Tryptophanyl tRNA Synthetase is an Alternative Synovial Biomarker for Diagnosis of Septic Arthritis in Knee Joint

Byung Hoon Lee[1], Jaeang Sim[2]
[1]Gachon University, Gil Medical Center, [2]Gachon University Gil Med Center

INTRODUCTION:
If severe acute pain and swelling without any special traumatic history is accompanied by intra-articular effusion, purulent arthritis should be differentiated between bacterial infection or noninfectious, inflammatory arthritis. Septic arthritis is a life-threatening purulent joint invasion by an infectious agent that produces arthritis. If untreated, septic arthritis causes structural damage to the joints. Antibiotic treatment is necessary after surgical treatment as soon as possible, and the delay in diagnosis and treatment accelerates damage to normal articular cartilage; thus, an early diagnosis is of paramount importance. Currently, there is interest in new types of synovial fluid biomarkers for the diagnosis of septic arthritis. A biomarker can be defined as a biochemical measure that is indicative of a biological process or the response to an intervention. Numerous biomarkers have been developed and become available, including synovial leukocyte esterase, synovial alpha defensin, and synovial CRP, specifically for the diagnosis of septic arthritis, and provide a rapid and accurate diagnosis. Tryptophanyl tRNA synthetase (WRS) is an essential enzyme, as it catalyzes the ligation of tryptophan to its cognate tRNA during translation. WRS plays unique roles in physiological homeostasis and immune defense, and its responses eliminate invading pathogens in a very early phase of infection. This study aimed to evaluate the diagnostic characteristics of tryptophanyl tRNA synthetase (WRS) for the diagnosis of septic arthritis of the knee joint and to determine whether it is a reliable and sensitive synovial biomarker for discriminating septic arthritis from other types of arthritis.
METHODS:
Patients joint effusions for which septic arthritis was suspected were prospectively recruited between January 2019 and September 2020. Nine patients had septic arthritis, 6 had acute gout attack, 1 had an acute flare of chronic rheumatic arthritis, and 46 had pseudogout or reactive arthropathy. Traditional inflammatory markers were measured, and their diagnostic abilities were compared. Neutrophil count, C-reactive protein (CRP) level, WRS, and human neutrophil a-defensin levels were assessed in the synovial fluids. Demographic parameters and biomarkers with a P-value < 0.05 in differentiating septic from non-septic arthritis were included in a multivariable model. A multivariable logistic regression with a stepwise selection was performed to build the final combined model. Receiver operating characteristic curves were used to establish optimal thresholds for the diagnosis of septic arthritis of the knee joint, and the area under the curve was calculated to determine the overall accuracy of these tests compared to non-septic inflammatory arthritis patients.
RESULTS:
Septic arthritis patients were more likely to display higher serum WBC and CRP levels, synovial neutrophil counts, and levels of two synovial biomarkers, including WRS and a-defensin. WRS showed the highest specificity (87.5%) and sensitivity (83.3%) among the three synovial biomarkers.
DISCUSSION AND CONCLUSION:
Tryptophanyl tRNA synthetase (WRS) is an essential enzyme, as it catalyzes the ligation of tryptophan to its cognate tRNA during translation. WRS can also further expand its functions via alternative splicing and proteolytic cleavage. WRS is localized not only in the nucleus, but also in the extracellular space, playing a key role in innate immunity, angiogenesis, and IFN-γ signaling. WRS is secreted into the extracellular space in response to certain stimuli. For example, upon pathogenic infection, but prior to tumor necrosis factor-α (TNF-α) production, WRS is rapidly secreted from monocytes without *de novo* synthesis, although the mechanism of secretion is still not completely known. In addition, the expression of WRS varies significantly in different tissues and pathological states, implying that it plays unique roles in physiological homeostasis and in immune defense. The secreted full-length (FL)-human WRS (FL-WRS) leads to the activation of innate immune responses, in which TNF-α and chemokine production, neutrophil infiltration, and increased phagocytosis are prominent. These responses eliminate invading pathogens in the very early phase of infection, implying that there is a crucial role of FL-WRS in countering infections and immune regulation. The laboratory-based ELISA test demonstrated that synovial fluid WRS showed the highest sensitivity and specificity for discriminating septic arthritis from other inflammatory arthritis, compared to other relevant synovial biomarkers. The sensitivity, specificity, negative predictive value, and positive predictive value for all tests were also comparable in both groups. To the best of our knowledge, this is the first study to use a metabolomics approach to classify patients with septic arthritis in inflamed knee joints and the first report on the use of WRS in discerning septic arthritis from inflammatory joint disease.
Synovial fluid WRS is a relevant biomarker in discriminating septic arthritis from other inflammatory arthritis and should be tested in an independent cohort.

Figure. 1 Receiver operating characteristic curves with the calculated area under the curve (AUC) comparing patients with septic and non-septic inflammatory arthritis. Cutoff values that were selected to maximize the sensitivity and specificity are indicated on each curve.