Current Understanding of Pathogenesis and Treatment of TMJ Osteoarthritis

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Abstract
Osteoarthritis is a common disease that can cause severe pain and dysfunction in any joint, including the temporomandibular joint (TMJ). TMJ osteoarthritis (TMJOA) is an important subtype in the classification of temporomandibular disorders. TMJOA pathology is characterized by progressive cartilage degradation, subchondral bone remodeling, and chronic inflammation in the synovial tissue. However, the exact pathogenesis and process of TMJOA remain to be understood. An increasing number of studies have recently focused on inflammation and remodeling of subchondral bone during the early stage of TMJOA, which may elucidate the possible mechanism of initiation and progression of TMJOA. The treatment strategy for TMJOA aims at relieving pain, preventing the progression of cartilage and subchondral bone destruction, and restoring joint function. Conservative therapy with nonsteroidal anti-inflammatory drugs, splint, and physical therapy, such as low-energy laser and arthrocentesis, are the most common treatments for TMJOA. These therapies are effective in most cases in relieving the signs and symptoms, but their long-term therapeutic effect on the pathologic articular structure is unsatisfactory. A treatment that can reverse the damage of TMJOA remains unavailable to date. Treatments that prevent the progression of cartilage degradation and subchondral bone damage should be explored, and regeneration for the TMJ may provide the ideal long-term solution. This review summarizes the current understanding of mechanisms underlying the pathogenesis and treatment of TMJOA.

Keywords: temporomandibular joint, temporomandibular disorders, mandibular condyle, bone remodeling, cartilage, inflammation

Introduction
The temporomandibular joint (TMJ) is a synovial joint that performs the most complicated movement in the human body. Osteoarthritis (OA) is a degenerative disease that is characterized by progressive cartilage degradation, subchondral bone remodeling, synovitis, and chronic pain (Zarb and Carlsson 1999). However, the etiology of the majority of TMJ osteoarthritis (TMJOA) is complex and multifactorial or unknown. TMJOA is also an important subtype of temporomandibular disorders (TMDs) (Zarb and Carlsson 1999). It is secondary to disc displacement, trauma, functional overload, and developmental abnormalities, such as secondary TMJOA (Tanaka et al. 2008).

Excessive mechanical loading on normal articular cartilage or normal mechanical loading on impaired articular cartilage is generally speculated to initiate the disruption of cartilage matrix homeostasis, resulting in OA (Tanaka et al. 2008). However, TMJOA may differ from OA in knee or hip, which is closely related to aging, obesity, and overload (Herrero-Beaumont et al. 2009). Overload of the TMJ, including severe malocclusion, skeletal jaw asymmetry, and muscle overuse, has been considered one of the main causes for TMJOA (Tanaka et al. 2008; Matsumoto et al. 2010; Krisjane et al. 2012), but the majority of TMJOA is difficult to attribute to overload. Therefore, the causes of impaired condylar cartilage in the TMJ remain unclear. Increasing attention has focused on the inflammation and remodeling of subchondral bone, but the pathogenesis of TMJOA remains controversial and unclear.

Patients with TMJOA usually have pain and dysfunction of the TMJ with reduced quality of life. The clinical diagnosis of TMJOA is mainly based on the radiographic features of the condyle and articular eminence, including erosive resorption, sclerosis, attrition, osteophyte formation, and cyst-like change (Zhao et al. 2011; Kalladka et al. 2014). Recently, cone-beam...
computed tomography (CBCT) has provided more detailed change of TMJ bone than conventional radiographic methods (tomography, Schuller’s projection, spiral computed tomography, etc.), demonstrating a special advantage in TMJOA diagnosis (dos Anjos Pontual et al. 2012). Treatment of TMJOA is directed at relieving pain, decelerating the progress of the disease, and restoring TMJ function. The pain of patients with TMJOA can be mostly managed effectively with nonsteroidal anti-inflammatory drugs (NSAIDs) or arthrocentesis (Machon et al. 2011). Given the limited understanding of its pathogenesis (dos Anjos Pontual et al. 2012). This review briefly summarizes the current understanding of mechanisms underlying the pathogenesis and treatment of TMJOA published from 2010 to 2014.

Part I. Pathogenesis of TMJOA

Inflammation

TMJOA is classified as a “low-inflammatory arthritic condition,” as opposed to rheumatoid arthritis, which is classified as a high-inflammatory condition (de Souza et al. 2012). However, considerable attention has been on the importance of inflammation in the progression of TMJOA. Interleukin (IL)–12 and several other inflammatory cytokines, including IL-1β, IL-6, and tumor necrosis factor (TNF)–α, are increased in the synovial fluid of patients with TMJOA (Vernal et al. 2008; Cevidanes et al. 2014). Monocyte chemoattractant protein (MCP)–1 is also elevated in the inflamed synovial tissues and fluids of patients with OA and is highly upregulated in IL-1β–stimulated synoviocytes of the TMJ (Ogura et al. 2010). MCP-1 is speculated to play an important role in recruiting mononuclear cells to inflamed synovial tissues. Expression of IL-1β and TNF-α is reported to be increased in the experimental chronic inflammation of rodent TMJs, implying that they can be one of the causes for the degenerative changes of TMJ; moreover, the biomechanical property of the disc is decreased in this model (Wang et al. 2014), implying that chronic inflammation in TMJ deteriorates the adaptive capability of the TMJ.

The concentrations of carboxy-terminal telopeptides I and II (CTX-I and CTX-II), serum cartilage oligomeric matrix protein, and prostaglandin E$_2$ (PGE$_2$) are higher in the synovial fluid of patients with TMJOA than in the knee joints of patients with OA (Voš et al. 2014). The levels of these markers are not significantly increased in the synovial fluid of patients with
Abnormal Remodeling of Subchondral Bone

The clinical diagnosis of TMJOA is mainly based on the radiographic features of the subchondral bone (Kalladka et al. 2014), indicating the important role of subchondral bone in TMJOA. The contribution of the cartilage to the pathology of TMJOA has been studied in depth. An increasing number of studies have recently focused on the effect of subchondral bone on TMJOA pathogenesis (Embree et al. 2011; Jiao et al. 2011; Wang et al. 2012). These studies suggest that increased turnover of subchondral bone plays a role in the initiation or progression of TMJOA.

In the TMJOA model induced by orthodontic disturbed dental occlusion, subchondral bone loss and decreased bone mineral density were observed following degradation of the cartilage. The chondrocytes within the degraded cartilage may regulate osteoclastogenesis by increasing the ratio of the receptor activator of nuclear factor (NF)-κB ligand (RANKL) and osteoprotegerin (OPG) and ultimately result in subchondral bone loss in TMJOA (Jiao et al. 2011). The active interaction of stromal cell–derived factor 1, which binds to its receptor on chondrocytes (CXCR4 chemokine receptor 4) and induces local increases in matrix metalloproteinase (MMP)–9 and IL-6, contributes to the remodeling of subchondral bone in a malocclusion-induced TMJOA model (Kuang et al. 2013).

The upregulation of genes involved in osteoclast activity and an increased RANKL/OPG ratio in subchondral bone likely contribute to the increased subchondral bone turnover of biglycan/fibromodulin-deficient mice during the early stage of TMJOA (Embree et al. 2011). Osteoblast-specific transforming growth factor (TGF)-β1 transgenic mice (aged 4 mo) with high levels of active TGF-β1 in the bone marrow were used to evaluate the effect of overexpressed TGF-β1 on TMJOA (Jiao et al. 2014). In this model, excessive apoptosis of the mandibular condylar chondrocytes; upregulation of MMP-9, MMP-13, and vascular endothelial growth factor (VEGF) in the chondrocytes; and fluctuant bone density of the condyle were observed, implying that TGF-β1 has an initiating role in decreasing bone mineral density and increasing subchondral bone turnover in TMJOA. Remodeling of mandibular condylar subchondral bone is frequently observed in the early stages of TMJOA, but the etiological role of subchondral bone turnover in TMJOA still needs to be further determined.

Chondrocyte Apoptosis

Chondrocyte death caused either by apoptosis or necrosis is assumed to be a central feature in the degeneration of osteoarthritic cartilage clinically or experimentally. In a rat model of iodoacetate-induced TMJOA, the apoptosis of chondrocytes is the prominent characteristic of the early phase of cartilage degradation, and the cytokines released by the apoptotic cartilage chondrocytes may contribute to the destruction of subchondral bone (Wang et al. 2012) (progression of iodoacetate-induced TMJOA in rats is shown in Fig. 1). In malocclusion-induced TMJOA in rat, enhanced chondrocyte autophagy accompanied by a reduction in mitogen-activated protein kinase kinase kinase kinase 3 and mammalian target of rapamycin activity is also observed in the early phase of cartilage degeneration of TMJ (Zhang M et al. 2013). In a senescence-accelerated mouse
model, malocclusion enhances chondrocyte apoptosis in the early stage of cartilage degradation of TMJ (Ishizuka et al. 2014). In addition, 1,25-hydroxyvitamin D (1,25(OH)2 D)–deficient mice display erosive cartilage degradation in the TMJ by inducing DNA damage, cellular senescence, and the production of senescence-associated inflammatory cytokines, indicating that 1,25(OH)2 D deficiency may play a role in the pathogenesis of TMJOA (Shen et al. 2013). Oxidative stress induced by H2O2 can elevate intracellular reactive oxygen species (ROS) and cause chondrocyte apoptosis and functional impairment in cultured TMJ chondrocytes (Ueno et al. 2011). Although antioxidant amino acid derivative N-acetyl cysteine (NAC) reduces intracellular ROS levels, prevents chondrocyte apoptosis, and increases the expression of aggrecan and type II collagen and production of proteoglycan in vitro (Ueno et al. 2011), the effect of NAC on osteoarthritic chondrocytes remains to be explored in vivo. Taken together, all the current evidence suggests that chondrocyte apoptosis plays an important role in the early phase of TMJOA.

### Catabolic Enzymes

The upregulation of catabolic enzymes in the cartilage matrix, such as MMP and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), is involved in the pathology of TMJOA. The expression of ADAMTS-5 is also upregulated in the condylar cartilage in the early stage of TMJOA (Li et al. 2014). Several studies have explored the molecular mechanisms of cartilage degradation because catabolic enzymes catabolize the extracellular matrix.

An in vitro study indicates that the molecular mechanism underlying the IL-1β–induced catabolism of mandibular condylar chondrocytes results from the upregulation of Wnt-5A by activating the NF-κB signaling pathway (Ge et al. 2011). Recently, the expression of high-temperature requirement serine protease A1 (HtrA1) is elevated in the articular cartilage of the TMJ from genetically mutated mouse OA models. This study showed that the upregulation of HtrA1 surrounding the chondrocytes during the early stages of TMJOA initiates the degradation of the chondrocyte pericellular matrix, especially type II collagen (Polur et al. 2010). This may enhance our understanding of the early steps in TMJOA pathogenesis. However, the study used collagen-deficient mice; thus, whether the HtrA1-collagen interaction affects collagen metabolism in nongenetically mutated animal models should be determined.

### Estrogen

TMJOA has a female preponderance and occurs mainly after puberty during the reproductive years (Zhao et al. 2011), suggesting a possible function of female hormones in the disease process. Therefore, the effects of estrogen on condylar
cartilage and subchondral bone have been evaluated. Conversion of estrone/17β-estradiol to proinflammatory metabolites can be found in OA synovial cells of the knee joint; this finding implies that proinflammatory metabolites in synoviocytes may be an important mechanism underlying the proinflammatory effects of estradiol in the inflamed TMJ (Schmidt et al. 2009). Estrogen inhibits the mandibular condylar chondrocyte proliferation via an estrogen receptor (ER)-β–dependent mechanism in ER-β knockout mice (Chen et al. 2014). Estrogen aggravates the degradation of cartilage and destruction of subchondral bone by upregulating Fas and caspase 3–related proapoptotic genes in an iodoacetate-induced rat model of TMJOA, and these effects of estrogen can be inhibited by an ER antagonist (Wang et al. 2013). These findings suggest that estrogen plays a role in the sexual dimorphism of TMJOA. By contrast, estrogen possesses a protective effect on the TMJ chondrocyte through inhibiting the expression of nitric oxide (Hu et al. 2013). Therefore, the role of estrogen in TMJOA pathogenesis is still inconclusive. Moreover, the effects of other female hormones, including progesterin and relaxin, on the progression of cartilage degradation in the TMJ should be evaluated further.

**Genetic Factors**

Animal models of TMJOA have been established using the transgenic method (Table). Several genes are associated with temporomandibular disorders (Smith et al. 2011). However, a recent genome-wide association study found no single-nucleotide polymorphisms associated with TMJOA diagnosed based mainly on pain and degenerative bony changes (Yamaguchi et al. 2014). The hypothesis of a genetic susceptibility or predisposition to TMJOA should be evaluated further.

Figure 2 shows the schematic view of TMJOA pathogenesis reported in recent studies.

**Part 2. Treatment of TMJOA**

TMJOA is a degenerative disease associated with inflammatory changes of the entire joint and can result in severe pain and impaired joint function (Zarb and Carlsson 1999). TMJOA therapy primarily aims to relieve symptoms, stop the disease progress, and restore TMJ function. The traditional treatment for TMJOA mainly includes nonsurgical options, such as physical therapies, occlusal splints, NSAIDs, and arthrocentesis with lubrication or corticosteroid (de Souza et al. 2012). In a review that aimed to evaluate the effect of interventions for the management of TMJOA, de Souza et al. (2012) found an equivalent pain reduction with diclofenac sodium compared with occlusal splints, as well as a similar degree of effectiveness with intra-articular injections that consisted of either sodium hyaluronate or corticosteroid. Some treatment strategies aim to reduce muscle-related overload in the TMJ. A recent retrospective clinical study reports that a stabilization splint is effective in inducing favorable condylar bone remodeling for patients with TMJOA (Ok et al. 2014). A randomized controlled trial (RCT) of 80 patients with TMJOA with single-joint symptoms suggested that arthrocentesis combined with the use of a splint improves the symptoms (Machon et al. 2011). By contrast, another RCT study on 80 patients with TMD (with only 8% patients with TMJOA) reported that a stabilization splint treatment had no additional benefit in relieving facial pain compared with counseling and masticatory muscle exercises alone in a 1-mo follow-up (Niemelä et al. 2012). Treatment of TMJOA should be directed at eliminating preexisting risk factors. A stabilization splint may be more suitable for the patients with TMJOA with evident muscle overuse or severe bruxism.

Surgery is the last recommendation for the treatment of TMJOA. Surgical intervention, such as joint replacement with autologous bone or an artificial joint, may restore joint function to some extent in severe cases with impaired joint function and intractable pain (Idle et al. 2014). However, joint replacement does not fully restore the destroyed organ, and the long-term prognosis is uncertain, with some cases requiring a second operation. Most of the treatments are effective in terms of decreasing
pain, and some treatments decelerate joint degeneration; how-
ever, treatment rarely restores the destroyed joint. RCTs, includ-
ing participants with a clear diagnosis of TMJOA, should be
couraged to provide high-level evidence for the effectiveness
of interventions for the management of TMJOA. The succe-
sing sections focus on recent studies of TMJOA treatment.

**Cytokine-based Therapy**

Cartilage is an avascular tissue with low healing potential.
Therefore, methods of stimulating the repair of cartilage by
intra-articular injection of cytokines or anticytokine have been
investigated. Intra-articular injection of IL-1 receptor antago-
nist or TNF-α inhibitors possesses cartilage-protecting effects
in the knee joint (Urech et al. 2010) but has not been attempted
to treat TMJOA.

TGF-β, promotes the synthesis of extracellular matrix in
co-cultures of fibrochondrocytes and chondrocytes (Kalpakci
et al. 2011). An in vivo study showed that the intra-articular
injection of TGF-β1 can increase the proteoglycan content in
degraded cartilage and prevent damage to subchondral bone in
TMJOA induced surgically by bilateral partial perforation of
the discs (Ying et al. 2013). The intra-articular injection of
NEL-like molecule-1 (Nell-1) into the TMJ with partial dissec-
tomy of rabbits upregulates the expression of type II collagen
and aggrecan messenger RNAs; this result suggests that the
intra-articular injection of Nell-1 is an alternative effective
treatment for the cartilage degeneration associated with
TMJOA (Xiao et al. 2012).

Platelet-rich plasma (PRP) is blood plasma that contains a
large quantity of growth factors released from highly concen-
trated activated platelets. PRP can improve bone formation in
surgically induced severe degenerative changes of TMJ in rab-
bets but shows no marked effect on repairing cartilage degra-
dation, and the long-term benefits remain unclear (Kütük et
al. 2014). Autologous conditioned serum (ACS) as a source of
IL-1 receptor antagonist (IL-1Ra) promotes the repair of carti-
lage and subchondral bone of the knee joint and is an alterna-
tive therapy for degenerative joint disease of the knee; however,
no reports exist on the use of ACS in the TMJ (Alvarez-Camino
et al. 2013). The effect of ACS on TMJOA warrants evaluation
because IL-1β also plays an important role in the initiation and
progression of TMJOA.

**NSAIDs**

Upregulation of proinflammatory cytokines is involved in the
destruction of the extracellular matrix of the TMOA and also
contributes to the chief complaint of TMJ-related pain. The
therapeutic effect of NSAIDs is mainly attributed to their inhi-
bition of cyclooxygenase (COX)-2 activity and reduction of
cytokine-induced damage to the mandibular condyle. A recent
study reported that the selective COX-2 inhibitor celecoxib
blocks the upregulation of COX-2, PGE2, aggrecanase, and
MMPs and reverses the downregulation of type II collagen and
aggrecan in the cultured mandibular condylar chondrocytes
applied with excessive cyclic tensile strain (Su et al. 2014). The
protective effects of celecoxib on the homeostasis of man-
dibular condylar chondrocytes under excessive mechanical
stress may explain the mechanism of action of NSAIDs in
TMJOA treatment.

**Viscosupplementation**

Joint lubrication is responsible for maintaining the low-friction
environment of the articular surfaces of the TMJ. The coeffi-
cient of friction of synovial fluid is higher in patients with
TMJOA than in healthy controls (Wei et al. 2010). Hyaluronic
acid (HA) is a component of normal synovial fluid and the carti-
lage matrix of the TMJ. It lubricates the joint, thereby reducing
friction and stress on the joint cartilage, and possesses an impor-
tant function in maintaining TMJ homeostasis. Supplementing
the concentration of HA in the joint with exogenous HA via
intra-articular injection after arthrocentesis has been proposed
as a treatment for joint diseases and is effective in relieving
symptoms (Guarda-Nardini et al. 2014). Intra-articular injec-
tions of sodium hyaluronate reduce the PA system activity in
the synovial fluid of patients with TMJOA, suggesting that the
protective effect of HA on TMJOA is associated with regulation
of the PA system (Tang et al. 2010). A comparative study
demonstrated that intra-articular injection of HA without
arthrocentesis is superior to NSAIDs in terms of relieving the
symptoms of TMJOA at 1-y follow-up (Triantaffilidou et al.
2013). An animal study also indicates the protective effect of
high-molecular-weight HA on iodoacetate-induced TMJOA
(Duygu et al. 2011).

However, discrepant findings have been reported. One
study reported no protective effect of HA or insulin-like growth
factor 1 (IGF-1) alone on cartilage and subchondral bone;
IGF-1 enhances proteoglycan synthesis in cartilage and improves
the repair of subchondral bone only in combination with HA in
TMJOA (Liu et al. 2011). The effect of intra-articular HA
injection on the progression of joint damage in OA and the
benefit of this treatment remain to be further evaluated.

**Regenerative Medicine**

Tissue regeneration resulting from cell-based therapy is gaining
increasing attention. Regenerative medicine emphasizes the use
of stem cells to produce specific tissues. Mesenchymal stem
cells (MSCs) are a candidate regenerative therapy for TMJOA
because of their ease of collection and ability to differentiate
into cartilage and bone. The association of MSCs with human
disease suggests novel mechanisms of pathogenesis and possi-
bleities for novel treatments. Bone- and cartilage-like structures
were observed after 7 d of in vitro culture of primary human
MSCs preconditioned in osteogenic and chondrogenic medium
and then seeded in opposite sides of a hyper-hydrated collagen
gel (Brady et al. 2011). The injection of stem cells into a defect
for regeneration of articular tissues has been proposed (Barry
and Murphy 2013). However, such studies mainly focus on OA
in the knee; few have evaluated the therapeutic effects of MSCs
in TMJOA. MSCs were reported to survive for at least 4 wk after injection into the upper compartment of the TMJ based on in vivo tracing. The intra-articular injection of MSCs can delay the destruction of cartilage, and the therapeutic effect is enhanced when the MSCs are induced to be chondrogenic in vitro prior to injection (Chen K et al. 2013). This result provides new insights into the role of MSCs in cell-based therapies for TMJOA. However, considerable uncertainty exists regarding the mechanisms and cellular interactions underlying the chondrogenic or osteogenic effects of MSCs in terms of retarding TMJOA progression. Moreover, the chondrogenic potential of MSCs has been reported most frequently in vitro, rarely in vivo. In addition to bone marrow MSCs, oral or dental MSCs should also be tested in TMJOA treatment.

Conclusions
1. Proinflammatory cytokines, including IL-1β and TNF-α, mediate the imbalance in the metabolism of articular chondrocytes during the progression of TMJOA. Chronic inflammation may deteriorate the adaptive capability of the TMJ.
2. Numerous studies have indicated that subchondral bone plays an important role in TMJOA pathology.
3. The relationships among inflammation, cartilage erosion, and subchondral bone destruction remain unclear. Mechanical sensing of the articular cartilage and subchondral bone may contribute to the understanding of TMJOA pathogenesis, but associated molecular mechanism and signal pathways are lacking.
4. RCTs, including participants with a clear diagnosis of TMJOA, should be encouraged to provide high-level evidence for the effectiveness of interventions for the management of TMJOA.
5. Most patients with TMJOA who have pain are treated effectively with NSAIDs or arthrocentesis. Disease-modifying OA drugs that prevent the progression of cartilage degradation and subchondral bone damage should be further explored.
6. Most anticytokine therapies are still in the animal study stage, and clinical trials are necessary.
7. Efforts directed toward engineering tissues for repair or replacement of the TMJ will facilitate the development of next-generation treatments and may provide the ideal long-term solution. The regeneration of TMJ cartilage and subchondral bone tissue with suitable mechanical and structural properties represents an attractive new area of research.

Author Contributions
X.D. Wang, contributed to conception, design, and data analysis, drafted and critically revised the manuscript; J.N. Zhang, contributed to data analysis, critically revised the manuscript; Y.H. Gan, Y.H. Zhou, contributed to conception and design, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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