Inflammation and Tissue Remodeling as Potential Therapeutic Targets

Review

Inflammation and Temporomandibular Joint Derangement

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Temporomandibular disorders (TMD) are a common stomatognathic disease affecting all age groups. Patients with internal derangement (ID) or osteoarthritis (OA) of temporomandibular joint (TMJ) often have TMJ synovitis. When TMJ synovial membrane is damaged, many inflammatory cytokines are produced and secreted from TMJ synoviocytes to synovial fluid of TMJ. It has been widely reported that many kinds of biologic factors are produced from TMJ synoviocytes stimulated with interleukin (IL)-1beta and tumor necrosis factor (TNF)-alpha. One of the major symptoms of TMD is pain of the TMJ. Many study groups have studied relations between the development of TMJ pain and biologic factors secreted into synovial fluid of TMJ. Here, we summarize previous reports trying to elucidate this correlation. On the other hand, it has been reported that a new molecular mechanism of IL-1beta secretion called inflammasome is involved in several diseases with sterile inflammation. Because TMJ synovitis with ID and OA of TMJ is also sterile inflammation, inflammasome may be involved in the development of TMJ synovial inflammation. This review describes some molecular mechanisms underlying inflammation in TMJ, especially in TMJ synovitis, which may be useful for the development of new therapies against TMD.

Key words temporomandibular joint (TMJ); temporomandibular disorders (TMD); inflammation; TMJ synovitis; inflammatory cytokine; inflammasome

1. INTRODUCTION

Recently, the number of people who complain of feeling incongruence of the temporomandibular joint (TMJ), for example, pain, joint noise, and restricted mandibular movement, has been increasing. These dysfunctions may impose several serious lifestyle impediments including eating or conversation. Especially, pain on TMJ or masticatory muscles may be a frequent symptom. The National Institute of Dental and Craniofacial Research (NIDCR) has reported that the most common cause of facial pain is a group of conditions called temporomandibular disorders (TMD). In U.S.A., Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) were published in early 2014 and many clinicians and researchers have assessed the diagnosis for TMD based on DC/TMD. In Japan, “definition of temporomandibular disorders” and “classification of temporomandibular disorders” were revised by the Japanese Society for Temporomandibular Joint in 2013; TMD was defined as myalgia of the masticatory muscle, arthralgia of TMJ, TMJ disc derangement (with or without reduction), and osteoarthritis/osteoarthritis (OA) of TMJ.

One of the main causes of TMJ pain is temporomandibular synovitis, inflammation on synovial membrane of TMJ. Temporomandibular synovitis occurs by excessive force to TMJ, which causes over-stretching and strain of the articular capsule, articular ligament, and surrounding tissue of articular disc, or OA of TMJ. Internal derangement (ID) or OA of the TMJ is often accompanied by TMJ synovial inflammation. The temporomandibular synoviocytes, which exist in the synovial lining, secrete synovial fluid and thereby enable smooth movement of TMJ. However, if inflammation occurs on TMJ synovial membrane, several biomarkers, for example, cytokines, eicosanoids, growth factors, and proteinases are secreted in synovial fluid of TMJ. These factors facilitate further expansion of inflammation on TMJ sites. Moreover, some research groups including our study team have reported the production and secretion of inflammatory cytokines or chemokines from synoviocytes or fibroblast-like synoviocytes derived from human or experimental animals after stimulation with proinflammatory cytokines, such as interleukin (IL)-1beta or tumor necrosis factor (TNF)-alpha in in vitro experiments. In future, it is conceivable that several cytokines in synovial fluid from TMD patients could be practically used as clinical biomarkers for the diagnosis and treatment of TMD. Moreover, TMD-specific inflammatory cytokines if identified, may be expected to establish a specific factor-targeted new innovative therapy or develop new therapeutic drugs.

The present review focuses on relations between inflammation of TMJ, especially TMJ synovitis, and inflammatory cytokines/chemokines, and summarizes previous reports on the structure of TMJ and TMJ synovial membrane, some inflammatory cytokines secreted from inflamed TMJ synoviocytes, and correlations with TMJ pain, as well as the possibility of involvement in the “inflammasome,” which is currently of great interest in the context of TMJ inflammation.
2. STRUCTURE OF TMJ AND TMJ SYNOVIAL MEMBRANE

TMJ is a synovial joint comprising the mandibular fossa of temporal bone and mandibular condyle. The articular disc is a hard-dense fibrous connective tissue with compressed collagen fibers lying bilaterally between the mandibular fossa of temporal bone and mandibular condyle (Fig. 1). The TMJ is covered with articular capsule, which is a thick connective tissue membrane. The articular capsule is largely divided into an outer fibrous layer and inner synovial membrane.4) The synovial membrane consists of layers of two types: a synovial lining cell layer, called the synovial intima; and a connective tissue sublining layer.4,5) Electron microscopy has revealed two different cell types in the synovial intima: macrophage-like type A cells and fibroblast-like type B cells.4,5) However, the lining cells are heterogeneous; therefore the detailed origin and functional differences of these cells remain unclear.4)

Some research groups including our team usually have used the primarily cultured cells derived from human or murine synovial tissues of the TMJ for in vitro experimental study without sorting macrophage-like A cells, fibroblast-like B cells, or fibroblast-like synoviocytes.8,13,16–18)

3. TMJ SYNOVITIS AND INFLAMMATORY CYTOKINES

In the TMJ synovial lining in patients with ID or OA of the TMJ, increase of capillary vessel or hyperemia and infiltration of inflammatory cells such as T cells or monocytes/macrophages are observed by arthroscopical or histopathological analysis.19–21) According to a number of reports, several cytokines/chemokines have been detected in synovial fluid from patients with ID or OA of TMJ.6,7,22–24) The most representative pro-inflammatory cytokines in synovial fluid from TMD patients are IL-1beta and TNF-alpha.6,7) These cytokines cause the expression of eicosanoids,25) chemokines, and proteins11,12) in TMJ synoviocytes. However, it remains unclear how synovial membrane stimulated with these cytokines promotes progression and expansion of inflammation in TMJ sites. Here, we investigated, using cells gained from synovial lining of the TMJ, the molecular mechanisms in TMJ inflammation and raised the possibility of relations between several cytokines and fibrosis and a shift to chronic inflammation.13)

We focused on monocyte chemoattractive protein-1 (MCP-1), one of the main migration-induced chemokines of monocytes/macrophages to inflammation sites.26) At first, we obtained TMJ synoviocyte-like cells (TMJSCs) from TMJ-surrounded tissues of adult mouse and confirmed that TMJSCs stimulated with IL-1beta produced and released MCP-1, which is thought involved in early stages of TMJ inflammation. It has been reported that human TMJ synoviocytes also increase MCP-1 production by IL-1beta stimulation.17) Intriguingly, we found that cell–cell interactions between IL-1beta-stimulated TMJSCs and monocytes/macrophages augment MCP-1 production in both a cell–cell contact-dependent and -indepen-

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Fig. 1. Anatomy of Temporomandibular Joint (TMJ)
Lateral view of cranial bone and sagittal section of human TMJ.

Fig. 2. Cell–Cell Interactions between Monocytes/Macrophages and Synoviocyte-Like Cells Promote Inflammatory Cell Infiltration Mediated by Augmentation of MCP-1 Production in Temporomandibular Joint
Schema summarized from Ibi et al.13) (Color figure can be accessed in the online version.)
dent manner. We also confirmed that this increase of MCP-1 production in co-culture consisting of TMJSCs and monocytes/macrophages without cell–cell contact is mediated by some soluble factors other than IL-1β. Therefore it is likely that MCP-1 may be the main factor that causes the initiation, subsequent progression, and chronicity of inflammation on TMJ synovial membrane (Fig. 2).

4. RELATIONS BETWEEN PAIN ON TMJ AND INFLAMMATORY CYTOKINES

Pain associated with TMJ in ID or OA may be inflammatory pain following damage of posterior tissues of the articular disc, synovial membrane, and cartilage, or referred pain. Inflammatory pain may be initiated by production of inflammatory mediators such as prostaglandins, leukotrienes, bradykinin, and serotonin, which are released by inflammatory cells. In general, these mediators are produced from arachidonic acid by the cyclooxygenase (COX)-1 and COX-2 in inflammatory sites. To suppress this signaling cascade, non-steroidal anti-inflammatory drugs (NSAIDs) may be used to inhibit COX enzymes and thereby prevent the production of prostaglandins and suppress pain of TMJ. 27)

Although it has been reported that these inflammatory mediators were detected in synovial tissues and synovial fluid with ID or OA of TMJ patients 28–30 and in vitro experiments related to suppression of prostaglandin E2 production, 31 further investigations are necessary for the deeper elucidation of relations among these inflammatory mediators and TMJ pain at cellular and molecular levels. 7) On the other hand, correlations between inflammatory cytokines and TMJ pain have been clinically studied by analyzing MRI images and synovial fluid from patients with ID or OA of TMJ 24,32,33) As for IL-1β and TNF, some study groups have demonstrated correlations between synovial fluid from patients with ID or OA of TMJ and TMJ pain level. 23,32,34) However, because ID of TMJ may be symptom free, associations between cytokines and TMJ pain levels also remain poorly understood. The degree of inflammation on TMJ seems important for the development of pain or symptoms. 7)

Other biomarkers such as proteases, growth factors, and proteoglycans have been detected in TMJ synovial fluid of patients with ID of TMJ 7,32,35) However, correlations between these biomarkers and TMJ pain have been little studied; one report found that matrix metalloproteinase-3 (MMP-3) activation in TMJ synovial fluid is a hallmark of TMJ pain. 26) Therefore these biomarkers may cause cartilage destruction of TMJ, such as OA of TMJ other than the pain of TMJ in ID. 7)

Although it has not been reported that MCP-1 is correlated to TMJ pain, a recent study found that macrophage/microglia activation is involved in the development of painful TMD in mice. 37) Hence MCP-1 might become a novel biomarker of pain in TMD patients. Further study is necessary to elucidate whether MCP-1 is closely related to the development of pain in TMJ sites.

5. POSSIBILITY OF INVOLVEMENT OF UNKNOWN MOLECULAR MECHANISMS IN TMJ INFLAMMATION

Many study groups have reported the involvement of IL-1β in inflammatory response on TMJ. 8,22,24) IL-1β may be the most potent pro-inflammatory cytokine in the pathogenesis of TMD. Recently, as a new mechanism of inflammation induction, especially the secretion of IL-1β and IL-18, “inflammasome” activation has been investigated in several diseases, for example, infections, metabolic syndrome, neurodegenerative disorders, and cardiovascular diseases. 35,39) The inflammasome is a cytoplasmic protein complex comprising a sensor protein such as absent in melanoma 2 (AIM2)-like receptor, ALR, or the NLR [nucleotide-binding domain (NBD) and leucine-rich-repeat-(LRR)-containing] family, an adaptor protein known as apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC), and azymogen procaspase-1. 40,41) When specific stimuli are sensed by cells, the active caspase-1 process from precursor of IL-1β and IL-18 (pro-IL-1β and pro-IL-18) to mature form of IL-1β and IL-18 into the cytoplasm. Consequently, IL-1β and IL-18 are secreted outside cells and evoke an inflammatory response. Because TMJ inflammation on ID and OA of TMJ are also sterile inflammations akin to atherosclerosis and Alzheimer’s disease, there is a possibility that the inflammasome may be a suitable target of therapy in TMJ inflammation. Recent experiments have investigated the possible involvement of NLRP3, one of the sensor proteins of inflammasome in OA pathology. 42) In TMJ inflammation, accumulation of further data may clarify the role of inflammasome including danger-associated molecular patterns (DAMPs) and identification of cells involved in inflammasome activation in the near future.

6. CONCLUSION

The pain, joint noise, and jaw movement dysfunction in TMD negatively impinge the lifestyles of those affected. Inflammatory cytokines secreted into synovial fluid of TMJ in inflamed TMJ sites may be involved in augmentation of inflammation, transition to chronicity, and the development of TMJ pain. Further investigations are necessary to better to elucidate their causal relations. Because IL-1β is a major proinflammatory cytokine in sterile TMJ inflammation, the inflammasome might be involved in the development of TMJ inflammation. Further work in this area promises to lead to the development of novel therapies against TMD.

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Conflict of Interest The author declares no conflict of interest.

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