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Higher Circulating Concentration of Interleukin-38 in Patients with Knee Osteoarthritis: Its Association with Disease Severity

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INTRODUCTION

Osteoarthritis (OA) is known as the most common form of arthritis which frequently affects joints of the hip, knee, hand, foot, and spine.1 Previous studies revealed that inflammation plays a pivotal role in the OA pathogenesis and various inflammatory mediators were altered in OA patients that strongly associated with disease progression, pain, and disability.2 Leukocytes infiltration particularly, macrophages and T cells could be observed in the synovium of OA patients that may play a fundamental role in the disease's pathogenesis.3,4 The possible mechanisms by which interleukin (IL)-38 inhibits inflammatory responses were exhibited in Figure 1. IL-38 is an anti-inflammatory cytokine that is mainly expressed in some organs such as the heart, placenta, fetal liver, skin, spleen, thymus, and tonsil.5 IL-38 exerts its anti-inflammatory properties partly through binding to the interleukin 1 receptor accessory protein-like 1 (IL-1RAPL1) or IL-36 receptor and prevent the downstream signaling pathways, such as nuclear factor-κB (NF-κB) which is involved in the expression of inflammatory cytokines including IL-1β, IL-6, and tumor necrosis factor-alpha (TNF- α).6 A remarkable association has been reported between IL-38 levels and inflammatory diseases, such as rheumatoid arthritis which is very similar to OA.7,8 However, the relationship between IL-38 levels with OA activity indexes and its clinical manifestations are still obscure. Due to the increased expression of inflammatory cytokines in diseases such as OA, in a compensatory mechanism, anti-inflammatory cytokines such as IL-38 have begun to increase, although its levels can be affected by a variety of factors, including injury, obesity, heredity, as well as overuse. Accordingly, this study aimed to determine the serum level of IL-38 in OA patients to clarify the positive or negative association with disease and its severity. The results can help to better understand the role of IL-38 in modulating inflammatory responses in OA patients.

MATERIALS AND METHODS

Totally 45 participants, including 23 newlydiagnosed OA patients and 22 healthy subjects were enrolled in this study. The Ethics Committee of Rafsanjan University of Medical Sciences approved the protocol of the study (IR.RUMS.REC.1397.230) and also the oral and written informed consent was also obtained from each participant. The OA group was selected among patients who were referred to the Ali- Ibn Abi-Talib (Alayh-e Salam) Hospital, Rafsanjan, Iran. The diagnosis of knee OA was done based on the clinical and radiologic criteria of the American college of rheumatology (ACR).9 The severity of the symptomatic OA was estimated based on the Western Ontario McMaster University Osteoarthritis Index (WOMAC).10 The patients with OA respond to the WOMAC questionnaire for the estimation of daily pain and function10 and the higher WOMAC scores indicate greater symptom severity.10 Additionally, a visual analog scale (VAS) was also used for the estimation of pain and was scored from zero (without pain) to ten.11 The clinical examinations were performed by expert rheumatologists.

Inclusion and Exclusion Criteria

Patients with knee OA based on ACR criteria grade I and II OA based on the Kellgren and Lawrence system were enrolled. Also, subjects with secondary OA, other inflammatory diseases and arthritis, use of anti-inflammatory drugs one month before sampling, and uncontrolled hypertension, history of knee trauma, joint infection, smoking, recurrent infections, cardiovascular disorders, diabetes mellitus, pulmonary dysfunction, allergic disorders, renal dysfunction, and neoplasia were excluded from the study.

Measurement of the IL-38 Concentrations

A peripheral blood sample (5 mL) was obtained from each person and the serum samples were separated and kept at −20°C until analysis.12 The serum IL-38 levels measured using human IL-38 enzymelinked immunosorbent assay (ELISA) kits (EK1662, BOSTER, Pleasanton, USA). According to the manufacturer's information, the sensitivity of the kit was reported <10 pg/mL.

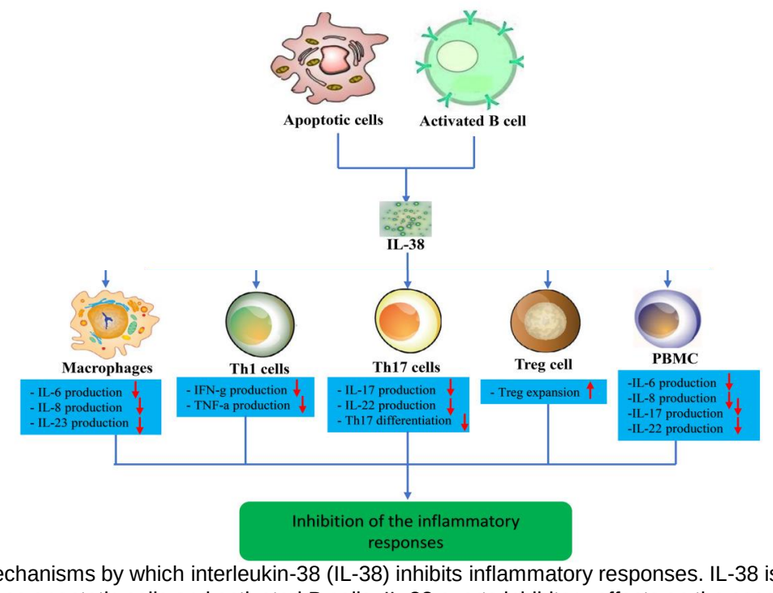
Statistical Analysis

The data were presented as mean±SD and analyzed by a statistical SPSS software (version 22, Chicago, IL, USA), and the suitable statistical tests, including ANOVA, Student t, or $\chi 2$ were used to analyze differences between groups. A p value of less than 0.05 was considered significant

RESULTS

Blood specimens were collected from two groups including 23 newly-diagnosed OA patients and 22 healthy sex and age-matched subjects as a control group. Serum IL-38 quantities were measured using enzyme-linked immunosorbent assay (ELISA).

Significantly higher IL-38 levels were detected in OA patients in comparison with the healthy group (265.78±41.27 pg/mL vs 44.23±6.04 pg/mL, p=0.0001). The IL-38 concentration in OA patients with Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores>40 and in OA patients with visual analog scale (VAS) scores>5 were higher than those with WOMAC scores<40, and VAS scores<5 (p=0.026 and p=0.035, respectively). The IL-38 levels in OA patients with body mass index (BMI)<25 were also significantly higher than in patientts with BMI>25 (p=0.05).



Possible mechanisms by which interleukin-38 (IL-38) inhibits inflammatory responses. IL-38 is produced by various cell types such as apoptotic cells and activated B cells. IL-38 exerts inhibitory effects on the secretion of pro-inflammatory cytokines from macrophages, peripheral blood mononuclear cells (PBMCs), T helper type 1 (Th1) cells, and Th17 cells. However, IL-38 enhances the proliferation of regulatory T cells (Treg).

DISCUSSION

According to our findings, WOMAC, VAS, and BMI indices may influence the IL-38 serum levels in OA patients and it may be elevated in OA patients to modulate inflammatory responses in a compensatory manner. The patients with OA, especially those with more severe disease express higher serum amounts of IL-38. Accordingly, IL-38 may be considered as a valuable marker for OA.