Molecular biology of frozen shoulder-induced limitation of shoulder joint movements

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Frozen shoulder is a chronic condition characterized by pain in the shoulder and restriction of movements in all directions. Some patients are left with long-term limitation of shoulder joint activity with various severities, which results in reduced quality of life. Currently, there is a paucity of literature on the molecular biology of frozen shoulder, and the molecular biological mechanism for periarthritis-induced limitation of shoulder joint movements remains unclear. Research in this field is focused on inflammation and cytokines associated with fibrosis. Repeated investigations confirmed alterations of specified inflammatory mediators and fibrosis-associated cytokines, which might be involved in the pathogenesis of frozen shoulder by causing structural changes of the shoulder joint and eventually the limitation of shoulder movements. The aim of this article is to review studies on molecular biology of frozen shoulder and provide a reference for subsequent research, treatment, and development of new drugs.

Key words: Cytokines, frozen shoulder, limitation of movements, molecular biology

DEFINITION AND BASIC CLINICAL DATA

The frozen shoulder is a multifactorial disease characterized by inflammatory adhesion and stiffness of the glenohumeral capsule, pain in the shoulder, and limitation of movements in all directions (especially abduction, external rotation, and posterior extension). The age of onset falls between 30 and 70 years, with an average of fifty.[1] More females are affected than males, with the left shoulder more often involved than the right.[1] The prevalence of frozen shoulder is about 2%–5%.[2,3] Risk factors include diabetes, thyroid diseases, stroke, and autoimmune diseases.[4] The prevalence of frozen shoulder in patients with diabetes is as high as 10%–20%[4-6] and in patients with paralysis 16%–84%.[7,8]

LIMITATION OF SHOULDER MOVEMENTS

The most typical manifestation of frozen shoulder is limitation of active and passive shoulder movements in all directions in spite of the application of analgesics,[9-11] which demonstrates that such movement limitation is mainly caused by pathological alterations of the shoulder joint, and pain is only a minor pathogenic factor. The natural course of frozen shoulder consists of three stages: pain, stiffness, and recovery.[2,9] It was believed that frozen shoulder is a self-limited disease, in which shoulder pain and function would fully recover after the typical three stages in most cases.[9,12] However, a majority of current reports state that under the current therapies such as medications, shockwave therapy,[13] and manipulation of the shoulder under general anesthesia,[14] complete functional recovery is almost impossible without surgical intervention.[2,10,11]

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In a follow-up study of 41 patients with frozen shoulders who did not receive surgical treatment, Reeves reported that over 60% of them suffered from limitation of shoulder movement at 5- to 10-year follow-up. Shaffer *et al*.[2] followed 61 patients for an average of 7 years and found that 50% still had shoulder pain and stiffness while 70% still had limitation of shoulder movement. Imaging studies of frozen shoulders revealed reduced joint volume and a thickened and shortened glenohumeral capsule. Magnetic resonance imaging showed a significant thickening of the coracohumeral ligament and the rotator cuff interval as well as obliteration of the fat triangle between the coracoid process and the coracohumeral ligament.[15,16] Histopathologic studies suggested that the pathognomonic sign is contracture of the glenohumeral capsule as well as chronic synovial inflammation and fibrosis. In summary, limitation of shoulder movement in patients with frozen shoulder is caused by pathological changes of the shoulder joint through inflammation and fibrosis. Although the molecular biology of such limitation remains unclear, ongoing investigations have demonstrated altered expression of certain inflammatory mediators and fibrosis-associated cytokines. These cytokines might participate in the pathogenesis of frozen shoulder, induce structural changes of the shoulder joint, and eventually cause limitation of shoulder movement.

Inflammation and relevant cytokines

In the acute phase of frozen shoulder, patients experience significant and enduring limitation of movement, especially abduction, external rotation, and posterior extension, which greatly affects quality of life. In 1896, Duplay *et al*. first stated that primary frozen shoulder is periarthritis of the shoulder joint caused by subacromial synovitis. Since then, molecular biological studies on frozen shoulder have focused on inflammatory cytokines. In 1997, Rodeo *et al*. performed biopsies of shoulder capsule and synovium in seven healthy individuals and 14 patients with frozen shoulder.[17] Immunohistochemical localization and quantitative polymerase chain reaction (qPCR) revealed increased levels of interleukin-1α (IL-1α), IL-1β, and tumor necrosis factor (TNF) and demonstrated upregulation of specific cytokines in the early stage of frozen shoulder. A myriad of relevant studies indicate that angiogenesis in the capsule occurs in the early stage of frozen shoulder. This process is closely related to inflammation in that inflammatory cytokines stimulate angiogenesis, which further enhances inflammation.[18] Hand *et al*.[19] identified chronic inflammatory cells in biopsy samples of the shoulder capsules in patients with frozen shoulder, which mainly include mast cells, T-lymphocytes, B-lymphocytes, and macrophages. Recently, Lho *et al*.[20] from South Korea compared the shoulder capsule and subacromial synovium between patients with frozen shoulder (experimental group)

and patients with shoulder instability (control group). Immunohistochemical analysis and qPCR of RNA extraction showed that the expressions of IL-1α, IL-1β, TNF-α, cyclooxygenase-1 (COX-1), and COX-2 were significantly upregulated in the shoulder capsule of the experimental group. A more important finding was that expressions of IL-1α, TNF-α, and COX-2 were also significantly upregulated in the subacromial synovium of the experimental group. Furthermore, immunohistochemical analysis confirmed the increased expression of COX-2 in the shoulder capsule and subacromial synovium of the experimental group.

Results of the above-mentioned molecular biological studies suggest that angiogenesis, infiltration of inflammatory cells, and increased expressions of inflammatory cytokines, for example, COX-1, COX-2, IL-1, IL-6, and TNF-α, are present in frozen shoulder. They proved that inflammation might be the initiating manifestation of frozen shoulder at the molecular level, and COX-1, COX-2, IL-1, IL-6, TNF-α, etc., might play an important role in the triggering, regulation, and remission of inflammation in frozen shoulder. Inflammation causes adhesion, edema, and pain, which eventually leads to reduced shoulder activity.

Fibrosis and associated cytokines

Frozen shoulder is characterized by thickening and contracture of the shoulder capsule, the mechanism of which is not fully understood. It is currently known that several proteins are associated with this pathological process. Some believe that thickening and contracture of the shoulder capsule is a proliferative fibrosis disorder, which might result from excessive accumulation of extracellular matrix or inhibition of matrix degradation.[19]

In 1995, Bunker and Anthony[21] collected samples of the coracohumeral ligament and shoulder capsule from 12 patients with frozen shoulder and performed immunocytochemistry staining on sampled cells using monoclonal antibodies. They identified a significant infiltration of fibroblasts and myofibroblasts in the sample. Immunohistochemistry revealed large amounts of nodular collagen fibers in the tissue. Such findings in the ligament and capsule were similar to that identified in the lesion of Dupuytren's contracture, a proliferative fibrosis disorder. Therefore, Bunker suggested that the nature of pathological changes in frozen shoulder is fibrous proliferation. Raykha *et al*.[22] found that levels of β-catenin and insulin-like growth factor-2 (IGF-2) mRNA, which encodes the IGF-2, from frozen shoulder tissues were significantly increased. Specifically, they collected tissues of the shoulder capsule from patients with frozen shoulder or rotator cuff tear through arthroscopy and determined β-catenin levels by Western blotting while levels of IGF-2 mRNA in fibroblasts of the sample by qPCR. Therefore, they concluded that

frozen shoulder and Dupuytren's contracture shared the same pathophysiological process of fibrosis of connective tissues, and IGF-2 might be directly involved in fibrosis of the shoulder capsule in patients with frozen shoulder.

A study revealed that matrix metalloproteinases (MMPs), tissue inhibitor of metalloproteinase (TIMP), and TGF-β play important roles in fibrosis diseases, including frozen shoulder.[23]

TGF-β is a multifunctional cytokine important for gene expression of extracellular matrix, proliferation and differentiation, stroma degradation, immunomodulation, apoptosis, etc.[24] TGF-β is also a fibrosis-facilitating factor, which promotes epithelial-fibroblast transformation. It stimulates extracellular matrix synthesis, for example, collagen, fibronectin, proteoglycan, etc., in fibroblasts, expression of protein-specific surface membrane receptors in extracellular matrix, and formation of extracellular matrix.[25] It has been demonstrated that expression of TGF-β is elevated in the shoulder capsule of patients with frozen shoulder compared with that of healthy individuals,[17,20,26] which proves that TGF-β might play an important role in the fibrosis of shoulder capsule.

MMPs interact with multiple cytokines and participate in tissue fibrosis. Currently, over 20 MMPs and 4 TIMPs have been identified, which are categorized as collagenases, gelatinases, stromelysins, elastases, membrane-associated MMPs, etc., This family of enzymes possesses diverse biological activities and is crucial in degradation and remodeling of extracellular matrix. Alteration of MMPs is often associated with significant fibrosis.[27] Among the MMP family, MMP-1 and MMP-2 are related to degradation of collagen fibrils.[28] Brown *et al.*[27] cultured fibroblasts from the shoulder capsule of patients with frozen shoulders (experimental group) and healthy participants (control group) and found that the level of MMP-1 in fibroblasts of the experimental group was reduced. Expression of MMP-7, MMP-9, MMP-12, and MMP-13 was not detected in either the experimental group or the control group. Expression of MMP-14 was evidenced in 50% of the control group but in none of the experimental group. Hence, they believed that MMP-1 and MMP-14 might be crucial in the pathological fibrosis in frozen shoulder. Recently, Lubis and Lubis[26] conducted a study in which patients with frozen shoulders were randomly assigned to either the intensive stretching group or the supervised neglect group.

Serum levels of MMP-1, MMP-2, TIMP-1, TIMP-2, and TGF-β1 were measured by enzyme-linked immunosorbent assay (ELISA) and compared between normal participants and patients with frozen shoulder. The results showed that serum levels of MMP-1 and MMP-2 were significantly lower in patients with frozen shoulder than in normal controls while levels of TIMP-1, TIMP-2, and TGF-β1 were significantly elevated. Serum levels of these cytokines in the two groups of patients with frozen shoulder were measured 6 weeks and 12 weeks from baseline, along with functional assessment of the shoulder joint. It was demonstrated that serum levels of MMP-1 and MMP-2 were significantly elevated from baseline levels, with greater elevation in the intensive stretching group. Serum levels of TIMP-1, TIMP-2, and TGF-β1 in the intensive stretching group were decreased while those in the supervised neglect group remained stable. The intensive stretching group exhibited greater functional improvement than the supervised neglect group. The researchers believed that serum levels of MMP-1, MMP-2, TIMP-1, TIMP-2, and TGF-β1 might be associated with frozen shoulder and related to the pathological fibrosis process in frozen shoulder. Active stretching is helpful for improving shoulder joint function in patients with frozen shoulder. Hagiwara *et al.*[29] from Japan reported a study on fibrosis and chondrogenesis in primary frozen shoulder and proved that organization of collagen fibers was dense in the capsular tissue of frozen shoulders but loosely arranged and orderly in the capsular tissue of shoulders with rotator cuff tears. Results of qPCR revealed that expressions of collagen Type I and Type III, calcitonin gene-related peptide, substance P, and platelet-derived growth factor were significantly increased in patients with frozen shoulder than patients with rotator cuff tears. Immunohistochemistry also demonstrated upregulated expression of collagen Type I in patients with frozen shoulder.

Ha *et al.*[30] in 2014 analyzed protein levels of acid-sensing ion channel 3 (ASIC 3) in subacromial bursa and joint capsule samples from 21 patients with a rotator cuff tear, 22 patients with frozen shoulder, and 20 with shoulder instability by Western blotting. The study demonstrated significantly increased expression of ASIC 3 in patients with a rotator cuff tear and those with frozen shoulder. A recent study by Cho *et al.*[31] from South Korea collected capsular tissue and synovial fluid from 18 patients with primary frozen shoulder and 18 patients with shoulder instability and measured mRNA and protein levels of ASIC 1-3 by reverse transcriptase-polymerase chain reaction and ELISA, respectively. The results showed that mRNA and protein levels of ASIC 1-3 were significantly elevated in patients with frozen shoulder, among which ASIC 3 registered the greatest increase, which indicates that ASICs might be involved in the pathological process of frozen shoulder.

The studies mentioned above demonstrated that thickening and contracture of the shoulder capsule in frozen shoulder is a proliferative fibrosis disorder. Cytokines such as IGF-2, ASIC, TGF-β1, MMPs, and TIMPs might be involved in the

fibrotic alterations in frozen shoulder. They cause increased expression of collagen Type I and Type III, fibrosis and the shoulder joint, contracture and thickening of the shoulder capsule, decrease joint volume, and eventually limitation of shoulder movements.

Metabolism disorder

Some articles reported that frozen shoulder is significantly correlated with diabetes mellitus;[32] from some of these articles,[33] we found that frozen shoulder is also associate with hyperlipidemia, especially a nationwide population-based cohort study[32] suggests that hyperlipidemia is an independent risk factor for frozen shoulder. Cumulative detrimental effects of hyperlipidemia on tendon properties were found. Increased risk of rotator cuff disease in patients with hypercholesterolemia is possible[34] and leads to secondary frozen shoulder.[35]

However, patients taking hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have an increased risk of shoulder stiffness[36] that may predispose to frozen shoulder. Therefore, the frozen shoulder maybe correlates with the metabolism of adipose tissue.

The effects of adiponectin in human synovial fibroblasts appear to be highly selective by inducing the main mediators of rheumatoid arthritis and osteoarthritis (OA) pathophysiology, IL-6, MMP-1, and MMP-3 through the p38 mitogen-activated protein kinase (MAPK) pathway.[37,38] It reveals that MAPKs, especially p38, maybe significant pathways in adiponectin signaling in chondrocytes. From the above, we presume the proliferation of synovium and the fibrosis of shoulder capsule because of the metabolic abnormality of lipid.

The actions of adiponectin, leptin, resistin, and other less studied adipokines in OA and other rheumatic diseases have recently been reviewed by Gómez *et al.*[39] and by Fowler *et al.*[40] There are many studies about leptin in the pathophysiology of arthritis, and leptin has been proven to have proinflammatory and catabolic roles in OA.[39,41,42]

In addition, some studies found cumulative effects of hypercholesterolemia are detrimental to tendon mechanics in the mice models which are deficient for apolipoprotein E representing a hypercholesterolemic group.[43]

In summary, hyperlipidemia maybe an independent risk factor for frozen shoulder but few studies about this currently. Some adipokine hormones, such as adiponectin and leptin, had been reported to have proinflammatory and catabolic roles in OA. It is worth to investigate whether they are associated with frozen shoulder. And whether HMG-CoA inhibitors are beneficial for hyperlipidemia with

frozen shoulder. Interestingly, MAPK pathways have been proposed as therapeutic targets in frozen shoulder.

DISCUSSION

Research on molecular biology of the limitation of shoulder joint movements mainly focuses on the pathological process of inflammation and fibrosis. Current molecular biological studies have largely proved that inflammation and fibrosis are the basic pathological changes of frozen shoulder. However, the trigger of frozen shoulder is still unclear, which might be immune reaction, degenerative changes, microinjury, etc.[4,15,19] Inflammatory mediators, for example, COX-1, COX-2, IL-1, IL-6, TNF-α, etc., might play an important role in induction, regulation, and remission of inflammation. Inflammation gives rise to adhesion, edema, and pain, which lead to reduced activity of the shoulder joint and subsequent fibrosis of the shoulder joint and thickening and adhesion of the shoulder capsule.

Cytokines such as IGF-2, ASIC, TGF-β, MMPs, and TIMPs might be involved in the fibrotic changes in frozen shoulder. Particularly, the balance disorder between TGF-β and MMPs may play a very significant role in fibrosis development of the frozen shoulder [Figure 1].

They contribute to increased expression of collagen Type I and Type III, fibrosis and the shoulder joint, contracture and thickening of the shoulder capsule, and eventually limitation of shoulder movements.

Future molecular biological studies on the limitation of shoulder movements in frozen shoulder may continue to focus on cytokines associated with inflammation and fibrosis as well as mechanisms of their interaction and regulation. The latest census showed that 25% of patients with frozen shoulder have diabetes mellitus,[4] for whom early intervention should be considered in clinical practice.[44-46] On the other hand, 10%–20% patients with diabetes suffer from frozen shoulder, and it has been demonstrated that the risk of limitation of shoulder movements in patients with
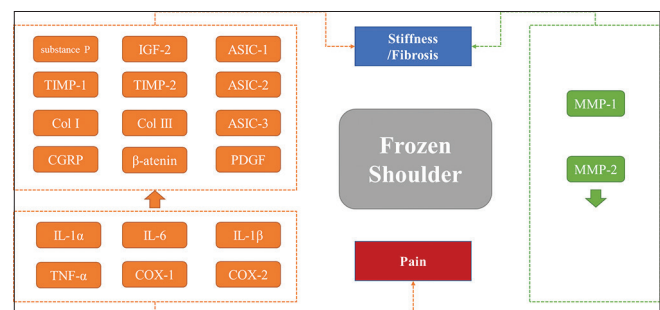

Figure 1: Cytokines and proteins related to the stiffness and pain in frozen shoulder. The orange color indicates that the expression is elevated, and the green color indicates decreased

diabetes is significantly increased.[5] Molecular mechanism of frozen shoulder or limited shoulder movements associated with diabetes might be emerging topics of interest for future research.

Conflicts of interest

There are no conflicts of interest.

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