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Revolutionizing Maxillofacial Regeneration Strategies: The Role of Scaffolds in Temporomandibular Joint and jawbone reconstruction

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Abstract: For the repair of maxillofacial bone defects, traditional surgical methods result in slow healing and often require a second surgery to remove implants. To promote of jawbone and temporomandibular joint (TMJ) regeneration, scaffolds capable of delivering cells and growth factors that stimulate bone and cartilage development have become a recent focus in the field of tissue engineering. This paper provides a comprehensive review of scaffold applications in oral and maxillofacial regeneration, detailing the commonly utilized scaffolds, the cells they load (such as stem cells and macrophages) and the associated bioactive factors that promote growth, angiogenesis, and osteogenesis. Scaffolds (hydrogels, bioceramics, etc.) can facilitate the repair of jawbone injuries and preservation of post-extraction socket sites. Moreover, multi-layer composite hydrogel scaffolds have the potential to simultaneously promote the regeneration of bone, cartilage, and the articular disc, offering a therapeutic approach for temporomandibular joint disorders. This review provides clinicians with scientific evidence and guidance in selecting appropriate scaffolds for different clinical situations.

1 Introduction

The maxillofacial region is susceptible to trauma due to external impact forces, leading to injuries. Traditional treatment methods (such as autologous bone grafting and titanium plate fixation) require extended healing periods. Therefore, novel therapeutic strategies are needed to facilitate tissue repair. In regenerative medicine, scaffolds primarily serve as carriers for cells and growth factors, fulfilling the roles of filling defects and promoting tissue regeneration. Commonly used scaffolds include hydrogels, bioceramics, decellularized matrices, and electrospun materials, which must possess high biocompatibility and certain mechanical properties to support the defect area without hindering tissue growth. Generally, scaffolds are often loaded with Mesenchymal Stem Cells (MSCs) as a cellular source and regulate stem cell differentiation into osteoblasts and chondrocytes through cytokine modulation [1].

2 Common Scaffold Materials

2.1 Hydrogel

Hydrogels are three-dimensional water-containing crosslinked polymers that exhibit excellent biocompatibility and convenient mechanical manipulability, which are widely used in biomedical and tissue engineering fields [2]. Moreover, the soft hydrogel is similar to the extracellular matrix, containing 90% water by volume, which is conducive to cell growth [3]. Hydrogels also feature a loose and porous structure, capable of carrying cells, cytokines, and drugs. They can serve for multiple use such as the repair of bone defects and the preservation of socket sites (Figure 1).

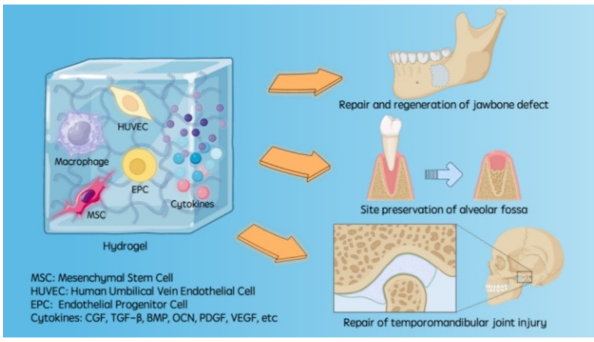

Figure1. Cytokines and cells loaded by hydrogel scaffold and their clinical applications in dentistry.

Hydrogels can be divided into natural and synthetic hydrogels. Natural hydrogels (chitosan, collagen, gelatine, hyaluronic acid, etc.) exhibit good biocompatibility and degradability, but their mechanical properties such as hardness and ductility are relatively weak. Synthetic hydrogels include polyvinyl alcohol, PEG derivatives, polyacrylamide, and polycaprolactone, which possess excellent mechanical load-bearing capabilities, but relatively low biocompatibility and degradability.

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Additionally, they can be modified by incorporating different functional groups to achieve specific responsiveness (e.g., pH-responsiveness, magneto-responsiveness) to precisely control the release of loaded substances [4]. For instance, anisotropic magneto-responsive hydrogels can be applied to treat articular cartilage defects [5].

2.2 Bioceramics

Bioceramics, including hydroxyapatite and bioactive glass, are inorganic non-metal materials with specific biological or physiological functions. They can exist stably in tissue with low rejection and have an ability of bone induction. Additionally, bioceramics can carry active biomolecules, growth factors, and drugs to meet various therapeutic needs [6].

Bioceramics are categorized into bioinert ceramics and bioactive ceramics. Bioinert ceramics are characterized by their wear resistance, chemical stability, and high mechanical properties, such as high-density, high-purity Al2O3 and ZrO2. However, these materials have low biodegradability and insufficient structural stability when integrated with surrounding tissues. Bioactive ceramics, on the other hand, possess excellent biodegradability, such as hydroxyapatite (HA), tricalcium phosphate (TCP), and calcium phosphate. Hydroxyl groups on their surfaces allow them to form strong bonds with adjacent tissues and facilitate the adhesion and growth of new cells on their surface. Nevertheless, active ceramic scaffolds have low mechanical strength, and the particles generated by excessive wear can trigger inflammatory responses. This limitation can be overcome with composite bioceramics, which are being applied in many fields. For example, nano-hydroxyapatite-collagen composite scaffolds can mimic the composition of natural bone, which is beneficial for cell adhesion and growth [7].

2.3 Electrospinning

Electrospinning is a special form of electrostatic atomization of polymer fluids, in which the material split from the atomization is not tiny droplets, but tiny polymer jets that can travel a considerable distance and eventually solidify into fibers [8]. This nanofiber structure endows electrospun scaffolds with high specific surface area and porosity, which can simulate the natural extracellular matrix environment [9].

Polymers, drugs, and cytokines used for synthetic electrospinning are prepared in volatile organic solvents, thus the scaffolds exhibit good biocompatibility and biodegradability. By modifying the parameters of the electrospinning system, the porosity and surface area of the scaffold can be adjusted to incorporate different cells, cytokines, and can also control the precise release of loaded drugs [10].

2.4 Decellularized Natural Tissue Scaffolds and Collagen-Based Composite Scaffolds

Decellularized matrices are derived from natural tissues of humans or animals, where cells and genetic materials are removed through physical, chemical, and biological methods, while the natural extracellular matrix (containing macromolecular polysaccharides, collagen, etc.) is retained, serving as a natural cell-carrying scaffold. Another commonly used type of natural biological scaffold primarily consists of collagen, which can be composited with inorganic or biological materials. They maintain a stable three-dimensional space for cell adhesion and development, widely applied in bone and cartilage regeneration [11]. For instance, collagen/hydroxyapatite biomimetic gradient scaffolds can mimic the natural composition of bone and cartilage, inducing a natural transition between bone and cartilage [12].

3 Scaffold-Carried Cells

3.1 Mesenchymal Stem Cells (MSCs)

MSCs are the most commonly carried cells on scaffolds due to their high differentiation potential, which allows them to differentiate into osteoblasts, chondrocytes, stromal cells, and more. They also possess low immunogenicity, making them suitable for allogeneic transplantation with relatively mild rejection. Moreover, MSCs have immune-modulatory functions, participating in both innate and adaptive immunity through cell-to-cell contact and the release of secretory factors. This helps to enhance the phagocytic action of immune cells and regulate excessive inflammatory responses [13]. Lotfy et al. [14] found that Bone Marrow-derived Mesenchymal Stem Cells (BMSCs) and Adipose-derived Stem Cells (ADSCs) exhibit paracrine activity, secreting exosomes and microvesicles encapsulating cytokines that play roles in anti-inflammatory and angiogenic processes.

Compared to traditional stem cell injections, MSCs carried on scaffolds have a higher differentiation potential due to their three-dimensional growth characteristics. They can also achieve the maximum contact with tissues in a three-dimensional space, thereby functioning more effectively. In addition, hydrogels with different substances and physical properties can be combined together to repair articular cartilage and subchondral bone at the same time [15].

3.2 Macrophages

Macrophages exhibit a high degree of plasticity and can be activated into different phenotypes based on signals from the microenvironment. For instance, M1-type macrophages release inflammatory factors and nitric oxide, which promote inflammatory responses. In contrast, M2-type macrophages are present during the tissue healing phase, capable of clearing apoptotic cells and downregulating immune responses by secreting anti-inflammatory factors and growth factors such as CD206, VEGF, TGF-β, BMP2, etc., which also promote angiogenesis and bone formation. Tian et al. found that scaffold materials can influence the polarization state of macrophages. Hydrophilic, soft, and rough-surfaced scaffolds promote the polarization of macrophages towards the M2 phenotype, effectively exerting anti-inflammatory and osteogenic functions.

3.3 Endothelial Progenitor Cells (EPCs) and Human Umbilical Vein Endothelial Cells (HUVECs)

During the process of bone regeneration, the support of blood supply is essential. Vascularization can provide sufficient nutrients for newly differentiated osteoblasts and remove metabolic waste, thereby improving the efficiency of bone regeneration. EPCs can differentiate into HUVECs under the stimulation of cytokines such as PDGF, VEGF, and EPO, forming blood vessels and establishing blood circulation in the bone repair area. Bouland et al. found that EPCs not only release BMP and TGF-β to promote osteogenesis but also can recruit MSCs and promote their osteogenic differentiation. Exosomes from HUVECs can induce M2 polarization of macrophages to alleviate inflammatory responses. Scaffold materials can carry EPCs or HUVECs to exert angiogenic effects in three-dimensional space.

4 Commonly Carried Cytokines on Scaffold Materials

4.1 Growth-Promoting Factors

Growth Factors (GFs) are a class of polypeptides that can promote cell growth. Commonly carried GFs include Transforming Growth Factor-beta (TGF-β), Fibroblast Growth Factor (FGF), and Insulin-like Growth Factor (IGF). TGF-β1 and TGF-β3, which are part of the TGF superfamily, can promote the differentiation and adhesion of osteoblasts and chondrocytes, as well as the synthesis of cartilage matrix [2]. FGF-18, a member of the FGF family, has been shown to recruit HUVECs to the bone defect area for angiogenesis and increase the rate of bone formation. IGF-1 not only induces the differentiation of MSCs into chondrocytes but also promotes the synthesis of collagen and proteoglycans, stabilizing the cartilage matrix. Concentrated Growth Factor (CGF) is a natural growth factor reservoir extracted from the patient's venous blood (containing PDGF, TGF, VEGF, FGF, IGF), and is widely used in bone grafting.

4.2 Osteogenic Factors

Within the TGF-β family, Bone Morphogenetic Proteins (BMPs) are potent osteoinductive factors. BMP-2 and BMP-7 have been approved by the U.S. Food and Drug Administration (FDA) for clinical bone regeneration treatments. However, BMP-2, while promoting osteogenesis, can also activate the PPARγ pathway associated with adipogenic differentiation, leading to the formation of bone cysts and attracting inflammatory factors such as interleukins, causing local inflammatory responses. Bharadwaz et al. suggested that BMP-9 could serve as a more reliable alternative to BMP-2, avoiding the formation of cystic bone. Osteocalcin (OCN), a non-collagenous protein secreted by osteoblasts, can accelerate the deposition of calcium ions in the bone matrix, thereby promoting the formation of hydroxyapatite.

4.3 Angiogenic Factors

Angiogenic growth factors commonly carried in scaffolds include Platelet-Derived Growth Factor (PDGF) and Vascular Endothelial Growth Factor (VEGF). These factors can stimulate the differentiation of EPCs into vascular endothelial cells by promoting macrophages to secrete FGF and TGF-β, thereby providing blood support for the osteogenesis process. VEGF-A can also promote the growth of new blood vessels and alleviate inflammatory responses in the bone regeneration area. Additionally, another cytokine, Erythropoietin (EPO), can effectively stimulate the differentiation of MSCs into endothelial cells and promote the transformation of mature red blood cells under hypoxic conditions in bone defect areas. Simultaneously, through the Erythropoietin Receptor (EPO-R) signaling pathway, it facilitates bone formation.

5 Clinical Applications of Scaffolds in Maxillofacial Bone Regeneration

5.1 Maxillofacial Trauma

The maxillofacial bones are the largest supportive structures of the face and play a crucial role in appearance and functional movement. Trauma and tumors are the main causes of maxillofacial bone injuries, significantly impacting patients' quality of life. Traditional surgical and fixation methods rely on the self-repair of bone tissue, which takes a long time, and implants often require secondary removal. Therefore, scaffolds with biodegradability and osteogenic potential are promising for clinical applications. Schönegg et al. used beta-tricalcium phosphate (β-TCP) scaffolds to restore the severely deficient mandibular body of a 63-year-old female patient. Nine months postoperatively, it was observed that the scaffold successfully integrated into the maxillofacial bone, and a sufficient amount of new bone formed, stably bonding with the scaffold, within two years post-surgery. In an animal experiment, Sajad et al. used 3D-printed nanohydroxyapatite (nHA)/β-TCP/collagen scaffolds carrying MSCs to repair mandibular bone defects in rabbits. They observed a significant amount of woven and lamellar bone formation, as well as neovascularization, within the implant area. Compared to maxillofacial trauma, due to the invasive nature of tumors, it is necessary to thoroughly remove tumor cells while repairing bone defects. In a study, graphene oxide-modified bioceramic scaffolds were able to ablate cancer cells and prevent their spread through photothermal effects.

5.2 Socket Preservation After Tooth Extraction

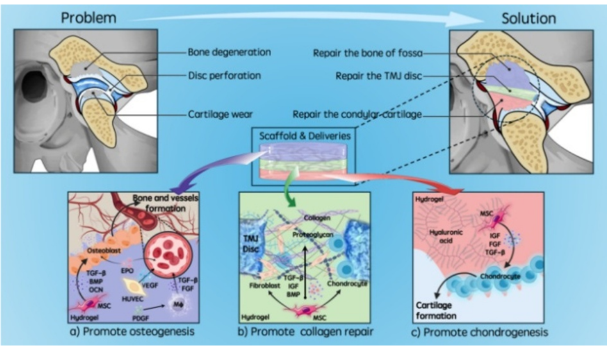
After the loss of tooth support, the alveolar bone surrounding the extraction socket undergoes resorption and remodeling. Within six months after tooth extraction, the height of the alveolar ridge can decrease by 40%, and the width can be lost by 60%, affecting the stability and aesthetics of dental implants. Socket preservation primarily involves the implantation of bone substitute materials, hydrogels, etc., to support the bone walls and promote bone regeneration.

Hydrogels used for socket preservation (such as chitosan, Tetra-PEG, etc.) possess a certain degree of elasticity, which can inhibit bleeding within the extraction wound and increase the rate of bone repair. If loaded with anti-inflammatory factors like IL-10, they can effectively suppress inflammation in the extraction socket and slow down bone resorption. Composite scaffolds are also commonly used for socket preservation. For example, NPP (nacre, polyurethane (PU), and polyhedral oligomeric silsesquioxane) photo-crosslinked 3D-printed scaffolds can guide the distribution of stem cells in the extraction socket, promoting new bone formation. The latest research by Sukpaita indicated that CS/BCP/TSA (a chitosan biphasic calcium phosphate loaded with trichostatin A) scaffolds exhibit superior osteoinductive capacity compared to traditional commercial osteogenic materials. These scaffolds effectively increase the amount of new bone within the extraction socket and preserve the buccal and central aspects of the alveolar ridge.

5.3 Temporomandibular Joint Disorders (TMD)

TMD have a high incidence rate in clinical practice, significantly affecting patients' basic physiological functions such as chewing and speaking. They can also lead to long-term chronic pain and functional impairment, negatively impacting mental health and reducing the quality of life. The disorders manifest as wear of the joint bones and cartilage, and perforation of the joint disc. Currently, clinical treatment often relies on conservative drug therapy, supplemented by physical therapy to restore TMJ movement function. These therapies are slow-acting and prone to relapse. For patients with severe wear, surgical repair or replacement of the joint disc is required, which carries risks of infection and rejection reaction. Therefore, designing materials that can simultaneously promote bone and cartilage regeneration can restore the natural TMJ structure and function in a shorter period.

In TMJ regenerative therapy, hydrogels are the most commonly used scaffolds due to their structure resembling the extracellular matrix and their sufficient mechanical strength, which allows them to effectively simulate the function of the joint disc during treatment. Monteiro implanted hydrogel scaffolds carrying stem cells into the mandibular condyles of rabbits and found that they effectively promoted the regeneration of condylar cartilage. However, the induction capacity of a single scaffold for stem cells is limited. To achieve simultaneous regeneration of bone, cartilage, and the joint disc, multi-layered scaffolds loaded with different cytokines and cells can be used (Figure 2). Li developed a biomimetic bilayer hydrogel scaffold that can effectively achieve simultaneous regeneration of cartilage and subchondral bone tissue. In a rat surgery model, 6 weeks post-implantation, the damaged area was observed to be filled with newly formed cartilage, indicating a smooth surface and hardness comparable to natural cartilage tissue. Furthermore, after 12 weeks post-surgery, continuous subchondral bone formation was observed.



a) Promote osteogenesis b) Promote collagen repair c) Promote chondrogenesis

Figure 2. Hydrogel used for Temporomandibular joint repair.

The upper part favoring for mandibular fossa osteogenesis contains cells (macrophage, MSCs, HUVECs etc.) and cytokines (TGF-β, IGF, VEGF, PDGF etc.). The middle part which promotes articular disc repair loads collagen, proteoglycan and cytokines facilitating MSC differentiation into fibroblasts. The lower part applied for condylar cartilage repair contains hyaluronic acid and MSC differentiating into chondrocyte.

6 Conclusion

Scaffolds commonly used for maxillofacial and TMJ repair include hydrogels, bioceramics, and electrospun materials, which can be loaded with functional cells and growth factors to regulate the microenvironment of the defect area, thereby promoting tissue regeneration. These scaffolds have shown promising results in clinical applications such as maxillary bone trauma repair and socket preservation after tooth extraction. Moreover, innovative multi-layer scaffold strategies have been developed to achieve simultaneous regeneration of TMJ bones, cartilage, and disc, paving new avenues for the treatment of TMJ-related diseases.

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