LOW AND MODERATE PHYSICAL ACTIVITY REDUCES LOCALISED IL-1B IN AN ACUTE MOUSE MODEL OF GOUT BY DOWN-REGULATING TLR2 EXPRESSION ON CIRCULATING NEUTROPHILS

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Background: While physical activity was originally believed to exacerbate inflammation in rheumatic disease, recent studies have shown significant reductions in inflammation with regular exercise. It has been previously shown that down-regulation of toll-like receptor (TLR)/2 and TLR4 expression correlates with increased physical activity in humans. Furthermore, birth trauma and TLR4 knockout mice are resistant to monosodium urate (MSU) crystal-induced gout. Additionally, mesenchymal stem cells (MSCs) can be immunosuppressive by secreting IL-1 receptor antagonist (IL-1RA) and have also been shown to be up-regulated with exercise.

Objectives: The aim of this study was to investigate the mechanism by which exercise suppresses gouty inflammation and to define the potential roles of TLR2, TLR4, and MSCs in the process.

Methods: NFκB reporter mice [BALB/C-Tg(NFκB-Luc)] were exercised daily by treadmill walking (45 min/day for 2 weeks) at low intensity (35% VO2max; 8 m/min), moderate intensity (55% VO2max; 11 m/min), and high intensity (75% VO2max; 15 m/min). Mice were then injected with MSU crystals (0.5 mg) into the tibio-tarsal joint (ankle). Localised NFκB activity was measured 16 hours later in the injected ankle by bioluminescent imaging. Tissue was collected and processed for immunohistochemical (IHC) analysis and whole blood was collected for both flow cytometry and serum analysis.

Results: Mice in the moderate/low-intensity exercise groups had decreased inflammation, F4/80+ macrophages, and MPO+ neutrophils at the site of MSU injection compared to high-intensity and non-exercised controls. Similarly, bioluminescent imaging of NFκB activity was significantly reduced in low/moderate intensity groups compared to high-intensity and non-exercised controls. Surface expression of TLR4 on peripheral monocytes or neutrophils showed little change among intensity groups. In contrast, expression of TLR2 on neutrophils in peripheral blood showed a significant increase in high intensity compared to low and non-exercised controls. Interestingly, we observed a strong decrease in the number of multinucleated osteoclasts as determined by TRAP staining, at day 8 after start of the cultures. In agreement with this, the cells showed a strongly reduced resorptive capacity after 10 days of culture. We demonstrated that already a 24 hour stimulation with S100A9 strongly reduced the osteoclastogenic potential of the CD14+ monocytes. Finally, to determine the mechanism of how this short S100A9 stimulation might reduce the osteoclast development, we determined the protein expression of the RANK receptor, which is crucial for osteoclast differentiation. We observed that S100A9 stimulation hampered the M-CSF-induced upregulation of RANK after 24 hours, suggesting that this underlies the hampered osteoclast differentiation. Interestingly, this S100A9-induced decreased RANK expression could be reversed by addition of the TNFα-inhibitor etanercept, but not by addition of IL1 receptor antagonist.

Conclusions: Whereas S100A8/A9 have been previously shown to stimulate the numbers and resorptive capacity of mature osteoclasts, we here show that stimulation of monocytes with S100A9 strongly inhibits their osteoclastogenic potential, possibly via TNFα-induced reduction of RANK expression. This suggests that S100A8/A9 does not solely stimulate osteoclast formation and function but rather that the timing of exposure to S100A8/A9 is an important determinant for monocyte-to-osteoclast differentiation.

Disclosure of Interest: None declared


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Pathophysiology and biomarkers in PsA: what impact?

**OP0321**

**PRECISION MEDICINE USING DIFFERENT BIOLOGICAL DMARDS BASED ON CHARACTERISTIC PHENOTYPES OF PERIPHERAL T HELPER CELLS IN PSORIATIC ARTHRITIS**

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Background: Biological DMARDs targeting TNF-α, IL-17, and IL-12/23 (p40) are available. The high efficacy of these drugs has been proven in numerous clinical trials. However, there are some cases in which a change from one bDMARDs to another one is necessary because of the refractory nature of the disease, and there is no established method to select the optimal bDMARDs according to the individual case, despite the fact that various drugs are available.

Objectives: We sought to investigate the selection of specific biological DMARDs based on characteristic lymphocyte phenotypes for treating PsA.

Methods: We performed this study to evaluate the efficacy of biologics therapy in 64 patients with PsA after 6 months of therapy, and to compare the results of

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