REVIEW ARTICLE

CONTENTS

Macrophages and their involvement in mandibular reparative osteogenesis: Current insights

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ABSTRACT

Aim: The purpose of this study was to analyze current literature data regarding the involvement of the macrophage population in the processes of reparative osteogenesis in the mandible.

Materials and Methods: The authors conducted a review of scientific sources available in databases such as PubMed, Web of Science, Scopus, Google Scholar, and ResearchGate.

Conclusions: It was shown by the authors that macrophages play a crucial role at all stages of reparative osteogenesis in the mandible. Their high degree of plasticity enables them to adapt to changes in the microenvironment by dynamically shifting their phenotype (from M1 to M2 and vice versa). Alterations in the morphofunctional state of macrophages and an imbalance between M1 and M2 populations under pathological conditions lead to disruptions in the reparative osteogenesis process. Currently, macrophages are recognized as key therapeutic targets for modulating reparative osteogenesis in cases of mandibular bone pathology.

KEY WORDS: macrophages, mandible, reparative osteogenesis, literature data analysis

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INTRODUCTION

Reparative osteogenesis in the mandible of humans and experimental animals is a complex process resulting in the restoration of the integrity and function of bone tissue. Bone tissue, as is well known, is one of the few types of tissue capable of healing without the formation of fibrous scar tissue. The process of reparative osteogenesis is characterized by the sequential progression through the inflammatory, proliferative-reparative, and remodeling phases [1]. An important role in both the initial and final stages of reparative osteogenesis is assigned to immunocompetent cells, among which macrophages are considered key players [2]. It has been proven that their effects on reparative osteogenesis are mediated by more than 100 secretory products. Investigating the role of the macrophage population in mandibular reparative osteogenesis remains highly relevant, as it expands the understanding of the underlying mechanisms and provides a foundation for improving existing treatment methods and developing new therapeutic approaches.

AIM

The purpose of this study was to analyze current literature data regarding the involvement of the macrophage population in the processes of reparative osteogenesis in the mandible.

MATERIALS AND METHODS

The authors conducted a review of scientific sources available in databases such as PubMed, Web of Science, Scopus, Google Scholar, and ResearchGate. Article selection was based on their relevance to the purpose of the study.

REVIEW AND DISCISSION

The cellular composition of mandibular bone tissue includes various macrophage populations, among which osteoclasts, osteomacs, resident macrophages of the periosteal and endosteal bone surfaces, and bone marrow macrophages are distinguished [3].

Numerous studies have demonstrated that macrophages are plastic cells capable of altering their phenotype in response to various environmental factors. Currently, macrophages are classified into three main states or phenotypes: M0, M1, and M2. Their biological plasticity underlies their ability to regulate intercellular interactions, coordinate reparative processes, and serve as targets for immune-mediated therapies in pathological conditions affecting bone tissue [4]. Also, M2 macrophages include several phenotypes, such as M2a, M2b, M2c, and M2d. M1 macrophages, induced by classical activation signals such as interferon-γ (IFN-γ), lipopolysaccharide (LPS), and tumor necrosis factor-α (TNF-α), are characterized by pro-inflammatory activity. In contrast, macrophages polarize into the M2 phenotype in response to alternative activation signals, including interleukins (IL) (IL-4, IL-10, IL-13) and exhibit anti-inflammatory properties [5].

Owing to their phenotypic flexibility, macrophages adapt their functions to the microenvironment, playing a key role in regulating tissue homeostasis and osteogenesis, particularly under conditions of injury [5].

It has been demonstrated that under physiological conditions, M2 macrophages predominate to maintain bone tissue homeostasis. In cases of mandibular bone injury, the distribution of macrophage phenotypes varies depending on the stage of reparative osteogenesis. During the first week following trauma, M1 macrophages prevail. They initiate the cascade of the inflammatory response, recruit immune cells, and secrete IL-1α, IL-1β, IL-6, monocyte chemoattractant protein-1 (MCP-1), granulocyte colony-stimulating factor (G-CSF), IL-12, IL-23, tumor necrosis factor-α (TNF-α), and inducible nitric oxide synthase (iNOS). By the end of the inflammatory phase, M2 macrophages become predominant, producing arginase-1, IL-4, IL-10, tumor necrosis factor-β (TNF-β), and promoting angiogenesis, mesenchymal stem cell migration, and osteoblast differentiation [1, 6].

Available experimental and clinical data confirm that impaired functional activity of the macrophage pool or an imbalance between M1 and M2 macrophage populations significantly reduces the effectiveness of reparative osteogenesis [7, 8].

Reparative osteogenesis in the mandible is characterized by the sequential progression through the inflammatory, proliferative-reparative, and remodeling stages, which are regulated by integrated mechanisms of inflammation, regeneration, and tissue remodeling [1].

The inflammatory phase begins immediately after bone tissue injury. During this period, neutrophils migrate to the injury site, followed by monocytes, which subsequently differentiate into macrophages. Among these, M1 macrophages predominate, producing pro-inflammatory cytokines and phagocytosing necrotic and apoptotic cells. It has been shown that M1-derived IL-1, TNF-α, and IL-6 enhance the proliferative potential and resorptive activity of osteoclasts, while simultaneously inhibiting the morphofunctional state of osteoblasts, thereby suppressing bone tissue formation.

Studies have shown that inflammatory macrophages inhibit osteocyte maturation and tissue mineralization via regulating the Notch signaling pathway [9].

IL-1 and TNF-α activate osteoclastogenesis by stimulating the expression of RANKL (Receptor Activator of Nuclear Factor Kappa B Ligand) and suppressing the production of osteoprotegerin by osteoblasts and fibroblasts. The signaling system composed of RANK (Receptor Activator of Nuclear Factor Kappa B), its ligand RANKL, and osteoprotegerin is known to be the primary regulator of the morphofunctional state of osteoclasts. Increased RANKL expression, followed by its interaction with RANK, induces genomic changes in bone marrow-derived osteoclast precursors, leading to their transformation into mature, active osteoclasts. Osteoprotegerin acts as a decoy receptor for RANKL [10].

Interestingly, M1 macrophages interact with mesenchymal stem cells and stimulate their transformation into osteogenic cells. This process is significantly enhanced when there is an increase in M2 macrophages accompanied by a reduction in M1 macrophages [11, 12].

Experimental studies have shown that selective depletion of macrophages at this stage leads to impaired osteogenesis and a reduction in the volume of newly formed bone tissue [8, 13].

The proliferative-reparative stage of osteogenesis follows the elimination of damaged tissues and is characterized by the predominance of M2 macrophages. Alternatively activated macrophages stimulate angiogenesis, produce osteoinductive factors such as transforming growth factor-beta (TGF-β) and bone morphogenetic protein-2 (BMP-2), and promote the proliferation and differentiation of mesenchymal stem cells toward the osteoblastic vector [14].

The remodeling phase is the final stage, lasting several weeks or months, and involves the replacement of primary bone tissue with lamellar bone. During this period, macrophages maintain the balance between bone resorption and formation by interacting with osteoclasts and osteoblasts, and also participate in the regulation of vascular network involution [1, 8].

Blood vessels are known to provide trophic support to bone tissue, which is essential for the

processes of reparative osteogenesis. It has been demonstrated that M2 macrophages are involved in angiogenesis and vascular remodeling. Specifically, M2a macrophages produce platelet-derived growth factor-BB (PDGF-BB), while M2c macrophages secrete matrix metalloproteinase-9 (MMP-9). Some studies have also indicated that M1 macrophages contribute to angiogenesis through the production of vascular endothelial growth factor (VEGF) [15, 16].

Reparative osteogenesis is highly sensitive to changes in the functional activity of macrophages. Various pathological conditions can significantly alter the course of bone regeneration by disrupting macrophage polarization or causing insufficient macrophage responses. It has been established that with aging, macrophages lose their ability to transition in a timely manner from the pro-inflammatory M1 phenotype to the reparative M2 phenotype, leading to delayed resolution of inflammation and impaired osteogenesis. A study using an aging rat model demonstrated reduced levels of M2 macrophages and decreased quality of newly formed bone tissue [17]. Similar results have been confirmed in studies utilizing engineered coatings to induce the transition from the M1 to the M2 macrophage phenotype under aging conditions, where a partial restoration of reparative function was observed [18].

Hormone-dependent regulation of macrophage functions in the process of osteogenesis should also be noted. For example, diabetes mellitus alters the immune microenvironment of regeneration, leading to a sustained dominance of the pro-inflammatory response. This is supported by findings in diabetic rat models, which show increased expression of M1 markers, impaired M2 polarization, and reduced angiogenesis and osteogenesis. However, it has been demonstrated that the use of nanostructured biomaterials, particularly PCLLA-nanoHA, helps restore the balance by activating M2 macrophages and improving tissue regeneration [19].

Under conditions of estrogen deficiency in ovariectomized mice, elevated levels of pro-inflammatory cytokines and disruption of the macrophage profile at the fracture site have been observed, which correlates with reduced quality of the regenerative bone tissue [20].

Due to the recognized role of macrophages in bone tissue regeneration, there is growing interest in methods aimed at therapeutically modulating their phenotype. The primary objective of such approaches is to induce the transition from the M1 to the M2 phenotype and to maintain the M2 profile, particularly during the critical phases of reparative osteogenesis [21]. Among the classical strategies is the use of IL-4, which stimulates M2 polarization. Experimental studies have shown that IL-4, in vitro, activates the production of anti-inflammatory mediators and enhances mineralization in cultures of osteogenic mesenchymal stem cells, particularly in the presence of low-activity macrophages [22].

Some studies have noted that RANKL-activated M1 macrophages exhibit osteogenic properties by modulating osteoblastic transcription factors, indicating the potential for controlled utilization of the M1 phenotype [23]. At the same time, immunoregulatory molecules such as VIP (vasoactive intestinal peptide) and PACAP (pituitary adenylate cyclase-activating polypeptide), despite their potential to stimulate the M2 phenotype, did not produce a significant effect in the context of alveolar bone healing, highlighting the complexity of such regulation [24].

Particular interest is drawn to the sex-specific effectiveness of regulating the transition of macrophages from the M1 to the M2 phenotype. Researchers have shown that the immunomodulatory response differs significantly between males and females, likely due to hormonal influences [25].

Modern tissue engineering strategies are increasingly incorporating the immunomodulatory potential of macrophages into the design of biomaterials aimed at enhancing reparative osteogenesis. In this context, modified biomaterials serve not only as physical scaffolds for cellular repair but also as active regulators of the cellular microenvironment by directing macrophage polarization and maintaining immune homeostasis at the osteogenic site. The concept involves not merely creating an inert matrix for cell adhesion and growth, but developing surfaces and carriers capable of modulating immune cell behavior, particularly by specifically inducing M2 macrophage polarization [26].

One of the promising approaches involves the use of calcium phosphate-based coatings, which stimulate the transition of macrophages from the M1 to the M2 phenotype. Experimental studies have shown that such coatings promote phenotypic transformation in aged macrophages, restoring their reparative activity [18]. Hybrid hydrogels and nanocomposites, which combine a structural carrier with active therapeutic functionality, are also of considerable interest. For instance, the application of a multimodal hydrogel containing exosomes and immunotherapy has been shown to simultaneously activate osteoblasts, osteoclasts, and M2 macrophages, thereby accelerating the reparative process [27]. Silane-based biomaterials, used as endodontic irrigants, have demonstrated the ability to alter the biochemical profile of tissues and promote macrophage polarization [28].

An immunoregulatory effect was observed in an experimental study involving the filling of mandibular bone defects in rats with nanostructured hydroxyapatite combined with local injection of thymalin into the surrounding soft tissues. This comprehensive therapy stimulated reparative osteogenesis by activating both innate and adaptive immunity, which morphologically manifested in the post-traumatic regenerate as an increased presence of T and B lymphocytes and macrophages. Among the latter, a decrease in M1 macrophages and an increase in M2 macrophages were noted [29, 30].

Another important strategy involves the use of PCLLA-nanoHA composites, which promote M2 macrophage polarization and enhance alveolar bone regeneration under diabetic conditions [31].

One of the promising directions is targeted immunomodulation, which involves the localized regulation of the M1/M2 macrophage ratio at specific stages of osteogenesis. This approach utilizes biomaterials with controlled release of signaling molecules or surface modifications that facilitate the recruitment of the desired macrophage phenotype. For example, in a study by Y.H. Kim et al., the concept of «springboard immunomodulation» was proposed, which envisions the active reprogramming of the local immune microenvironment as a launching platform for osteoregeneration [26].

Currently, the field of macrophage or macrophage precursor transplantation is developing as a potential form of cell therapy. Particular attention is being given to methods involving ex vivo induction of the desired phenotype prior to transplantation into the defect site, as this approach allows for predictable therapeutic activity while minimizing undesired immune responses [31].

Another promising direction involves the use of exosomes – nanovesicles produced by cells, including macrophages, which contain active molecules such as mitochondrial RNA, proteins, and lipids. Exosomes derived from M2 macrophages have demonstrated the potential to stimulate osteogenesis and angiogenesis, acting as natural signaling mediators without directly interfering with the cellular structure of the microenvironment [27].

Systematic reviews highlight the emerging concept of «smart» biomaterials, which not only serve as matrices for cell growth but also actively interact with the immune system, functioning as regulatory platforms. These materials may contain embedded immunotherapeutic agents, control cytokine release in response to external stimuli, or alter their behavior depending on the phase of healing [11, 32]. A key aspect in this context is the issue of timing: premature or prolonged activation of a particular macrophage phenotype may lead to adverse outcomes. Therefore, the current paradigm of immunoregulation in osteogenesis is based not only on the binary distinction between M1 and M2 phenotypes, but also on the dynamic monitoring and modulation of the plastic transitions between these states in accordance with the specific phase of reparative osteogenesis [33].

CONCLUSIONS

Macrophages play a crucial role at all stages of reparative osteogenesis in the mandible. Their high degree of plasticity enables them to adapt to changes in the microenvironment by dynamically shifting their phenotype (from M1 to M2 and vice versa). Alterations in the morphofunctional state of macrophages and an imbalance between M1 and M2 populations under pathological conditions lead to disruptions in the reparative osteogenesis process. Currently, macrophages are recognized as key therapeutic targets for modulating reparative osteogenesis in cases of mandibular bone pathology.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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