Table 1. T cell subsets in Rheumatoid Arthritis and Osteoarthritis.

<table>
<thead>
<tr>
<th>CD4 subtype</th>
<th>RA</th>
<th>OA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=80</td>
<td>N=30</td>
</tr>
<tr>
<td>PB</td>
<td>Th1</td>
<td>26.65 ± 5.59</td>
</tr>
<tr>
<td>SF</td>
<td>Th2</td>
<td>5.19 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>Th17</td>
<td>14.05 ± 3.29</td>
</tr>
<tr>
<td></td>
<td>Treg</td>
<td>10.68 ± 2.47</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

**P<0.05

Conclusion: Tregs in RA may be converted to Th1 and Th17 phenotype on exposure to inflammatory cytokine in the synovial fluid, thus losing their regulatory functions. Understanding factors influencing stability of Treg cells may help improve future therapeutics.

References:


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Disclosure of Interests: None declared.

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AB0095

PRECLINICAL CHARACTERIZATION OF CJ-15314, A HIGHLY SELECTIVE JAK1 INHIBITOR, FOR THE TREATMENT OF AUTOIMMUNE DISEASES

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Background: Janus kinases (JAK1, JAK2, JAK3, and TYK2) play critical roles in mediating various cytokine signaling, and has been developed as a target for disease-dependent manner. In the rat AIA model, CJ-15314 at 30 mg/kg dose showed 95.3% decrease in arthritis activity score, 51.2% in fibrotic at 30 mg/kg, 97.7% showed baricitinib at 10 mg/kg. CJ-15314 showed superior anti-arthritic efficacy than filgotinib. CJ-15314 also minimally affected anemia-related parameters but not brutinib end of the 2-week treatment. In the rat CIA model, like 10 mg/kg of brutinib, 30 mg/kg of CJ-15314 also has a similar effect, with a significant reduction in histopathological scores.

In biomap diversity panel, CJ-15314 inhibited the expression of genes such as MCP-1, VCAM-1, IP-10, IL-8, IFN-α, sTNF-α and HLA-DR confirming the possibility of expansion into other diseases beyond arthritis.

Conclusion: CJ-15314 is a highly selective JAK1 inhibitor, demonstrates robust efficacy in RA animal model and is good candidate for further development for inflammatory diseases.

CJ-15314 is currently conducting a phase I trial in south Korea.

References:


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AB0096

FCER1G GENE METHYLATION AND MIR-106/MIR-17 AS A NEW POTENTIAL EPIDEMIC MARKERS IN RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to joints destruction. One of the most important cytokine responsible for this process is interleukin 6 (IL-6). Fc receptor gamma chain (FcRγ), encoded by FCER1G gene, is responsible for neutrophils activation, phagocytosis, cell surface signaling pathway as well as IL-6, IL-6, IL-10 and tumor necrosis factor production. Epigenetic factors, including DNA methylation and micro-RNAs (miRs) expression regulate the genes expression on transcriptional and post-transcriptional mechanisms. There are miRs responsible for cytokines production, for example GU rich miRs, miR-106b and miR-155 were associated as IL-6 overproduction.

Objectives: The aim of our study was to evaluate FCER1G gene methylation and miR-17 family members as epigenetic markers associated with RA, disease activity and IL-6 expression.

Methods: Bioinformatics analysis were applied to select the miRs with a possible target sites in a promoter region of FCER1G gene. The Mir-17 family members, including mir-17, mir-93 and mir-106b were selected for investigation. A total of 74 individuals, 50 RA patients, 84% female, aged 53,7±12,3 years (mean±SD) and 24 healthy controls (HC), 87.5% female, aged 53,8±4,9 years were enrolled. RA patients were selected based on DAS-28 scoring. RA patients with high disease activity (DAS28 >5,1, 58%) and remission (≤2,6; 42%) were included in the analysis. DNA was extracted from a whole blood and miRs were extracted from plasma. Quantitative real-time PCR was used for analyze both methylation and expression levels. In a randomly selected samples (16 from high
disease activity group; 9 from remission and 19 from HC) the level of IL-6 in serum was evaluated.

Results: Patients with RA in comparison to HC have had a lower FCER1G methylation (0.98 [0.73-1.14] vs 1.96 [1.44-3], p<0.00001; median [interquartile range]) and miR-106b (0.79 [0.49-1.68] vs 1.54 [0.82-2.51], p=0.008) and miR-17 (1.26 [0.41-2.04] vs 2.44 [2.09-3.47]; p=0.0001) expressions. No difference in methylation between high and remission RA groups was found. MI-R-106b and miR-17 expressions were different between RA patients with high disease activity and remission (p=0.009 and p=0.003, respectively), however a high disease activity group was not different to HC (p=0.82 and p=0.12, respectively). Detailed results are presented in Table 1. A strong correlation between IL-6 levels and FCER1G methylation (r = -0.46) was found.

<table>
<thead>
<tr>
<th>High disease activity, n =29</th>
<th>Remission, n = 21</th>
<th>HC, n = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCER1G methylation</td>
<td>1.11 [0.83-1.52]</td>
<td>0.96 [0.61-1.18]</td>
</tr>
<tr>
<td>miR-106b expression</td>
<td>1.36 [0.63-1.76]</td>
<td>0.54 [0.19-1.19]</td>
</tr>
<tr>
<td>miR-93 expression</td>
<td>0.63 [0.49-1.21]</td>
<td>0.59 [0.15-1.5]</td>
</tr>
<tr>
<td>miR-17 expression</td>
<td>1.46 [1.05-2.54]</td>
<td>0.34 [0.11-1.26]</td>
</tr>
</tbody>
</table>

Data are given by median [interquartile range]. FCER1G, Fc receptor gamma chain; HC, healthy controls; miR, micro-RNA; RA, rheumatoid arthritis patients.

Conclusion: FCER1G methylation was found as a new epigenetic marker of RA, which is independent of disease activity and may be associated with IL-6 production. Plasma miR-17 and miR-106b can be considered as a novel molecular biomarkers of disease severity in RA.

Methods: We examined 88 women with documented diagnosis of RA and mean disease duration of 6.56±0.88 years. We used EULAR/ARA 2010 criteria to diagnose the patients. Female patients with II degree of disease activity (DA2SB2), Steinbrocker stage II (erosive), rheumatoid factor- and anti-cyclic citrullinated peptide antibody-positive were prevalent. We excluded patients who had surgery or developed an infection within the last 8 weeks, pregnant and breast-feeding women, those with severe heart, liver or kidney disease, immune deficiency, leukopenia or chronic infection.

A control group of 45 healthy females aged of 25 and 59 years were included in the study. There were no reported findings of joint pain and RA symptoms in the group. The groups were adjusted for age (p=0.05) and showed no statistically significant differences.

We measured serum fetuin A, nesfatin, hemerin, leptin, adiponectin, resistin, visfatin levels (µg/ml) using ELISA commercial test systems. We used spectrophotometer with wavelength of 450nm to detect the test results (+Multiskan-immunoenzyme analyzer, Finland). We plotted a curve using computer software. We diagnosed OP using dual-energy X-ray absorptiometry with LUMBAR DXP PRO (GE, USA).

Results: At the first stage, the level of pro-inflammatory cytokines was studied in a group of healthy individuals. Then, the reference values of these indicators were measured as M ± 2S. Patients with OP and RA had significantly higher levels of serum pro-inflammatory cytokines (p<0.001). For example, mean serum Adiponectin levels in RA patients who had normal bone density and had no OP were 35.21±0.6 µg/ml. Mean serum Adiponectin levels in RA/OP patients with low bone mineral density were 52.42±0.69 µg/ml. Adiponectin levels of 44 µg/ml and higher were associated with osteoporosis. Adiponectin levels of 43.9 µg/ml and lower were associated with normal bone density. Other pro-inflammatory cytokines have demonstrated similar dynamics of level serum.

Conclusion: Thus, we revealed that fetuin A, nesfatin, hemerin, leptin, adiponectin, resistin, visfatin levels depend on osteoporosis presence in RA patients. The test may be used to reduce the risk of low-energy fractures and to improve the quality of life in RA.

References:

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Tissue cytokines as new diagnostic biomarker of bone metabolism disorders in rheumatoid arthritis
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Background: The paracaspase Malt1 is a cysteine protease, which forms a complex leading to the activation of the proinflammatory transcription factor NFκB in lymphocytes with CARMA1 and Bcl10. Previously, we showed that the myeloid equivalent of CARMA1, Card9 is important in neutrophils in Fc receptor-mediated cytokine release together with Bcl10 and Malt1. In line with these findings, we observed a significant decrease in the severity of autoantibody-triggered arthritis in the absence of Card9 and Bcl10.

Objectives: Our aim was to directly investigate whether the genetic deficiency of Malt1, the third component of the complex altered the process of the K/BxN serum transfer arthritis (that resembles to the effector phase of rheumatoid arthritis).

Methods: We used wild type and Malt1−/− mice for our experiments. Autoantibody-mediated arthritis was induced by a single intraperitoneal injection of K/BxN serum. Clinical signs of joint inflammation were scored on a scale based on the cardinal inflammatory clues for two weeks. Ankle thickness was measured by a spring-loaded caliper.

Results: Similar to the deficiency of the other two components of the complex, Malt1−/− mice showed a partial, but significant decrease in the macroscopic joint inflammation compared to arthritic serum-treated wild type animals during the entire experimental process. In line with this phenomenon, Malt1−/− animals had reduced autoantibody-triggered ankle thickening.