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ORIGINAL ARTICLE

Involvement of synovial matrix degradation and angiogenesis in oxidative stress–exposed degenerative rotator cuff tears with osteoarthritis

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Background: Shoulder osteoarthritis is a gradual wearing of the articular cartilage concomitant with degenerative rotator cuff tears (RCTs). This pathologic disorder is related to inflammation, oxidative stress, and angiogenesis. Degenerative alterations may prompt production of cytokines and angiogenesis-related proteins, evoking rotator cuff diseases. This study tested the hypothesis that oxidative stress–responsive mediators can influence joint inflammation of patients with RCT.

Methods: Twelve healthy RCT patients not suffering shoulder osteoarthritis were categorized as the control group, and 24 patients were allocated to 2 RCT groups (RCTP1 and RCTP2), according to severity of RCT and glenohumeral arthritis. Cytokines, growth factors, and angiogenic biomarkers in synovial fluids, blood, platelet-rich plasma (PRP), and tendon tissues were analyzed with enzyme-linked immunosorbent assay, immunoblotting, and collagen zymography.

Results: Induction of interleukin 8, tumor necrosis factor α, and interleukin 1β was considerably elevated in synovial fluids of RCTP groups ($P = .0398$, $P = .0428$, $P = .0828$, respectively). The joint inflammation highly enhanced insulin-like growth factor 1 and transforming growth factor β1 (TGF-β1) in the synovial fluids and serum. Angiogenesis-related angiopoietin (Ang) 1 and 2, Tie-2, and hypoxia-inducible factor 1α were upregulated in reactive oxygen species–exposed RCTP synovium ($P < .05$). The production of matrix metalloproteinase 1 markedly increased in synovial fluids of the RCTP group ($P = .043$), whereas tissue collagen type I expression diminished with reduction of connective tissue growth factor expression ($P = .032$). Although the secretion of platelet-derived growth factor AB and vascular endothelial growth factor was marginal in the circulation ($P = .714$, $P = .335$), platelet-derived growth factor AB, TGF-β1, Ang-1, and matrix metalloproteinase 1 were enriched in PRP of the RCTP group ($P < .001$, $P = .002$, $P = .0389$, respectively).

Conclusions: Synovial matrix degradation and oxidative stress–triggered angiogenesis may be involved in inducing RCT with joint inflammation. TGF-β1, Ang-1, and Ang-2 are the major components to repair RCT and to alleviate joint inflammation in PRP therapy.

This study was approved by the Institutional Review Board of Kangnam Sacred Heart Hospital, Hallym University College of Medicine: No. 2016-04-33. All patients provided informed consent.

Kyu-Cheol Noh and Sin-Hye Park contributed equally to this study.

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Degenerative arthritis is a disease in which articular cartilage in the joints is gradually worn out and disappears, resulting in increase in the friction between the bones and causing severe pain and stiffness of the joints.[28] The rotator cuff tear (RCT) is the most common cause of chronic pain in adult shoulders.[27,34] In addition, it can occur in adults who heavily use their arms or repeatedly perform intense exercise.[19,34] Although numerous factors cause shoulder osteoarthritis and degenerative RCT, their occurrence increases with advancing age.[34] RCT induces local inflammatory response and steady progression of glenohumeral arthritis.[1] Early rotator cuff lesions have no apparent changes in arthritis of the glenohumeral joint, but RCT expedites arthritis progression and accompanies local inflammation.[1,11] Osteoarthritis cartilage produces various cytokines and contributes to local inflammation and pain.[32]

Previous studies focused on clinical treatments of glenohumeral arthritis and RCT,[16,21] but current studies aim to elucidate molecular mechanisms underlying fundamental causes.[31] A recent study has shown that the supplementation of platelet-rich plasma (PRP) alleviates pain due to arthroscopic repair of full-thickness RCT.[7] PRP is composed of various constituents, such as growth factors, signal transducers, and cytokines required for the early stage of wound healing.[8,9] Potentially therapeutic growth factors are platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), insulin-like growth factor (IGF), and vascular endothelial growth factor (VEGF).[9] Because several cytokines play critical roles in chemotaxis, cell proliferation and differentiation, and angiogenesis, the cytokines may enhance RCT healing and tendon tissue repair.[12] However, the effectiveness of optimal PRP application in arthroscopic rotator cuff repair is still conflicting and currently being investigated.

There are alterations of cytokine levels in synovial fluid and peripheral blood of osteoarthritic patients that may contribute to the diagnosis and severity of osteoarthritis.[20] Some growth factors are markedly upregulated after tendon injury and activated at manifold stages of the tendon healing process.[24] The synovial fluid exhibits an inflammation-evoking and matrix-degrading environment after intra-articular ankle fracture that takes place in the subacromial bursa of RCT patients.[2] The collagen expression declines in acutely injured menisci excised from knee joint operations.[23] In fact, the degenerative changes in rotator cuff diseases produce inflammation- and vascular angiogenesis-related cytokines for the immune response to arthroscopic surgery.[29] Tendinopathy and RCT result from hypoxic damage, leading to the induction of hypoxia-inducible factor (HIF-1α) and VEGF, important inducers of neoangiogenesis.[3]

This study tested the hypothesis that synovial TGF-β1, angiopoietin 1 (Ang-1), and Ang-2 can influence joint inflammation of patients with RCT as major components to repair of RCT. Expression profiles of growth factors, cytokines, and angiogenesis-related proteins were determined in synovial fluids, serum, and PRP from patients with both RCT and shoulder osteoarthritis and from patients without clinical symptoms of these diseases. The modulation of growth factors and oxidative stress–responsive mediators may be a potential therapeutic option to prevent degenerative RCT.

Materials and methods

Materials

Reagent chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA), unless specifically stated elsewhere. Antibodies of human procollagen type I and collagen type I involved in tendon healing and antibody of human angiopoietin receptor Tie-2 were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Cell Signaling Technology (Boston, MA, USA) provided human antibody of connective tissue growth factor (CTGF) involved in tissue wound repair. Jackson ImmunoReserach Laboratories (West Grove, PA, USA) provided horseradish peroxidase (HRP)-conjugated immunoglobulin G.

Patient recruitment and classification

From January 1, 2016, to November 30, 2016, patients who failed to respond to conservative management and continued to experience unacceptable pain and weakness in the distressed shoulder were enrolled as RCT patients (RCTPs). RCTPs were diagnosed with chronic RCT confirmed by preoperative magnetic resonance imaging. The tear sizes were <4 cm in width, and all the RCTPs had degenerative features of the glenohumeral joint on radiologic images. Fifteen patients with shoulder joint instability or superior labrum anterior-posterior lesions were enrolled as the control group. All patients aged between 19 and 80 years were scheduled for arthroscopic surgery. Patients who had acute or subacute trauma history were excluded, and patients who had previous operations on a distressed shoulder or medical problems such as cardiac disease, respiratory disease, or pre-existing coagulopathy were also excluded. After exclusion, a total of 36 patients participated in this study, and no one declined or dropped out. Twelve patients aged 19-32 years (21.6 ± 3.7 years), all men, were classified as the control group. The remaining 24 patients aged 46-75 years (57.4 ± 8.3 years; 14 men and 10 women) were allocated to the RCTP group. The mean age of the RCTP group was significantly higher than that of the control group ($P < .001$). The RCTP group was further subdivided into RCTP1 and RCTP2 groups by determining glenohumeral joint inflammation and extension of RCT according to the Walch classification of