparticles

Silica is a biocompatible compound with great chemical stability and defined surface properties. Silica is able to induce plethora, therefore has wide biomedical applications in imaging and drug delivery, either itself or as a coating of other compounds [148,149]. Treatment of RAW 264.7 murine macrophage cell line by lipopolysaccharide (LPS) induces inflammation and oxidative stress. The application of silica in the form of sodium metasilicate for the treatment of these cells significantly reduces inflammation and oxidative

Table 1
The biological effects of inorganic nanomaterials on bone-related events.

Type of material	Combined with:	Major biological effect	Status	Ref
Polymers				
Poly (citric acid-1,8-octanediol–1,4-bis(2-hydroxyethyl)piperazine (BHEp)) (POPC)	β-tricalcium phosphate (β-TCP) porous scaffolds	Enhance adhesion and the proliferation of BM-MSCs	In vivo	[131]
ZFuze polymer	Zeolite	ZFuze promoted an M2-like phenotype with expression of Fizz1 and BMP4 while decreased expression of IL-1 β and TNF-α	In vitro	[132]
Poly (lactic-co-glycolic acid) (PLGA)	Calcium phosphate cement (CPC)	Good proliferation and growing ALP activity of MSC. Osteoblasts and new bone tissue were detected inside the scaffold in vivo	In vitro/ In vivo	[133]
poly (DL-lactic-co-glycolic acid) (PLGA)	Nano-hydroxyapatite (nHA)/	Osteogenic differentiation of BM-MSCs with nHA/PLGA (50/50) were better than those with nHA/PLGA (20/80) but nHA/PLGA (20/80) exhibited better bone formation than nHA/PLGA (50/50)	In vitro/ In vivo	[134]
Dendrimers				
Four-armed dendrimer	Heparan sulphate (HS)	Dendrimers/HS enhance BMP-2-mediated osteogenesis and ALP activity in murine C2C12 cells.	In vitro/ In vivo	[135]
Mannose-decorated globular lysine dendrimers (MGLDs)	–	MGLDs accelerates M2 macrophage polarization and increased production of TGF-β1, IL-4 and IL-10, MGLDs enhanced collagen deposition and angiogenic effects	in vivo	[136]
Ceramic materials/Silica NPs				
Strontium-doped hydroxyapatite (SrHA HA) gel	poly (epsilon-lysine) dendrons with 3rd-generation exposing phosphoserine (G3-K PS)	strontium and G3-K PS elevated osteogenic gene markers such as osteoprotegerin (OPG), ALP, OCN and COL-I. G3-K PS to HA could dramatically promote new bone regeneration	In vitro/ In vivo	[137]
CaSiO3 (CS)	β-Tricalcium phosphate (β-Ca3 (PO4)2, β-TCP)	CS induced shift from the M1 to M2 type whereas β-TCP caused a shift toward the M1 type. CS upregulated oncostatin M (OSM)- promoting osteogenic differentiation of BMSCs.	In vitro/ In vivo	[138]
Calcium phosphate groups				
β-tricalcium phosphate (β-TCP)	–	β-TCP upregulated calcium-sensing receptor (CaSR) and BMP2 toward M2 polarization and osteogenic differentiation of BM-MSCs, respectively.	In vitro	[139]
Amorphous Calcium phosphate (ACP) NPs	–	ACP NPs induced polarization into M1 type and weaken the osteogenic ability of BMSCs	In vitro	[140]
Nano Hydroxyapatite (HA) particles	–	nanoHA particles treated macrophages enhances MSC osteogenesis in an IL-10 dependent manner by enhancing expression of BMP2 and ALP in MSCs	In vitro/ In vivo	[100]
Metallic NPs				
Cerium oxide nanoparticles (CeONPs)	Titanium Surface	Increases in the $Ce4^{+}/Ce3^{+}$ ratio exhibit better cytocompatibility with rat BMSCs and also elevate the polarization of the M2 phenotype cells	In vitro/ In vivo	[141]
Cu-containing mesoporous silica nanospheres (Cu-MSNs)	Growth factors	The macrophages switched to the M1 phenotype in response to Cu-MSNs. Robust osteogenic differentiation of BMSCs via the activation of OSM pathway	In vitro	[142]
Gold nanoparticles (AuNPs)	-loaded mesoporous silica nanoparticles (Au-MSNs)	Au-MSN-conditioned macrophages increased the osteogenic differentiation capability of MC3T3 cells and accelerate new bone formation in	In vitro/ In vivo	[143]
AuNPs	-decorated PEG-Hydroxyapatite Composites	Induction of CD163 (as a marker of M2) and Runx-2 gene expressions, eNOS production and promoted endothelialization	In vitro/ In vivo	[144]
Magnetic NPs				
Magnetic Fe_3O_4 NPs	Static magnetic field (SMF)	Osteogenic differentiation of MC3T3 cells by upregulation of RUNX-2 activity, and reduction of 4B12osteoclastogenesis by the induction of apoptosis	In vitro	[145]
Magnetic Fe_3O_4 NPs	-loaded in HAP/PLGA scaffolds	Inhibition of osteoclastic activity and promotion of osteoblast differentiation in rat skull defects.	In vivo	[146]
Super magnetic Fe_3O_4 NPs	Coated on hydroxyapatite	Suppression of osteoclast differentiation through TRAF6−p62−CYLD signaling, and activation of MSC osteogenic differentiation by TGF-β, PI3K-AKT and Ca signaling pathways.	In vivo	[147]

stress [150]. Mesoporous silica nanoparticles (MSNs) are widely applied in bone regeneration for local drug delivery, it is indicated that MSNs cause a lower amount of pro-inflammatory cytokines released from macrophage cells in contrast to nonporous silica compounds which indicates the anti-inflammatory effect of silica on macrophages [151,152]. Recently licorice isoliquiritigenin-encapsulated mesoporous silica nanoparticles were used to treat the mouse primary bone marrow-derived macrophages which were induced by LPS. The results indicated an anti-inflammatory role in macrophages for this compound [152].

Silica can be used for the synthesis of mesoporous silica rods with large cone-shaped pores (MSR-CP) which has a high capacity for bulk proteins. It is clearly understood that cone-shaped pores on the surface of the MSR-CP can modulate the immune response to decrease the pro-inflammatory reaction of stimulated macrophage in fracture site. Also, MSR-CP mediated bone morphogenetic proteins 2 (BMP-2) delivery to these sites provokes osteogenic differentiation and stimulates osteogenesis of bone marrow stromal cells [153]. Treatment of RAW264.7 cells by Dexamethasone-laden mesoporous silica nanoparticles from titanium implant surface indicated a promising role in the induction of M2 phenotype in macrophage cells which is in benefit of promoting osteogenesis [154].

Nanostructured membranes are novel strategies in bone repair, Nanostructured membranes of (MMA)1-co-(HEMA)1/(MA)3-co-(HEA)2 loaded with 5% wt of silicon dioxide-nanoparticles (HOOC–Si-Membrane) which also were doped with zinc (Zn–HOOC–Si-Membrane) or doxycycline (Dox–HOOC–Si-Membrane) used to treat bone defects in rabbit skull, to support bone regeneration and vascularization. This compound indicated a promising effect on promoting osteogenesis, it is clear that Zn–HOOC–Si-Membranes stimulate M2 macrophages phenotype as pro-healing cells at the defect site that subsequently develops bone regeneration [155].

4.7. Metallic nanoparticles

4.7.1. Gold

Periodontitis is a chronic inflammatory disease which is due to bacterial infection which can destroy teeth supporting structures such as alveolar bone, cementum, periodontal ligament, and gingiva [156,157]. The main therapeutic approaches for periodontitis treatment are the reduction of inflammation and regeneration of the lost tissues including alveolar bone regeneration and cementum regeneration [158,159]. Gold nanoparticles (AuNPs) are previously reported to have regulatory effects on macrophage function and the promotion of osteogenesis in stem cells and osteoblasts [159]. The 45 nm AuNPs were used to treat the LPS-activated RAW 264.7 cell line, as a model macrophage cell line. The treatment didn't indicate any inflammatory or oxidative stress response which is due to the high biocompatibility of the AuNPs. The 45 nm AuNPs suppressed the LPS-mediated inflammation and reversed the induced M1 phenotype in macrophages to M2 phenotype. Also, the 45 nm AuNPs upregulated the BMP-2 secretion in macrophages which is a promoter for bone regeneration [160].

Osteoclasts are crucial cells in the maintenance of bone tissue homeostasis; these cells can break down bone integrity. It is indicated that AuNPs can effectively inhibit the formation of osteoclasts under influence of the receptor activator of nuclear factor-κB ligand (RANKL) in bone marrow-derived macrophages. AuNPs reduce the expression levels of tartrate-resistant alkaline phosphatase (TRAP) which leads to limited activation of nuclear factor (NF)-κB. These nanoparticles decrease the concentration of the reactive oxygen species in response to RANKL and upregulated RANKL-induced glutathione peroxidase-1 in bone marrow-derived macrophages, which is considered the main strategy to prevent osteoclast formation [161].

4.7.2. Silver

It is previously reported that silver nanoparticles (AgNps) are promising particles in the induction of osteogenesis [162]. Titanium nano-scaffolds containing silver-doped nano-hydroxyapatite/polyamide-66 materials are applied to overcome osteomyelitis. AgNps indicate anti-inflammation and also anti-bacterial effects in vivo and stimulate bone formation at the damage sites of osteomyelitis which is accompanied by neovascularization [163]. AgNps can prevent recruitment of the inflammatory cell into the damaged tissues, therefore inhibiting inflammation which is a promising characteristic for implant transplantations and drug delivery strategies. AgNPs coated onto the surface of absorbable braided suture using a layer-by-layer deposition indicated notable anti-inflammatory response in mice. Assessment of the AgNps at the damaged sites by immunohistochemistry confirms decreased macrophage infiltration which is accompanied with reduced production of inflammatory cytokines such as IL-10, IL-6, and TNF-α [164]. Macrophages express CD-68 as a direct hallmark of inflammatory cell infiltration. Upregulation of CD-68, IL-6, and TGF-β in damaged sites causes delayed wound healing. Alginate/AgNPs composite can stimulate overexpression of the anti-inflammatory cytokines such as IFN- γ and IL-10 which activates M2 pro-healing macrophage phenotype in the benefit of tissue regeneration [165,166]. Also, it is reported that phospholipid-coated AgNPs immobilized on plasma-coated surfaces can significantly reduce the pro-inflammatory cytokines in bone marrow-derived macrophages [167].

There are conflicting reports on how AgNPs affect macrophages, but in a recent study, it is indicated that treatment of the RAW264.7 with AgNPs induces inflammatory markers such as IL-10 and TNF-α. However, treatment of the LPS exposed RAW264.7 results in the reduced expression level of pro-inflammatory cytokines and can lead to M2 to M1 polarization of the macrophages [168].

4.8. Magnetic nanoparticles

Magnetic nanoparticles (MNPs) indicate promising proprieties in targeted hyperthermia to avoid damage to surrounding normal tissues, MNPs can promote osteoblastic activity and bone formation (Fig. 2). [146]. Currently, magnetic hyperthermia is mostly based on the role of MNPs, which mainly include Fe_3O_4 particles with 10 and 20 nm diameters [142]. The α-Fe_2O_3/γ-Fe_2O_3 nanocomposite (IOs) represent magnetic properties, exposure of MC3T3 osteoblast, 4B12osteoclasts and RAW 264.7macrophages models to IOs in the presence of magnetic field decrease inflammation by diminishing macrophages polarization towards M1 phenotype, increases

osteogenic differentiation of osteoblasts (by increasing expression of OPN, Coll-1, OCN, DMP-1, and BMP-2) and stimulates osteoclasts apoptosis [169].

5. Conclusion and prospective

Recent research recommends that stimulation of specific interactions through cells and grafts can improve immune acceptance and integration. The capacity of biomaterials to modify macrophage polarization and function has been objected of different studies. Whether macrophage participation leads to a positive or negative outcome which greatly depends on appropriate polarization towards an M1 or an M2 phenotype in macrophage cells and the ability to change and resolve polarized responses. Particularly, nanomaterials provoke the shift of macrophages from M1 to M2 phenotypes and inhibit the differentiation of macrophages toward M1, which is considered to be in favor of tissue regeneration. M2 phenotypes recruit other cells such BM-MSCs that are crucial in the bone tissue healing process. Modulation of biological nanomaterials not only supports the increased biosafety of the treatment strategies but also results in more effective approaches for bone regeneration.

The incorporation of nanotechnology in tissue engineering applications enlightens promising opportunities and hopes for future

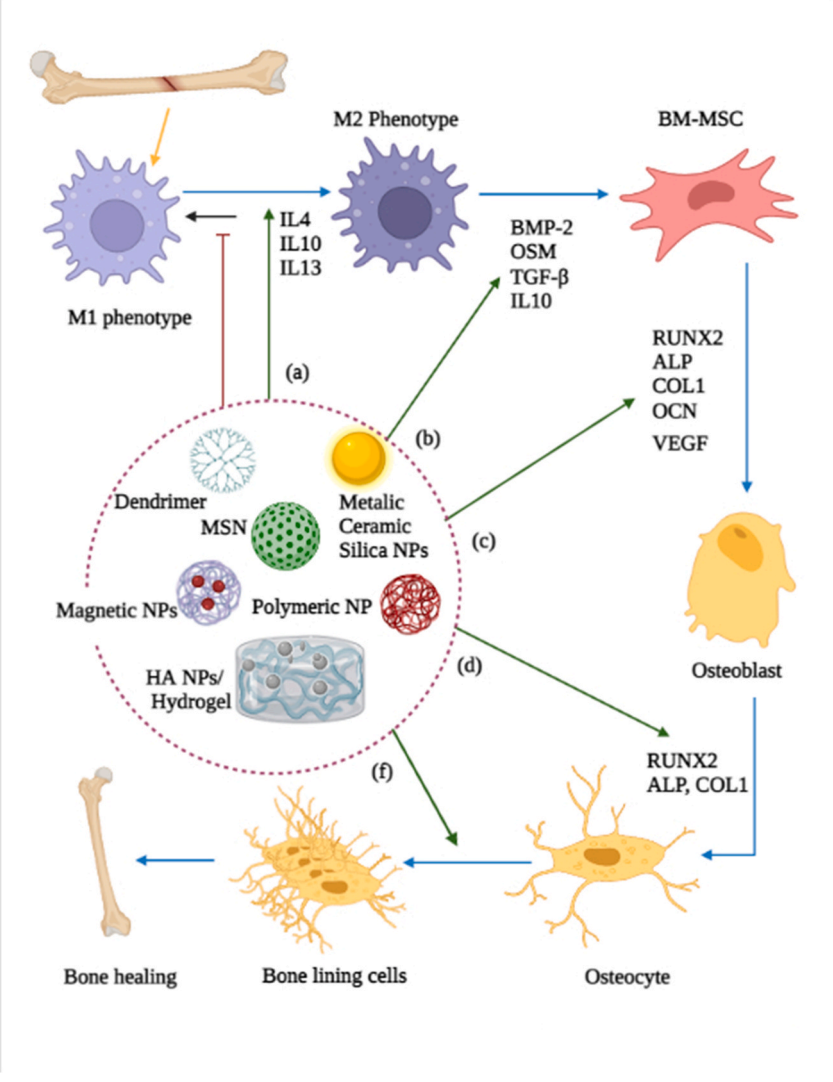

Fig. 2. Schematic potentials of bio/nanomaterials for bone tissue regenerating. Nanobiomaterials such as dendrimers, metallic NP, silica NPs, ceramic NPs, polymeric NPs, magnetic NPs and hydroxyapatite (HA) loaded hydrogel involved macrophages and MSCs toward bone healing though: (**a**) upregulating anti-inflammatory cytokines/chemokines-deriving M2 type polarization, (**b**) stimulation of M2 type cells to produce mediators of MSCs activation and differentiation, (**c** and **d**) upregulating osteogenic gene and pathways in MSCs and osteoprogenitor/osteoblast cells toward osteocyte differentiation, and (**f**) supporting of osteocyte proliferation and acceleration bone healing by sustained release of osteogenic biomolecules or ions while inhibited the osteoclastogenesis.

clinical applications. Regarding the rapid increase of NPs applications in biomedical, it is still essential to completely understand the interaction mechanisms through NPs and living organisms. Due to their small dimensions, the material properties are altered and chemical reactivity is highly amplified which means that size-dependent and dose-dependent mechanistic paradigms of bulk materials are inaccurate when used with NPs. Moreover, nano-sized materials can easily redistribute and deliver ions over biological membranes of bone-resident cells and affect their function toward bone regeneration. The majority of the studies have emphasized cytotoxicologic aspects; however, that is inadequate to explore the real toxicological effect of NPs but researcher should try to select materials with high biosafety profiles. Therefore, nanotoxicology is an area that requires to grow along with nanotechnology, providing safety profiles for each type of NPs. These studies should include a comprehensive characterization of NPs, regarding their amount, fabrication techniques, size, material, shape, charge, and application mode. For example, a detailed investigation of signaling pathways that are engaged by nonmaterial will pave the way to develop biologically safe biomaterials as well as determine the doses required for administration. Regarding the cell viability and perfusion of nutrients throughout the full bone structure, the inorganic materials should have combined with polymers to offer better strength, adequate biodegradability, and immune response. Overall, designing and fabrication of biomimetic biomaterials with incorporated growth factors, and immunomodulatory and angiogenic modulators are considered the most promising ones to enhance in situ bone regeneration.

As mentioned above, the clinical application of tissue engineering for bone regeneration is very limited, and much work is still needed to determine the optimal approaches to obtain optimal outcomes in this field.

Due to the complex interactions of bone implants in vivo, there are many variables that can affect the host immune response and bone regeneration as discussed earlier, moreover, the immune modulating mechanism of bone regeneration is not yet clear and we do not know how immunity selects the correct one. Cells and immune factors as therapeutic targets for bone regeneration, so researchers need to study different aspects of these mechanisms and plan to modulate adverse effects to promote bone tissue regeneration. More experimental research is needed to reveal the internal mechanism of different immune cell responses induced by different scaffolds and biomaterials, and yet various challenges continue to attract researchers. Furthermore, researchers are always trying to improve and enhance biomaterial fabrication techniques and strategies to modulate biomaterial surface physicochemical properties and safety microenvironments to achieve optimal results.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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