Review Article

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Temporomandibular Joint Regenerative Medicine: A Review.

Abstract:
The temporomandibular joint (TMJ) is an articulation formed between the temporal bone and the mandibular condyle which is commonly affected and course with pain and dysfunctions of the temporomandibular joint. These affections are often so painful during fundamental oral activities that patients have lower quality of life. The treatment of these disorders includes systematically administered drugs (especially non steroid anti-inflammatory drugs and corticoids), physical therapies, and minimally invasive therapies that require intra articular injections. Limitations of therapeutics for severe TMJ diseases have led to increased interest in regenerative strategies combining stem cells, implantable scaffolds and well-targeting bioactive molecules. Recent advances in tissue engineering may provide an alternative to traditional strategies to repair and regenerate the TMJ. To succeed in functional and structural regeneration of TMJ is very challenging. Innovative strategies and biomaterials are absolutely crucial because TMJ can be considered as one of the most difficult tissues to regenerate due to its limited healing capacity, its unique histological and structural properties and the necessity for long-term prevention of its ossified or fibrous adhesions. The ideal approach for TMJ regeneration is a unique scaffold functionalized with an osteochondral molecular gradient containing a single stem cell population able to undergo osteogenic and chondrogenic differentiation such as BMSCs, ADSCs or DPSCs. The key for this complex regeneration is the functionalization with active molecules such as IGF-1, TGF-beta 1 or bFGF. This regeneration can be optimized by nano/micro-assisted functionalization and by spatiotemporal drug delivery systems orchestrating the 3D formation of TMJ tissues. Preceding the current trends in tissue engineering is an analysis of native tissue characterization, toward identifying tissue engineering objectives and validation metrics for restoring healthy and functional structures of the TMJ.

Keywords: Temporomandibular joint; Regenerative medicine; Stem cells; Scaffolds; Growth factors

Introduction

Temporomandibular Joint (TMJ)

The temporomandibular joint (TMJ) is an articulation covered by dense fibro cartilage formed between the mandibular condyle and the temporal bone. The temporal articular surface is large and consists of the mandibular fossa and the articular tubercle. Along this large articular temporal surface, each mandibular condyle has a wide motion range, consisting of both rotation and translation. Fibro cartilaginous disc cushions mechanical stresses that exist between the temporal and mandibular articular surfaces. The high collagen content of this disc provides great rigidity and durability. The TMJ disc has no direct vascularization or innervations by itself. However, its posterior attachment, known as retrodiscal tissue, features many vessels and nerves which are crucial during physio-pathological processes.[1]

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Temporomandibular Joint Disorders (TMD)

TMD (temporomandibular joint disorders) are very common, their prevalence being around 52%.[2] TMD is a general term actually covering a large number of clinical occurrences affecting the TMJ and masticatory-related structures. They cover in various etiologies: traumatic, inflammatory, and congenital. TMD are also characterized by deficient wound healing and fibrosis caused by continuous and irreversible injuries.

Pain, malocclusion, limited range of motion, deviation, joint clicking and clenching are most of time associated with TMD.

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These disorders are often so painful during basic oral activities (eating and speaking) that quality of life of patients is greatly impacted.[3] Pain is the primary symptom and the main reason why patients are referred to practitioners to seek treatment.

Osteoarthritis-like degenerative joint disease belonging to TMD is a destruction of bone and cartilage with a consecutive inflammation which enhances tissue destruction. TMJ degeneration features are: displacement, thickening and/or disc perforation, whole destruction of articular fibro cartilage and crucial modifications of bone remodeling such as sclerosis or periarticular osteophyte formation.

Tissue Engineering:

Tissue engineering has appeared with the purpose of regenerating damaged tissues, restoring their function without the need for replacing the diseased tissue. This field is based on three fundamental principles, namely: (I) the cells, responsible for synthesis of the new tissue matrix; (II) growth factors that promote and facilitate cell function; (III) and scaffolds that act as an extracellular matrix, allowing cell differentiation, proliferation and biosynthesis. The basic strategy of bone tissue engineering is to corporate into the target site one or more of the fundamental elements necessary for bone formation such as scaffolds, osteoprogenitor cells (mesenchymal stem cells), bioactive factors, or genes to stimulate cellular proliferation and differentiation, while guiding the tissue-repairing function of the living body. A tissue engineering approach to the craniomaxillofacial bones provides several potential benefits including the lack of donor-site morbidity, no limitation of availability, no risk of immunoreactivity, and disease transmission.

Within the TMJ, the fibro cartilaginous disc has received the most attention thus far, but efforts are underway to engineer the mandibular condyle cartilage and bone as well.[1]

Current Status of Temporomandibular Treatments Current Therapies:

The treatment can vary according to the severity of the disorder: non-invasive, minimally invasive and invasive procedures. Occlusal orthodontics, medications, physical therapy and acupuncture are the most common non-invasive treatments. Non-invasive medications consist anxiolytics, muscle relaxants, non-steroidal anti-inflammatory drugs and opioids. Minimally invasive treatments of TMJ itself include intra-articular injections, arthrocentesis, and arthroscopy. Invasive treatment is the only option for patients suffering from ankylosis, neoplasia, dislocation, and developmental disorders.

The limitations of current therapeutics for TMD have led to an increased interest in regenerative strategies combining cells, implantable scaffolds and well-targeting bioactive molecules. Currently, the repair and replacement of TMJ tissue components constitutes an unmet need, highlighting the importance of developing novel approaches toward treating patients with TMD.

Challenging Regeneration:

Anatomic, structural, and functional regeneration of TMJ is very challenging. Innovative strategies and biomaterials are absolutely crucial because TMJ can be considered as one of the most difficult tissues to regenerate.
The challenge in TMJ regeneration is to promote matrix synthesis and tissue maturation of chondrogenic and osteogenic cells in suitable scaffolds containing active molecules which are able to separately orchestrate osteogenesis and chondrogenesis.

The success of TMJ regenerative strategy is not only measured by the restoration of function but also by the long-term prevention of ossified or fibrous adhesions which are the main complications of engineered TMJ replacements.4 Thus, pro-regenerative active molecules incorporated in scaffolds of engineered TMJ must also prevent any ossifications and any adhesions.1

Histology and Macromolecular Biology of the TMJ:

There is a continuous debate about the embryonic origin of mandibular articulating surface:

blastemal or periosteal origin.[5,6] The thickness of condylar fibro cartilage in humans can reach 0.48 mm as a maximum

and is subject to variations caused by age and functional conditions.[7,8] The articular surface of most synovial joints is covered by hyaline cartilage. It is not the case of the TMJ which has an articular surface covered by a layer of fibrous tissue. This fibrous zone contains abundant type I collagen, while collagen type II is minimally present. Underlying this superficial fibrous zone, a fibro cartilage layer is described which can be subdivided schematically into proliferative and hypertrophic zones. (Figure 1 and 2)[1]

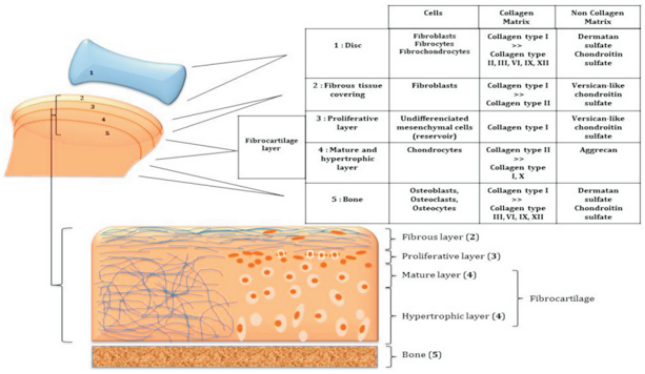

Figure 1.Scheme of the composition of the five compartments of TMJ to regenerate. Their cellular and macromolecular compositions differ of lot. An osteochondral molecular gradient of functionalization able to orchestrate the 3D formation of different TMJ tissues is the key of its regeneration.[1]

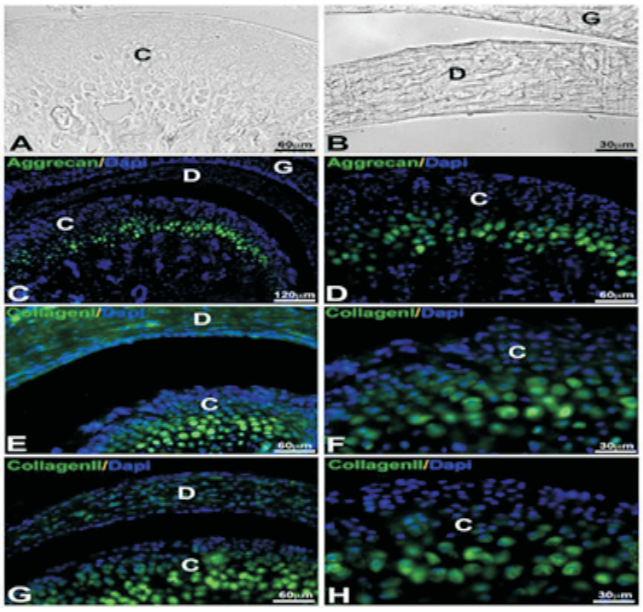

Figure 2. Expression of different conjunctive macromolecules in murine TMJ detected by Immunofluorescence. TMJ observed by phase contrast microscope (A,B), Aggrecan expressed by chondrocytes in hypertrophic layer of mandibular condyle (C,D), type I collagen in the disc and in the fibrocartilage layer of mandibular condyle (E,F) and type II collagen in the fibrocartilage layer of mandibular condyle (G,H). Nuclei were stained with 4′,6-diamidino-2-phenylindole (DAPI). Condyle (C); Disc (D); Glenoid fossa (G)[1].

TMJ Tissue Engineering: Cell Strategies:

Two methods are possible in cartilage and bone engineering: (1) in situ tissue engineering, which involves an incorporation of an acellular scaffold matrix attracting local cells (cell homing) guiding the process of regeneration; (2) ex vivo cell seeding on the scaffold, which provides enough competent cells to orchestrate the regenerative mechanism.[9]

Autogenic cells are the ideal cell source for tissue regeneration. Fibrochondrocytes from mandibular condyle seeded on polyglycolic acid (PGA) scaffolds showed weaker regenerative capacities than chondrocytes from ankle joint. Notably, they produced less GAGS and collagens.[10, 11] In the same way, TMJ disc cells as compared to costal chondrocytes have inferior biochemical qualities and so produce less GAGs and collagens.[10, 11]

To regenerate TMJ condylar cartilage, primary costal-chondrocytes or hyaline cartilage cells from all cartilages in the body can be used.11, 12

Bone marrow mesenchymal stem cells (BMSCs) provide a high rate of cell growth and division. Their advantage is the important volume of cells available and the numerous kind of possible differentiation. They can promote bone and cartilage regeneration of TMJ. Their disadvantage is their tendency to endochondral ossification.[13, 14]

Adipose stem cells (ADSCs) could be a potential cell source for TMJ engineering.13 They are pluripotent mesenchymal stem cells that present multilineage differentiation. These stem cells reaped from adipose tissue are easily obtainable whatever the quantity needed.[14]

Different tooth-derived stem cells are also potential competent cells for TMJ regeneration. Periodontal ligament stem cells (PDLSCs) and stem cells from apical papilla (SCAPs) similar to mesenchymal stem cells (MSCs)15 are able to differentiate into chondrocytes and osteoblasts.16 Dental follicle progenitor cells (DFPCs) which are stem cells from dental follicles involved in early tooth formation phases can also differentiate into chondrocytes and osteoblasts.[15]

Dental pulp stem cells (DPSCs) mesenchymal stem cells from dental pulp[17] are known to differentiate into different kinds of cells, such as osteoblasts and chondrogenic cells.[15] They are particularly adequate for regeneration of mineralized tissue. Their multipotency, proliferation rate and availability appear better than those of BMSCs. The capacity of osteogenic differentiation of DPSCs is well-documented. DPSCs and collagen sponges showed excellent results inside human mandibular defects.[16]

For regeneration of discal fibrocartilage, dermal fibroblasts are promising. Easily available, these autologous cells seeded in quantity and treated with IGF-1 showed a high chondrogenic potential.[18]

Scaffolds for TMJ Cartilage Regeneration:

Hyaluronic acid (HA) is a polysaccharide abundant in cartilaginous matrices, which constitutes an ideal chondrogenic microenvironment, ideal for cartilage regeneration.[18]

Agarose is a polysaccharide extracted from seaweed, used as agar for cell culture. Its advantage is its adaptable stiffness, which allows an easy variation of mechanical features of the scaffold.19 Agarose scaffolds promote differentiation of different stem cells, such as MSCs and ADSCs into chondrocytes.[20,21]

Poly-vinyl alcohol (PVA) is a hydrophilic polymer which is also very appropriate for cartilage regeneration due to its high water content and its elastic properties.[22] Its capacity to promote repair of articular cartilage is well-documented.[23]

Poly-L-lactic-co glycolic acid (PLGA) is a synthetic polymer approved by the FDA for clinical applications which is greatly interesting for cartilage regeneration. The versatility of its structure allows also a modulation of mechanical properties of the scaffold. PLGA scaffolds promote colonization and differentiation of MSCs in vivo.[24]

Scaffold for Fibrocartilage Regeneration:

An aporous scaffold of polyglycerol sebacate (PGS), an elastomer, was used for regeneration of the TMJ disc. PGS scaffolds revealed to be favorable for culture of goat fibrochondrocytes and therefore for TMJ disc regeneration.[25] A mixed scaffold made by polytetrafluorethylene monofilaments, PLA monofilaments, polyamide monofilaments, and natural bone has been shown to support human and porcine disc cells culture and expansion.[26]

Scaffold for Osteochondral Regeneration:

Collagens are natural polymers very convenient for osteochondral regeneration and also for total TMJ disc reconstruction .[27] Collagens can be used as a gel which gives the opportunity to be injected into the narrow space of TMJ. Rigidity must be weak enough to allow intra-articular injection and important enough to allow cell adhesion and proliferation.

Gelatin, derived from the lysis of collagen is also appropriate for osteochondral regeneration. Gelatin extracellular environment is favorable to the adhesion and colonization of chondrocytes.[28]

Nanofibers constitute pro-regenerative biomimetic extracellular matrices very interesting for tissue regeneration. The electro spinning technique makes it possible to obtain different matrices made of synthetic and natural polymers whose nanofiber diameter is close to the size of the collagen nanofibers (50–500 nm). The network of electro spun nanofibers as well as the micro pores formed (less than 100 m in diameter) mimics the structure of the connective tissue matrix.[29, 30] Poly (e- caprolactone) (PCL) is a biodegradable synthetic polymer, approved by the FDA for

clinical applications. Electro spun matrices of PCL show favorable results for osteochondral regeneration[31] (Figure 3)[1]

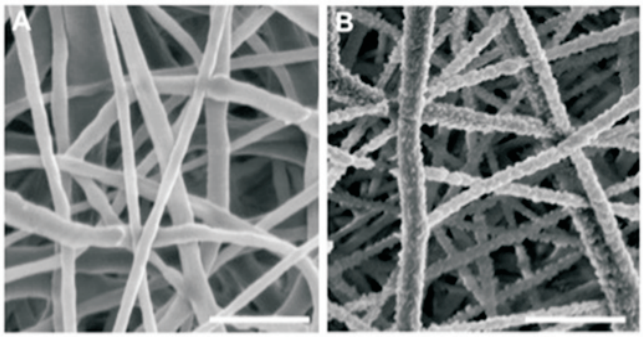

Figure 3.Scanning electron microscopy (SEM) observations of nanofibrous pro-regenerative

Biomimetic implants: Poly (e-caprolactone) implant with an electro spun nanofiber network mimicking the pattern of the connective tissue matrix (A); Poly (e-caprolactone) implant unctionalized with nanoreservoirs of growth factors on the surface[1]

Growth Factors of Interest:

Growth factors help tissue regeneration at different levels. They can promote the differentiation and proliferation of cells. They can support extracellular matrix synthesis and its mineralization.[32] They can also biologically modulate the regeneration in order to be self-limited and prevent ossification and fibrous adhesion.[4]

The three key growth factors for TMJ regeneration are basic fibroblast growth factor (bFGF), Insulin-like growth factor 1 (IGF-1) and transforming growth factor-_1 (TGF-_1). They are able to maintain disc-like tissue in culture[33, 34] and to induce BMSCs differentiation into fibroblast-like cells, synthesizing discal matrix of type I collagen and glycosaminoglycans (GAGS).[35, 36, 37]

Platelet derivative growth factor (PDGF) significantly increases the proliferation rate of the TMJ-disc derived cells, collagen and Hyaluronic acid synthesis in engineered TMJ disc. It upregulates RNA levels of type I and II collagens, matrix metalloproteinases (MMPs), and their specific tissue inhibitors (TIMPs).[38]

Drug Delivery Systems:

The best drug delivery system can be achieved by incorporating active molecules into the scaffold. Immersion of scaffold in a solution of growth factors allows a snappy release in random distribution. Covalent binding of growth factors to the scaffold improves the control of the release.

Functionalization can otherwise be accomplished by gene therapy. Gene transfer can also be conducted by viral or non-viral transduction. For tissue regeneration, the most appropriate method for gene transfer uses retroviruses, adenoviruses or adeno-associated viruses.[39, 40, 41]

Nano functionalization of scaffolds made of electro spun nanofibers is possible by different

techniques: plasma or wet chemical treatment, surface graft polymerization and co-axial electrospinning.[42] The co-axial technique consists of incorporating active molecules into the polymer solution to be electro spun and so of encapsulating them inside the nanofibers for a delayed action.43 Electro spinning can be associated with electro spraying in order to functionalize nanofibers during their production.[44] The strategy of nanofibers functionalization by BMP-2 or BMP-7 nanoreservoirs is very effective for bone regeneration. This strategy also allows the differentiation of MSCs, and accelerates the tissue regeneration in vivo.[45, 46, 47]

Osteochondral Regeneration:

Bone and cartilage regeneration occur in very different competing conditions. To engineer a biphasic osteochondral implant is therefore challenging. Ideal approaches for TMJ regeneration are a single scaffold functionalized by an osteochondral molecular gradient and a unique stem cell population associated using rapid and synchronized tissue engineering techniques.

3 D Regeneration of TMJ:

Current TMJ replacement is made by prostheses. These alloplastic strategies are constantly improving in order to obtain personalized 3D prosthesis. Personalized prostheses of TMJ fabricated by 3D-printing were designed and implanted in patients. Compared with stock devices, these personalized 3D prostheses present better biomechanical and clinical outcomes. This 3D-printing technique also improves the surgery. Indeed, the positioning of an implant is easier, due to its optimal shape and to the opportunity to have an optimal 3D surgical guide.[48,49] These crucial clinical advances of personalized 3D prosthesis benefit regenerative strategies. Indeed, personalized 3D scaffolds can be considered. In that direction, the computer-designed nanofibrous and micro porous scaffolds proposed by Chen et al. are very attractive and lead the way of a personalized 3D bone regenerative nanomedicine.[50]

Currently, different techniques exist to produce 3D scaffolds such as phase separation, self-assembly, electro spinning and bioprinting. 3D bioprinting can reproduce structure and shape of tissues identical to those found in vivo.[51] This technique works in a layer-by-layer fashion, in which cells and growth factors can be included, allowing the control of the entire architecture of the tissues to be reproduced. These technologies participate to significant advances in tissue engineering and are promising for future clinical regenerative strategies. A personalized 3D polyamide implant coated by nanoscale hydroxyapatite was rapidly designed and manufactured by computer in replacement of mandibular condyle. Its implantation into a patient showed positive clinical outcomes.[52]

Conclusions:

Prevalence of affections of TMJ is important. Severe affections are preferentially concerned by regeneration. Currently, they are treated by arthrotomy and implantation of prostheses. The recent advances in regenerative medicine for orthopedics may provide solutions for TMJ regeneration. However, anatomic, structural, and functional regeneration of TMJ is very challenging and specific. The fibro cartilaginous property of the mandibular condyle and its tight link with its fibro cartilaginous disk contribute to modifying issues. The difficulty is not to obtain a pure hyaline cartilage with an underlying bone as for the other articulations. The main issue is to get a long-term fibrocartilage well-separated from its underlying bone without ossifications or fibrous adhesions which are dramatic for crucial oral functions of patients. At present, concrete progress of TMJ arthroscopy allows adequate visualization and manipulation of pathological intra-articular tissues and motivates the emergence of innovative and specific regenerative strategies of TMJ. Numerous proposals of interest have been presented focusing on suitable cells, scaffolds or active molecules for TMJ regeneration.

Global strategies, able to support the entire mandibular condyle regeneration, are very attractive. So, the desired approach is a unique scaffold inducing an osteochondral molecular gradient containing a single stem cell population able to undergo osteogenic and chondrogenic differentiation such as BMSCs, ADSCs or DPSCs. The key to this complex regeneration is the functionalization by active molecules such as IGF-1, TGF-_1 or b-FGF. This regeneration can be optimized by nano/micro-assisted functionalization and by spatiotemporal drug delivery systems orchestrating the 3D formation of TMJ tissues.

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