Ashdin Publishing
Journal of Orthopaedics and Trauma
Vol. 10 (2020)

Research Article

Increased expression of CD161 in the advanced stage of Osteoarthritis

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Keywords: Osteoarthritis, Pathophysiology, Osteoarthritis, Articular cartilage

Abstract

Background Osteoarthritis (OA) one of the most frequent joint disorders is traditionally believed to be a degenerative disease of articular cartilage. Increased understanding about its pathophysiology suggests its etiology to be multifactorial. Evidences suggest that inflammation precedes structural deterioration and plays a crucial role in its pathogenesis. Since inflammation is strongly implicated during OA disease progression, anti-inflammatory agents to block potent inflammatory cytokines such as TNFα and IL-1β have gone into preclinical trials; however, larger controlled trials still need to be established [1, 2]. In addition, CD161, a type II transmembrane glycoprotein, is expressed on the surface of Th17 cells and regulated by the RAR-related orphan receptor C transcription factor [3, 4]. An increased percentage of CD161+CD4+ T cells have been found to be associated with disease severity and inflammation during rheumatoid arthritis [5]. Based on this observation, a role of CD161+ T cells in driving the local inflammation during osteoarthritis could be speculated. No specific drug therapy is available. Unravelling role of inflammatory mediators & their downstream signaling pathways leading to OA progression is a thriving area of research. Increasing evidence suggests a role of inflammation during the pathogenesis of Osteoarthritis (OA).

Aim of the present study was to evaluate the local and systemic inflammation during OA disease progression and to identify a potential phenotypic marker to distinguish low and high KL grade patients.

Methods The local and systemic inflammation was studied in 33 patients of different KL grades, grade2 (n=11), grade3 (n=6) and grade4 (n=16). The levels of cytokines, adipokines, and matrix metalloproteinases (MMPs) were measured in serum and synovial fluid (SF) by flow cytometry and ELISA respectively. The frequency of T cells and CD161 expression was measured by flow cytometry. The levels of cytokines (IL-1β, IL-6, IL-8, IL-12, TNF-α and

IL-10) were determined using BD cytometric bead array system (CBA Human Inflammation Kit, BD Biosciences) in the serum and synovial fluid samples. Briefly, 50 µL of mixed capture beads and 50 µL of serum or synovial fluid samples were added to the assay tubes followed by incubation for 1.5 hours at room temperature. After washing, 50 µL of PE detection reagent was added and tubes incubated for another 1.5 hours. The levels of MMP9 and MMP13 (Qayee-bio) were measured in both serum and SF samples using ELISA. The levels of adiponectin (Calbiotech) and leptin (DRG Diagnostics) in serum and synovial fluid were also measured using ELISA on an Infinite M200 PRO spectrophotometer (Tecan). The levels of IL- 17 were measured in the serum of patients using ELISA (Diaclone), and results were expressed as pg/mL. The expression of CD161 [PE] was analysed on all these cell populations by calculating the median fluorescent intensity (MFI) using FACSDivaTM software (BD Bioscience). Appropriate isotype control (IgG1 κ [PE]) for CD161 was used.

Results: The levels of IL-1β, IL-6 and IL-10 were significantly higher in sera and SF of OA patients as compared to healthy control's serum. Higher levels of MMP9, leptin and lower levels of adiponectin were observed in SF as compared to serum. The MMP9 in SF and MMP13 levels in serum and SF decreased in KL grade 4 cases. In these patients, higher levels of leptin and lower levels of adiponectin were observed in SF versus patients of lower grades. There was increased infiltration of CD8+T cells in SF of OA cases with decreased frequency in grade 4 cases. The expression of CD161 on T cells was significantly higher in SF than peripheral blood with significant upregulation in grade 4 patients. We observed a strikingly significant increase in the expression of CD161 on not just CD4+ and CD8+ T cells, but also on other lymphocyte cell subsets in the patients of advanced OA. Moreover, an increased expression was observed in the synovial fluid as compared to circulating cells indicating an accumulation

of CD161+ cells in the local milieu where inflammation was also high. The CD161 expression had significant positive correlation with IL-17 in the serum of patients. The ROC curves of CD161 expression significantly distinguished grade 2 and grade 4 patients.

Conclusion: An elevated CD161 expression on T cells in circulation and synovial compartment clearly differentiates lower and higher grade patients warranting studies to assess its role as a contributing factor towards OA progression.

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