Review

The Role of TNF- α in the Pathogenesis of Temporomandibular Disorders

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Temporomandibular disorder (TMD) is an oral dentofacial disease that is related to multiple factors such as disordered dental occlusion, emotional stress, and immune responses. In the past decades, tumor necrosis factor- α (TNF- α), a pleiotropic cytokine, has provided valuable insight into the pathogenesis of TMD, particularly in settings associated with inflammation. It is thought that TNF- α participates in the pathogenesis of TMD by triggering immune responses, deteriorating bone and cartilage, and mediating pain in the temporomandibular joint (TMJ). Initially, TNF- α plays the role of “master regulator” in the complex immune network by increasing or decreasing the production of other inflammatory cytokines. Then, the effects of TNF- α on cells, particularly on chondrocytes and synovial fibroblasts, result in pathologic cartilage degradation in TMD. Additionally, multiple downstream cytokines induced by TNF- α and neuropeptides can regulate central sensitization and inflammatory pain in TMD. Previous studies have also found some therapies target TMD by reducing the production of TNF- α or blocking TNF- α -induced pathways. All this evidence highlights the numerous associations between TNF- α and TMD; however, they are currently not fully understood and further investigations are still required for specific mechanisms and treatments targeting specific pathways. Therefore, in this review, we explored general mechanisms of TNF- α , with a focus on molecules in TNF- α -mediated pathways and their potential roles in TMD treatment. In view of the high clinical prevalence rate of TMD and damage to patients' QOL, this review provides adequate evidence for studying links between inflammation and TMD in further research and investigation.

Key words temporomandibular disorder (TMD); inflammation; cytokine; pain

1. INTRODUCTION

Temporomandibular disorders (TMD) refers to a group of clinical problems involving the temporomandibular joint (TMJ), the masticatory musculature, and related structures.¹⁾ A comprehensive taxonomic classification released by the American Academy of Orofacial pain showed that osteoarthritis, arthritis, *etc.* are common in TMD.²⁾ Clinically, TMD is characterized pain of muscles and TMJ, clicking of the joint, irregular and limited jaw motion, or restriction of joint function during mandibular movement.^{3,4)} TMD causes great damage to patients' QOL.⁵⁾ The highest incidence is found in women aged 20 to 40.^{6,7)} However, the etiology of TMD has not been fully elucidated.⁸⁾ Multiple factors entailing direct trauma, aberrant occlusal relationships, and loading imbalance of the masticatory system all contribute to pathogenesis of TMD,^{9,10)} leading to derangement of TMJ extracellular matrix, displacement of the joint disc, and release of cells and cytokines in synovial fluid (SF).¹¹⁾

Specifically, proinflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8) have been found in higher concentration in the SF of patients with TMD.^{12–15)} TNF- α , in particular, exerts critical effects in the inflammatory reactions.^{16,17)} In response to stress, infection or injury, TNF- α is released within TMJ by both immune and non-immune cells such as macrophages and synoviocytes and neurons associated with the trigeminal ganglion, causing TMJ inflammation and myofascial pain in TMD patients.¹⁸⁾ As a pleiotropic cy-

tokine that can induce cell apoptosis and necroptosis, TNF- α is thought to play a central role in the development of TMD by promoting inflammation within the joint, leading to an increase in pain nociception around the trigeminal ganglion and degeneration of the cartilaginous tissue and bone of the TMJ.^{19–22)} TNF- α is a commonly recognized contributor to pathogenesis of TMD, and there is evidence to support the role of IL-1 β and IL-6 acting synergistically with TNF- α .²³⁾

Therefore, TNF- α -related TMD is an attractive model for studying the association between inflammation and TMD. The aim of this review was to summarize the effect of TNF- α on TMD pathology and to explore possible solutions for treatment of TMD.

2. TNF- α IS ASSOCIATED WITH INFLAMMATION IN TMD

The production and concentration of TNF- α are highly involved in pathogenesis of TMD, with multiple direct or indirect impacts on the joint tissues, muscles, and their associated structures. There are many studies showing that TNF- α participates in the development of inflammation in TMD by regulating other inflammatory cytokines,²⁴⁾ causing neutrophil migration²⁵⁾ and promoting the expression of degrading enzymes.²⁶⁾

2.1. TNF- α Can Regulate Other Cytokines That Participate in the Inflammatory Process Mounting evidence has highlighted TNF- α as a “master regulator” in the inflammatory process since it can promote the production of

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Table 1. The Production of Inflammatory Cytokines by TNF- α in Temporomandibular Disorders Is Increased in the Cells Shaded in Light Gray and Decreased in the Cells Shaded in Gray

Downstream inflammatory cytokines of TNF- α	Pathogenic pathways involved	Effect on TMD	<i>In vitro</i> or <i>in vivo</i>
IL-1 β (Interleukin-1 β) ^{27,29)}	TLR4/MyD88	Blocks the chondrogenic differentiation of SFMSCs Regulates chondrocyte reaction Mediates cartilage destruction	<i>In vitro</i> & <i>in vivo</i>
IL-6 (Interleukin-6) ^{28,29)}	NF- κ B, p38, MAPK, JNK, MAPK	Directly sensitizes the primary afferent nerves and causes pain	<i>In vitro</i> & <i>in vivo</i>
IL-8 (Interleukin-8) ^{28,29)}	NF- κ B	Induces the neutrophil migration Attracts leukocytes from the blood into the inflamed tissue	<i>In vitro</i>
CCL20 (C-C motif chemokine ligand 20) ²¹⁾	NF- κ B, ERK, p38		<i>In vitro</i>
CXCL10 (C-X-C motif chemokine ligand 10) ¹⁹⁾	NF- κ B, JAK2		<i>In vitro</i>
MCP-1 (monocyte chemoattractant protein-1) ³¹⁾	MAPK, NF- κ B		<i>In vitro</i> & <i>in vivo</i>
CINC-1 (cytokine-induced neutrophil chemoattractant-1) ²⁵⁾	NF- κ B		<i>In vitro</i> & <i>in vivo</i>
RANTES (regulated on activation, normal T-cell expressed and secreted) ³²⁾	NF- κ B		<i>In vitro</i> & <i>in vivo</i>
GM-CSF (granulocyte-macrophage colony-stimulating factor) ³⁰⁾	NF- κ B, PI3K/Akt	Activates the monocyte/macrophage lineage. Induces HLA class II expression and cytokine synthesis in these target cells	<i>In vitro</i>
SDF-1 (stromal cell-derived factor-1) ²⁵⁾	NF- κ B	Induces the neutrophil migration Attracts leukocytes from the blood into the inflamed tissue	<i>In vitro</i> & <i>in vivo</i>
IL-1Ra (Interleukin-1Ra) ^{41,42)}	NF- κ B	Inhibits the inflammation and connective tissue degradation	<i>In vitro</i>

TLR4: toll-like receptor 4; MyD88: myeloid differentiation factor; NF- κ B: nuclear factor-kappa B; p38 MAPK: p38 mitogen-activated protein kinase; JNK: Janus Kinase; ERK: extracellular signal-regulated kinases; JAK2: Janus kinase 2; PI3K/Akt: phosphatidylinositol-3 kinase/protein kinase B.

other inflammatory cytokines.²⁴⁾ By modulating the network, TNF- α directly or indirectly participates in the pathogenesis of TMD.

It was shown by several studies that the cytokines TNF- α induces include, but are not limited to, IL-1 β ,²⁷⁾ IL-6,^{28,29)} IL-8,^{28,29)} granulocyte-macrophage colony-stimulating factor (GM-CSF),³⁰⁾ C-C motif chemokine ligand 20 (CCL20),²¹⁾ C-X-C motif chemokine ligand 10 (CXCL10),¹⁹⁾ monocyte chemoattractant protein-1 (MCP-1),³¹⁾ cytokine-induced neutrophil chemoattractant-1 (CINC-1)²⁵⁾ and regulated on activation, normal T-cell expressed and secreted (RANTES),³²⁾ and all of them play important roles in TMD with different effects. Their pathogenic pathways and effects on TMD are listed in Table 1.

It was demonstrated *in vitro* that TNF- α and several other proinflammatory cytokines, including IL-1, IL-6, IL-8, and GM-CSF, were spontaneously and chronically produced by dissociated synovial mononuclear cells of TMD patients *in vitro*.^{33–35)} When the biological activity of TNF- α was blocked, the production of both IL-1 protein and IL-1 β mRNA was significantly reduced, and the biological activity of IL-1 was neutralized.³⁶⁾ Therefore, the cytokines are not generated randomly but regulated by a network in which TNF- α exerts essential effects³⁷⁾ (Fig. 1).

TNF- α and other cytokines such as IL-1 β induced by TNF- α regulate chondrocyte reaction and mediate cartilage destruction.^{38,39)} TNF- α promotes the production of IL-8,^{28,29)} CCL20,²¹⁾ CXCL10,¹⁹⁾ and MCP-1³¹⁾ in human cell samples, while some rat studies show that TNF- α promotes the production of CINC-1²⁵⁾ and RANTES,³²⁾ which induces neutrophil migration and attracts leukocytes from the blood into the inflamed tissue. GM-CSF induced by TNF- α can activate the monocyte/macrophage lineage and induce HLA expression and cytokine synthesis in these human cells, causing more severe inflammation in TMD.³⁰⁾ Moreover, TNF- α is able to up-regulate crucial integrins and adhesion molecules on vascular

endothelium, including E-selectin and vascular cell adhesion molecule-1 (VCAM-1), which can promote the production of more chemokines to enhance inflammation.⁴⁰⁾

Interestingly, some studies have reported that TNF- α can regulate anti-inflammatory mediator interleukin-1Ra (IL-1Ra) *in vitro*,^{41,42)} signifying a complicated role TNF- α plays in the development of inflammation.⁴³⁾ TNF- α also reduces the production of stromal cell-derived factor-1 (SDF-1) in rats,²⁵⁾ which can induce neutrophil migration and attract leukocytes from the blood into the inflamed tissue.

2.2. TNF- α Induces Neutrophil Migration in Inflammation and Promotes the Expression of Degrading Enzymes Neutrophil migration is one of the central reactions in inflammation because neutrophils are innate effector cells that are able to rapidly respond to danger signals and mobilize.⁴⁴⁾ TNF- α itself is capable of inducing neutrophil migration, which means that TNF- α can increase the recruitment of neutrophils into the rat joint *in vivo*, playing an important role in the inflammatory process.²⁵⁾ Additionally, TNF- α can activate the release of several chemokines, including IL-8, CCL20, CXCL10, MCP-1, SDF-1, CINC-1, and RANTES, that can induce neutrophil migration, attract leukocytes from the blood into the inflamed tissue, and initiate inflammation (Table 1).

Moreover, TNF- α -induced inflammation is closely correlated with bone and cartilage degradation as a result of degradative enzymes released from joint tissues.²⁶⁾ TNF- α produced by the synovium and the chondrocytes can promote the expression of degrading enzymes such as matrix metalloproteinases (MMP) and collagenase. In TMJ in arthritic juvenile rats, it has been found that the delicate balance between synthesis and degradation in normal cartilage is disturbed because of high levels of MMP-13 induced by TNF- α .²⁵⁾ MMP-13 can degrade the core protein of aggrecan and collagen in rabbits, which facilitates spontaneous resorption of disc tissue in

Fig. 1. The Cytokines and Their Pathways Induced by TNF- α in Temporomandibular Joint Disorders

TMJ.⁴⁵⁾ Simultaneously, mandibular condylar cartilage of the human patients was degraded excessively.

2.3. Multiple Signaling Receptors and Pathways Are Involved in TNF- α -Mediated Inflammation In response to pathological conditions, TNF- α can trigger both gene activation and cell death in rats, thus promoting inflammatory reactions.¹⁷⁾ The biological effects of TNF- α are mediated by two cell-membrane receptors: tumor necrosis factor receptors (TNFR) 1 and 2.⁴⁶⁾ Zhang *et al.*⁴⁷⁾ showed the central role of TNFR1 in mediating all phases of inflammatory pain and the unique role of TNFR2 in mediating early-phase inflammatory pain in mice. The binding of TNF- α to TNFRs leads to the activation of several pathways, including nuclear factor-kappa B (NF- κ B),¹⁹⁾ p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK),²¹⁾ Janus kinase (JNK)/signal transducer and activator of transcription (STAT),¹⁹⁾ and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)⁴⁸⁾ and the triggering of cell death through apoptosis or necroptosis,²⁰⁾ leading to the production of several critical cytokines (Table 1, Fig. 1).

Most of the cytokines, including IL-6, IL-8, GM-CSF, CCL20, CXCL10, MCP-1, CINC-1, RANTES, SDF-1 and IL-1Ra are induced through the NF- κ B pathway that is initiated by TNF- α binding to TNFR1 and TNFR2, inducing phosphorylation of I κ B α . Then the activated NF- κ B translocates into the nucleus to stimulate the target inflammatory-related genes, thus causing production of these inflammatory cytokines.

Several pathways can be activated to regulate the same cytokine. CCL20 is one of those cytokines that attracts leukocytes from the blood into the inflamed tissue, playing a critical role in TMJ inflammation. It is induced *in vitro* by TNF- α

through the signaling pathways of p38 MAPK and ERK, JNK/STAT and NF- κ B in human synovial fibroblast-like cells in the TMJ.^{49,50)} In turn, CCL20 exerts its leukocytes chemoattractant activity by binding to a receptor named CCR6 and has a chemoattractant effect on CCR6-expressing leucocytes such as memory T cells, naïve B cells, and immature dendritic cells.

In addition, apoptosis, one of pathways triggering cell death, also can be regulated by TNF- α in TMD. The cytokine was demonstrated to reduce chondrocyte apoptosis in rats by triggering anti-apoptotic family proteins such as bcl-2, which can inhibit apoptosis.⁵¹⁾

2.4. The Role of TNF- α in Inflammation Induced by Mechanical Loading Mechanical loading is one of the principal causes of TMJ disc displacement, giving insight into pathogenesis of TMD.⁵²⁾ Researchers found that cyclic tensile strain can reduce TNF- α -induced MMP-13 expression in isolated juvenile porcine condylar cells, helping to reduce the catabolic effect of TNF- α .⁵³⁾ After injecting TNF- α bilaterally into the TMJ capsule, the nocifensive response to mechanical stimulation of the cutaneous tissue above the TMJ increased significantly and was correlated with increased expression of several cytokines, giving better understanding of the temporal response of TNF- α in TMD pathology.²²⁾ At the cellular level, TNF- α seems to trigger hyperalgesia in rats by inducing peripheral and central sensitization to mechanical stimulation, on the basis of TNFR1-mediated signals *in vivo*.^{54,55)} It seems these reactions of pathological mechanical loading are induced by similar signaling as that of TNF- α , including the JNK, ERK, and p38 pathways.^{22,56)} However, nothing more is known about the site of interaction. It has been speculated that the interaction between TNF- α and mechanical loading in

Fig. 2. The Pathogenesis of TNF- α Leading to (a) Bone and Cartilage Degradation and (b) Pain in Temporomandibular Joint Disorders

condylar cells is located at the level of TNFR1.⁵³⁾

Recently, researchers also found that in age-related TMJ osteoarthritis (TMJ-OA) mice with disordered occlusion, cartilage degeneration in the condylar cartilage could be induced by an aberrant level of transforming growth factor $\beta 1$ (TGF- $\beta 1$) signaling.⁵⁷⁾ Whether there is an interaction between TGF- $\beta 1$ signaling and TNF- α and greater effects of mechanical loading on inflammation in TMD might be explored in the future.

3. TNF- α IS INVOLVED IN THE MODULATION OF BONE AND CARTILAGE DEGRADATION IN TMD

It has been shown that TNF- α has various effects on various cell types within the TMJ such as chondrocytes and synovial fibroblasts, in the context of TMD as a whole-joint disease. One of the important pathologic changes in TMD is cartilage degradation, accompanied by an inflamed synovial membrane and aberrant subchondral bone activity.^{58,59)} These pathologic changes could further lead to mandibular movement dysfunction and other severe complications (Fig. 2).

Previous *in vitro* studies on human cells have linked multiple mechanisms with TNF- α -induced cartilage degradation in TMD. In TMJ-OA,⁶⁰⁾ TNF- α are reported to induce chondrocyte apoptosis^{61,62)} by activating the apoptosis receptor pathway and mitochondrial pathway,⁶³⁾ whereas the apoptosis effect can be partially combated by TNF- α inhibitors. Peculiarly, the caspase 8-dependent mitochondrial pathway is exclusively involved in biomechanical stimulation-induced TMD without activation of apoptosis receptor pathway.⁶³⁾ TNF- α could also enhance expression of other cytokines such as IL-6,⁶⁴⁾ thus consecutively renewing local inflammatory mediators.^{65–69)} These mediators have osteocatabolic effects because of their promotion of osteoclast activity and suppression of osteoblast activity that induce the degradation of bone and cartilage.³⁹⁾

In juvenile idiopathic arthritis of TMJ, TNF- α alters aggrecan production of the condylar cells in a dose-dependent manner. It has inhibitory effects when present in high concentration and promotional effects at low concentration. Upregulation of MMP-13 was also observed in condylar cells *in vitro* responsive to TNF- α , and the impact can be aggravated by mechanical loading. This might explain how TNF- α -induced synovitis is caused by excessive mechanical stress⁴⁸⁾ and highlight MMP-13 as a potential therapeutic target in condylar cartilage degradation.

Several studies *in vivo* have shown that TNF- α participates in pathogenesis of psychological stress-induced TMD as well. Psychological stress could alter the ultrastructure of TMJ and increase TNF- α in mandibular condylar cartilage. According to Lv *et al.*, psychological stress could give rise to corticosterone and adrenocorticotropin hormone (ACTH) in plasma and induce high levels of TNF- α in a time-dependent manner. The cytokine interferes with the normal processes of cartilage turnover, leading to pathologic anabolism and catabolism of the chondrocytes *in vitro*.¹⁸⁾ Mechanically, relief of TNF- α leads to an elevated osteoprotegerin (OPG) level in SF, which could activate the receptor activator of the NF- κ B ligand pathway to modulate activity of chondrocytes *in vitro*.^{70,71)} Moreover, Jiao *et al.*⁷²⁾ found promoted CD163 expression in TNF- α -stimulated chondrocytes, concurrent with enhanced phagocytosis and migration of these cells. Blocking CD163 expression with neutralizing antibodies significantly inhibited the TNF- α -induced phagocytosis of CD163+ chondrocytes, indicating a novel function for TNF- α in promoting self-clearance of cartilage.

Apart from chondrocytes, TNF- α also affects TMD by targeting synovial fibroblasts. According to Nogami's research, TNF- α contributes to TMD in an experimental model by inducing synovial fibroblast proliferation and facilitating the secretion of pro-inflammatory cytokines such as IL-6. Another hypothesis suggests that TNF- α modulates synovial fibroblast activity *via* regulation of MMPs *in vitro*.⁷³⁾ A study by Tian *et al.*⁴⁸⁾ noted that TNF- α drove production of MMP-3 through repression of the PI3K/Akt signaling pathway in TMD patients, probably resulting in a mandibular fracture. Simultaneously, increased MMP-2, MMP-9, and MMP-13 are also described as associated with internal derangement of the TMJ.^{74,75)} Furthermore, TNF- α gives rise to inflammatory chemokines such as IL-8, CXCL1, CCL9, CXCL10, CXCL11, and CXCL20 in TMJ synovial fibroblasts *in vivo*, thus accentuating inflammation. Nakazawa *et al.*⁷⁶⁾ showed TNF- α was a promotor for Notch1 expression and NICD1 nuclear translocation in synovial fibroblasts. Since enhanced Notch cascade advances the process of TMD, TNF- α involvement could thereby intensify the disease.

Additionally, TNF- α may also act upon osteoblasts and osteoclasts, which are the predominant cell types within bone tissue.⁷⁷⁾ In rheumatoid arthritis-induced bone loss in mice, the cytokines potentiate expression of receptor activator of nuclear factor kappa B ligand (RANKL) to generate mature

osteoclasts and hamper establishment of bone matrix by abrogating osteoblast differentiation.⁷⁸⁾ However, there is no direct evidence showing the influence of TNF- α on osteoblasts or osteoclasts in TMD, and the exact role of TNF- α in TMD-initiated bone and cartilage degradation still needs further investigation.

4. TNF- α PARTIALLY CONTRIBUTES TO THE PAIN IN TMD

TNF- α is highly expressed in the synovial fluid of patients with TMD, and both SF TNF- α levels and pain levels increase in patients with internal derangement as the stage of disease progresses.⁷⁹⁾ Nordahl *et al.* revealed that the level of TNF- α in the SF was related to the pain associated with mandibular movement and tenderness in the mandibular joint synovium.⁸⁰⁾ Increasing results have shown that TNF- α plays a key role in the pain caused by TMD *via* regulation of synaptic plasticity (central sensitization) and inflammatory pain, leading to an increase in pain nociception in the tissues surrounding the joint and the trigeminal ganglia.²⁵⁾

Mechanically, the pain is correlated with dysregulation of TNF- α and malfunction of TNF- α receptors in rats.³²⁾ Activation of TNFR1 and TNFR2 can increase the spontaneous excitatory postsynaptic current (sEPSC) of spinal lamina II neurons in mice, which induces pain allergy.⁴⁷⁾ This is due to the decrease in pain threshold as a result of the regulation of the voltage-dependent sodium channel, leading to a much more sensitive reaction to the pain.⁸¹⁾ Also, the receptors have different patterns: induction of increased *N*-methyl-D-aspartate (NMDA) receptor activity induced by TNF- α involves only TNFR1, while TNFR2 has no obvious response. Furthermore, in the case of thermal hyperalgesia after inflammation in mice, TNFR1 continues to be effective at all times (1–10d), but TNFR2 primarily produces a marked effect in an early stage of thermal hyperalgesia.⁴⁷⁾

As mentioned previously, TNF- α can stimulate the production of multiple downstream cytokines to aggravate TMD pain. Studies have shown that the injection of TNF- α could increase the release of ciliary neurotrophic factor (CNTF), fractalkine (FKN), IL-1, IL-6, IP-10, vascular endothelial growth factor *in vitro*, and the levels of thymic chemokines CCL2, CXCL9, CXCL10, and RANTES in synovial tissue, serum, and trigeminal ganglion in the TMJ capsule in 2h. At 24h after TNF- α injection, the sustained increase of CNTF and thymic chemokine CCL were associated with amelioration of pain sensitivity in trigeminal nociceptive neurons *in vivo*.³²⁾ Concurrent with the increase of various pro-inflammatory factors, levels of the anti-inflammatory factors IL-1Ra and IL-4 were reduced, and the combination effect of these two inversed factors could promote chronic inflammation and a hypersensitivity reaction in the mouse model of TMJ.³²⁾ In addition to the cytokines, the mechanism by which TNF- α increases the nociceptive sensation of the trigeminal ganglion is also related to the stimulatory release of calcitonin gene-related peptide (CGRP) in neuronal cell bodies of rats. CGRP has been demonstrated to promote the release of cytokines in satellite glial cells and maintain the inflammatory environment, thereby enhancing pain sensitivity and nociception.²²⁾

In patients with TMD, TNF- α works in synergy with neuropeptides to potentiate synaptic plasticity and inflammatory

pain (Fig. 2). The double plate area of TMJ increases sensitivity to peripheral and central pain by activating the synovial neurons and glia. Pain is induced when neuropeptides stimulate synovial tissues to produce cytokines such as IL-1, IL-6, and TNF- α *in vitro*.¹⁹⁾ Release of TNF- α and IL-6 in female rats stimulates the synthesis of prostaglandins and sympathomimetic amines, which can act directly on nociceptors to cause pain allergy due to the decrease in threshold.^{43,81)}

5. TNF- α AND RELEVANT PATHWAYS MIGHT BE POTENTIAL THERAPEUTIC TARGETS IN TREATMENT FOR TMD

TNF- α may be associated with the degeneration of the TMJ cartilage and bone, the neuropathic and inflammatory pain of TMJ, and inflammation; therefore, both blocking TNF- α production and TNF- α effects are potentially valuable alternatives for future therapy of TMD.

TNF- α inhibitors or anti-TNF α agents, which have been used to reduce the production of TNF- α , can be structurally classified into two main types: one type is generated as a monoclonal antibody (mAb) such as infliximab against human TNF- α , and the other type is engineered from human soluble TNF receptors, such as etanercept. Wang *et al.* induced inflammation in the 7-week-old female Sprague–Dawley (SD) rats by double complete Freund's adjuvant (CFA) injections. Upon application of TNF- α inhibitors in these SD rats, reduced inflammation and cartilage hyperplasia were observed in rats' TMJ, highlighting TNF- α as a potential therapeutic target in treatment for TMD.⁸²⁾ Infliximab was able to partially alleviate the bite force reduction in a mouse model of TMJ pain induced by CFA⁸³⁾ and reversed the progression of TMJ arthritis in some human patients with refractory disease.⁸⁴⁾ Further investigations are still in process to evaluate the effects of the TNF receptor etanercept. Präger *et al.* constructed TMJ arthritis rabbit models using ovalbumin. Injection of etanercept in the rabbit model of TMJ arthritis showed improvement mandibular and condylar volume development but did not re-establish an entirely normal rate of growth *in vivo*.⁸⁵⁾

Other than these two types of TNF- α inhibitors, there are some other effective therapy methods that inhibit the synthesis and release of the pro-inflammatory cytokine TNF- α . Pretreatment with thalidomide can reduce pain perception by reducing the production of TNF- α *in vivo*.^{86,87)} Vale *et al.*⁸⁶⁾ found that thalidomide has anti-nociceptive activity in articular knee joint incapacitation in rats. Antinociceptive effects in neuropathic pain have also been reported in rat and mouse models. The pain in TMD can be neuropathic pain, and the structure of the TMJ and knee joint have something in common, so the application of thalidomide might reduce pain in TMD.⁸⁷⁾ β -Blockers such as propranolol are also effective in treating TMJ pain in female rats with inflammation induced by carrageenan *via* β -adrenergic receptor blockade.⁴³⁾ Specifically, strontium ranelate and *Abelmoschus esculentus* lectin (AEL) achieved their antinociceptive effects by promoting an inflammatory nociceptive threshold in rats, as well as decreasing levels of TNF- α and IL-1 β in TMJ tissue and the trigeminal ganglion.

Blocking TNF- α -induced pathways might be another potentially valuable alternative for treatment of TMD. The inhibition of Notch1 suppressed cartilage destruction in

animal models by modulating the balance between MMPs and TIMP-1 as well as suppressing the nuclear translocation and phosphorylation of NF- κ B p65.⁸⁸⁾ The blockade of Notch1 can also prevent the IL-1 β -induced inflammatory response partly by inhibiting the NF- κ B signaling pathway in temporomandibular chondrocytes in rats.⁴⁰⁾ In addition, pre-treatment with pyrrolidine dithiocarbamate (PDT), one of the NF- κ B inhibitors, can reduce the expression of cyclooxygenase-2 (COX-2) protein induced by TNF- α , alleviating joint pain and synovitis in patients with chronic pain in masticatory muscles because of TMD.⁸⁹⁾

Mesenchymal stem cell-based therapy, especially synovial fluid-derived mesenchymal stem cells, has great therapeutic potential for joint cartilage repair in patients.⁹⁰⁾ IL-1 β , IL-6, and TNF- α can significantly enhance the expression of substance P (SP) and CGRP in neurogenic TMJ synovial mesenchymal stem cells (SMSCs). In turn, the neuropeptides SP and CGRP also gave rise to the secretion of IL-1 β , IL-6, and TNF- α by neurogenic SMSCs. These findings indicated that TNF- α with other inflammatory cytokines and neuropeptides may interact mutually in TMD pain by affecting SMSCs *in vitro*.⁶⁴⁾ IL-1 β , one of important factors in TMD, was crucial in regulating chondrogenic differentiation related to mesenchymal stem cells, and NF- κ B pathway activation also contributes to this biological behavior *in vitro*.⁹¹⁾ However, whether TNF- α has more potential to treat TMD by regulating mesenchymal stem cells is still unclear, but this could become another therapeutic target.

The central role of TNF- α in the development of TMD is to trigger immune responses in TMD, inducing neutrophil migration, promoting the expression of degrading enzymes, and regulating other proinflammatory cytokines through multiple signaling pathways including NF- κ B, MAPK, ERK, and JNK/STAT pathways. Also, TNF- α participates in the modulation of bone and cartilage degradation in TMD, altering activities of osteoblasts and osteoclasts *via* induction of MMP and several proinflammatory cytokines such as IL-6. Additionally, TNF- α partially contributes to the pain in TMD by activating nociceptive trigeminal ganglion neurons. Inhibitors blocking the production of TNF- α and pathways have already shown therapeutic effects on TMD *in vivo*. All these findings may highlight TNF- α as a new therapeutic target for TMD treatment and therefore provide new insight for therapeutic intervention in TMD. Further studies aiming to elucidate the connection between TNF- α and TMD may lead to the development of novel therapies for TMD.

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