Międzynarodowa Szkoła Doktorska
Uniwersytetu Medycznego w Łodzi

Towards new biomarkers of psoriatic arthritis – the role of microtrauma, alarmins and lipid mediators in development and resolution of inflammation.

Alaa Sherri, MD. Department of Rheumatology
Email: alaa.sherri1@stud.umed.lodz.pl
Supervisor: dr hab. n. med. Anna Lewandowska-Polak

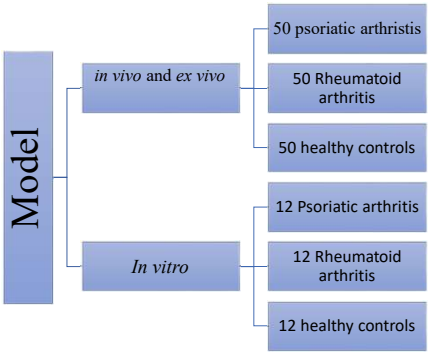
Background

Psoriatic arthritis (PsA) is a chronic systemic inflammatory disorder and counted as one of the most prevalent inflammatory arthritis. Because of significant heterogeneity and lack of autoantibodies that can help to pose the diagnosis, psoriatic arthritis remains a clinical challenge for practitioner. Recent studies suggest that that in genetically susceptible individual's microtrauma at entheseal sites leads to inflammation, which then spreads to secondarily involved structures such as the synovium or the nail. The exact mechanism how mechanical stress or microtrauma leads to initiation of psoriatic arthritis is not known, but it is speculated that damaged cells release danger signals leading to cytokine and growth factors production. It was necessary to understand the balance between biomarkers and substances promoting and resolving the microtrauma and acute inflammation and among those mediators are Lipid mediators, synthesized from arachidonic acid, which have both pro and anti-inflammatory properties like Leukotrienes and lipoxins, and Alarmins which are a member of damage associated molecular pattern (DAMP) proteins playing an important role in inflammation and damage in arthritis.

Aims

- To study the effect of monocytes as one of the main sources of Proinflammatory mediators and the generation of mediators in response to alarmins and the modulatory role of lipoxin A4 in this process
- To examine the immunological response to injury in patients with psoriatic arthritis and the role of mechanical injury in initiation of inflammatory process in entheses and joints of psoriatic arthritis patients.
- To study the generation of pro- and anti inflammatory mediators in response to mechanical injury and to verify if this process differs between healthy individuals, patients with rheumatoid arthritis and patients with psoriatic arthritis
- To asses the possibility of using alarmins and lipid mediators as potential biomarker in early diagnosis of psoriatic arthritis.

Target population



Methods

- Clinical Assessment of patients :

The detailed clinical history using a detailed questionnaire about clinical symptoms, onset of the disease, comorbidities and medication will be filled by patients. Physical examination, clinical scales , Laboratory tests (ESR&CRP), and ultrasonography will assess PsA activity and subtypes .

- Assessment of lipoxin A4, resolvin E1 and alarmins in serum:

The lipoxin A4, resolvin E1 and alarmins (S100A8/S100A9, HMGB1, IL33) concentration in serum from patents with PsA will be assessed by ELISA method

- Assessment of eicosanoids in urine:

Eicosanoid concentration in urine will be measured in subgroups of patients with PsA (n=10), RA (n=10), and healthy controls (n=10) using HPLC-tandem mass spectrometry

- The expression of key enzymes for lipoxins (i.e. 5-lipoxygenase, 12-lipoxygenase and 15-lipoxygenase) and lipoxin A4 receptor :

in synoviocytes collected from PsA patients will be assessed by examining the level of mRNA expression (qRT-PCR)

- PBMCs cultures:

The peripheral blood will be collected from patients PBMC isolated from peripheral blood will be further stimulated with LPS and the modulatory effect of analogue of lipoxin A4 on generation of cytokines (TNF, IL10, IL23, TGF beta) and eicosanoids will be assessed. The level of cytokines in PBMC culture supernatants will be quantified with Cytometric Bead Array kit

- Fibroblast-like synoviocyte (FLS) cultures

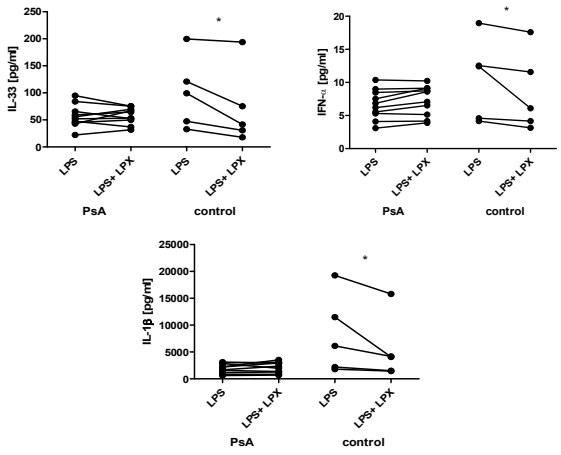
Cells for primary cultures (fibroblast-like synoviocytes) will be obtained from patients from the Department of Rheumatology and from the Department of Orthopedics and Traumatology who will be qualified to arthroscopy due to trauma, patients without any acute or chronic inflammatory condition. Monocytes for cocultures will be purchased from ATCC.

- Assessments of injury and repair: and assessment of alarmins eicosanoids generation in supernatants of cultured FLS

The generation of alarmins (S1000A8/S100A9, HMGB1, IL33) and eicosanoids (PGE2, LTB4, LTC4, 15-HETE and lipoxins) will be assessed in supernatants of injured cells by immunoenzymatic method

Advances in research

A set of preliminary experiments were performed for the aim of comparing the influence of lipoxin A4 on the synthesis of pro-inflammatory cytokines by PBMCs from patients with PsA and healthy individuals. The basal and LPS-induced pro-inflammatory cytokine production by PBMCs was lower in PsA patients as compared to healthy subjects. Strikingly, co-stimulation with LXA4 resulted in a significant increase in pro-inflammatory cytokine secretion in PsA, in contrary to the reduction observed in healthy subjects. In the figure below, the effect of lipoxin A4 on LPS-induced release of selected cytokines by PBMCs in PsA patients and healthy controls.



Conclusion

Psoriatic arthritis is one of the most common inflammatory arthritis, leading to deterioration in the quality of life, disability and shortening of life expectancy Understanding the process which initiates inflammation in PsA will potentially enable the therapeutic intervention at early stages of the disease, and contribute to the prognosis improvement. According to the preliminary results Lipoxin A4 shows a promising effect as a marker and other aspects of the study should be investigated .