Background: STING (stimulator of interferon genes) is a cytosolic protein that is found in endoplasmic reticulum (ER) membrane, mitochondria and mitochondria-associated membranes. Although it is well established that STING plays an important role in innate immune responses, its potential involvement in rheumatic disease processes remains to be clarified (1).

Objectives: The aims of this study were to evaluate the levels of STING and its relationship with local inflammation in the synovial fluid (SF) of patients with psoriatic arthritis (PsA), rheumatoid arthritis (RA), gout, calcium pyrophosphate (CPP) crystal-induced arthritis (CPP-IA), osteoarthritis (OA) and OA with CPP crystals (OA+CPP).

Methods: SF was collected from the knees of 60 untreated patients: 10 with PsA, 10 with RA, 10 with gout, 10 with CPP-IA, 10 with OA and 10 with OA+CPP. SF was examined under optical light microscopy. White cell count (WBC) and the polymorphonuclear cell (PMN) percentage were determined in SF according to standard procedures. SF IL-6, IL-1β, and extra- and intra-cellular STING levels were assayed by ELISA.

Results: The levels of WBC were higher in SFs from gouty patients (27.7±20.56 10³/mm³), while OA and OA+CPP patients showed the lowest WBC count (0.34±0.3 10³/mm³, 0.3±0.28 10³/mm³). SFs from inflammatory arthritis contained elevated percentages of PMN (gout: 85.5±10.86%, CPP-IA: 84±13.31%, RA: 80.3±8.14%, PsA: 42.6±35.97%). Extracellular STING was determined in OA (440±413.31 pg/ml), OA+CPP (225±205.06 pg/ml) and CPP-IA (475±707 pg/ml). SF was not detectable in RA, PsA and gout. Intracellular STING levels were similar and the highest in SFs from gout (96.4±23.13 pg/ml), while remained under detection limit only in SFs from PsA. SF concentration of IL-6 was lower in OA (354.87±377.56 pg/ml) and OA+CPP (389.56±104.14 pg/ml) as compared with inflammatory arthritides (PsA: 3870.14±489.86 pg/ml; RA: 1725±233.87 pg/ml; gout: 1935±84.85 pg/ml; CPP-IA: 20389.56±104.14 pg/ml). The patients with gout and RA had the highest levels of IL-8 (2159.54±347.09 pg/ml; 2036±67.94 pg/ml) and IL-1β (35.93±20.46 pg/ml; 44.38±23.16 pg/ml), while OA showed the lowest concentrations (IL-8: 23.21±11.32 pg/ml; IL-1β: 0.47±0.13 pg/ml). In the total group of patients, we found a negative correlation between extracellular STING and IL-8 (r = -0.53; p<0.004) and IL-1β (r = -0.47; p<0.012). There was a positive correlation between intracellular STING and IL-8 (r = 0.54; p=0.017), IL-1β (r = 0.77; p<0.001) and IL-6 (r=0.69 p=0.009).

Conclusion: This study is the first to define the presence of STING in SF of different arthritides. The levels of extracellular STING in OA, OA+CPP and CPP-IA sera may be due to the activation of factors that reduce its interaction with the SF. The effect of downregulating factors in PsA might explain the low concentration of intracellular STING in these patients.

References:

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OA, aetiology, pathology and animal models

AB0063 AGING CARTILAGE IN WILD-TYPE MICE: AN OBSERVATIONAL STUDY

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Background: Many animal models of osteoarthritis (OA) have been used to study the pathogenesis of cartilage degeneration. In mice, spontaneous OA can occur in wild-type or genetically modified animals. The first report of spontaneous OA developing in wild-type mice was published in 1956 and changes affecting the knee joint were further related to OA by using ultrastructural histochemical analyses. However, a quantitative assessment of age-related evolution of OA-type cartilage lesions is lacking. The OA Research Society International (OARSI) grading score was adapted to semi-quantify histopathological changes occurring in OA animal models, including mice. The OARSI score has been used to describe changes occurring in induced or genetic mouse models but not to describe spontaneous age-related evolution of OA-type cartilage lesions in wild-type mice.

Objectives: We aimed to describe the spontaneous evolution of OA-type cartilage lesions affecting knee joint articular cartilage, walking speed and a serum biomarker of cartilage remodeling in C57Bl/6 wild-type male mice.

Methods: Histological changes were assessed by the OARSI score in newborn, 1-week- and 1-, 3-, 6-, 9- and 12-month-old C57Bl/6 wild-type male mice, walking speed by the Locotronic system, and serum C-terminal telopeptide of type II collagen (CTX-II) concentrations in wild-type C57Bl/6 male mice.

Results: Treatment of newborn mice with Tofacitinib led to a decreased IL12B co-stimulus. The decreased IL12B mRNA expression also resulted in lower production of IL-12 p40 and IL-23 proteins in mDCs.

Conclusion: In this work, we demonstrated for the first time that Tofacitinib can suppress the expression of IL-12/IL-23 subunits in mDCs, upon the condition that an active type II IFN signalling is also present in these cells. This observation indicates that specific factors, such as endogenous IFN-y levels in the serum of PsA patients, can possibly predict differential responses to Tofacitinib treatment.

References:

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Table 1. Evolution of cartilage changes, walking speed and serum C-terminal telopeptide of type II collagen (CTX-II) concentrations in wild-type C57Bl/6 male mice.

<table>
<thead>
<tr>
<th>Age</th>
<th>New-born</th>
<th>1 week</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>OARSI score (0 to 6)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.2 (0.3)</td>
<td>1.3 (0.6)*</td>
<td>3.3 (0.6)*</td>
<td>3.7 (0.6)</td>
<td>4.3 (0.6)</td>
</tr>
<tr>
<td>Walking speed (cm.s-1)</td>
<td>-</td>
<td>-</td>
<td>10.5 (1.5)</td>
<td>11.3 (4.3)</td>
<td>11.4 (1.8)</td>
<td>3.2 (0.8)*</td>
<td>-</td>
</tr>
<tr>
<td>CTX-II concentration (pg/ml)</td>
<td>-</td>
<td>-</td>
<td>12.2 (8.5)</td>
<td>24.8 (6.4)*</td>
<td>11.1 (4.0)</td>
<td>4.0 (3.8)</td>
<td>-</td>
</tr>
</tbody>
</table>

N ≥ 3 per timepoint. All results are means (standard deviation), *p<0.05 as compared to the previous timepoint using the non-parametric Mann-Whitney U-test.

Figure 1. (A) New born, 1-week- and 1-, 3-, 6-, 9- and 12-month-old wild-type C57Bl/6 male mice. (B) C57Bl/6 male mice were evaluated for cartilage changes following OARSI recommended guidelines by 3 independent readers. Each point represents the mean of OARSI score per mice as scored by 3 independent readers. (B) 1-, 3-, 6- and 9-month-old wild-type C57Bl/6 male mice were evaluated for walking speed using the Locotronic system. Each point represents the mean of 3 measures of walking speed per mice. All results are means (SD), *p<0.05 as compared to the previous timepoint using the non-parametric Mann-Whitney U-test.

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AB0064 CHANGES IN THE VASCULAR ENDOTHelial GROWTH FACTOR A (VEGF-A) SPlicing AXIS IN HUMAN SYNOVium ARE RELATED TO INFLAMMATION IN ARTHRITIS

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Background: VEGF-A is a key regulator of rheumatoid (RA) and osteoarthritis (OA). During articular inflammation in OA and RA there is increased synovial angiogenesis and upregulation of angiogenic growth factors such as VEGF-A. VEGF-A comprises two splice variant families, VEGF-Aa and VEGF-Ab (xxx represents the number of amino acids, from 121 to 206), resulting from alternative splice site selection in exon 8. This site selection is controlled by Serine/Arginine Rich Splicing Factor Kinase 1 (SRPK1), which phosphorylates Serine/Arginine Rich Splicing Factor 1 (SRSF1), inducing it to translocate to the nucleus. In most normal tissues, VEGF-Aa isoforms predominate, with anti-nociceptive and anti-angiogenic functions. In contrast, in pathological conditions such as inflammation and solid tumours, VEGF-Ab isoforms predominate, with pro-nociceptive and pro-angiogenic functions. VEGF-A has been proposed as

References: