the partial in vivo phenotypic responses: Aconite showed more AI changes than MTX did in 4, 5, and 6 weeks. However, we found the presence of partial FcγRIIB affinity of binding modulation that MTX/aconite could enhance preventing monocyte/macrophage activation via immune complex in RA pathogenesis, as was other benefits of the combination except direct synergies.

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AB0081 REACTIVE OXYGEN SPECIES INHIBIT CATALYTIC ACTIVITY OF PEPTIDYLARGININE DEIMINASE

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Background: Protein citrullination is catalysed by pepdidylarginine deiminase (PAD) and plays an important pathogenic role in anti-citrullinated protein antibody (ACPA)-positive rheumatoid arthritis (RA), and possibly in other inflammatory diseases. PAD activity is dependent on calcium and reducing conditions.

Objectives: To determine the ability of H_2O_2 and reactive oxygen species (ROS) induced by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase to regulate PAD activity.

Methods: Activity of recombinant human (rh) PAD2, rhPAD4 and PADs released from phorbol 12-myristate 13-acetate (PMA)-stimulated leucocytes was measured using an in-house PAD activity assay detecting citrullination of fibrinogen. PAD2 released from cells was measured using a luminex-based assay. The NADPH oxidase inhibitor diphenyleneiodonium (DPI) was used to inhibit ROS production in cells.

Results: At concentrations above 40 μM, H_2O_2 inhibited the catalytic activity of reduced rhPAD2 and rhPAD4. The inhibitory effect increased with increasing H_2O_2 concentration, reaching complete abrogation at 600 μM. PMA-stimulated leucocytes showed markedly higher PAD activity following inhibition of ROS formation with DPI. At a concentration of 10,000 μM, exogenously added H_2O_2 inhibited the catalytic activity of PAD released from PMA-stimulated leukocytes.

Conclusions: The ROS H_2O_2 directly inhibits enzymatic activity of PAD, and generation of ROS by NADPH oxidase down-regulates the activity of PAD released from stimulated leucocytes. This mechanism may play an important role in preventing hypercitrullination of proteins and thereby generation of self-antigens in RA.

Disclosure of Interest: None declared

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AB0082 ALKALINE PHOSPHATASE ELICITS PROPHYLACTIC AND THERAPEUTIC EFFECTS IN ARTHRITIC RATS

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Background: Alkaline phosphatase (AP) functions as a gate-keeper of the innate immune system [1] by detoxifying inflammation triggering moieties (ITMs). As an ectophosphatase, AP thus acts extracellularly by dephosphorylating ITMs that originate and are released from endogenous sources, e.g. by converting ADP and ATP nucleotides into adenosine to establish a key signalling anti-inflammatory effect. Consequently, AP activity prevents the production of pro-inflammatory cytokines by activated leucocytes and their downstream effects. Due to its broad mechanism of action, AP may potentially serve as an attractive therapeutic moiety in chronic inflammatory disorders, including rheumatoid arthritis (RA).

Objectives: To examine the anti-arthritic effects of prophylactic and therapeutic AP interventions in arthritic rats.

Methods: Wistar rats were immunized twice with methylated bovine serum albumin (mBSA), followed by local arthritis induction (intra-articular (i.a.) mBSA injection with 3 repeated injections) in the right knee (arthritic knee) with the contralateral left knee serving as internal control [2]. Interventions were performed using 200 μg human recombinant placental AP, administered subcutaneously, either before i.a. mBSA injections (2x, every 3 days, 2 rats/group; *prophylactic* setting) or after arthritis induction (4x, every 3 days, 4 rats/group; *therapeutic* setting). After *ex vivo* tissue distribution, knees were excised, fixed, decalcified and paraffin-embedded. Knee sections were examined for synovial macrophage infiltration by immunohistochemistry with ED1 (∼CD68) and ED2 (∼CD163) macrophage specific antibodies. Results were compared with untreated arthritic rats and arthritic rats receiving MTX therapy (1 mg/kg, intraperitoneally, 4x, every 3 days, 4 rats/group).

Results: Prophylactic and therapeutic schedules of AP treatment were well tolerated and reduced knee swelling comparable with MTX treatment. Following AP prophylactic intervention, synovial macrophage infiltration in the arthritic knees was reduced 4-fold (ED1) and 6-fold (ED2) when compared with affected knees of untreated arthritic rats, approaching macrophage counts in contralateral (non-arthritic) knees of AP treated rats. Therapeutic AP interventions resulted in 3.5-fold lower synovial infiltration of both ED1 and ED2 macrophages in arthritic knees, comparable with effects of MTX treatment.

Conclusions: AP, both as prophylactic and as therapeutic intervention, demonstrated favourable anti-arthritic efficacy in a rat model of arthritis. These studies warrant further preclinical and clinical evaluation as a putative novel therapeutic entity for arthritis.

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AB0083 SINGLE NUCLEOTIDE POLYMORPHISMS IN LEP – 2548 G>A AND LEPR + 668 A>G IN RHEUMATOID ARTHRITIS MEXICAN MESTIZOS ARE ASSOCIATED WITH AGE AT DIAGNOSIS, DISEASE ACTIVITY AND ANTI-CCP ANTIBODIES

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Background: The role of adipose tissue in RA pathogenesis has been acknowledged since the high frequency of dyslipidemia and insulin resistance in these patients. Leptin, a pleiotropic adipokine, has been associated with inflammation markers and articular damage in RA and the anti-citrullinated protein antibodies. Notwithstanding, these findings have not been constant across different populations. These points towards that single nucleotide polymorphism (SNP) in leptin and its receptor might influence the participation of this adipokine in RA pathogenesis.

Objectives: To determine the association of the SNPs *LEP* -2548 G>A and *LEPR* 668 A>G with adiposity, metabolic and inflammation markers in RA patients.

Methods: We enrolled 116 patients with RA (ACR 1987) matched with 133 control subjects by age, gender, and body mass index (BMI). Subjects were evaluated for fat mass and skinfold thickness. Also, serum glucose, insulin, lipid profile, serum leptin (sLep), soluble leptin receptor, TNFa. In patients with RA we evaluated disease activity and anti-CCP. Genotypes of *LEP* -2548 G>A and *LEPR* 668 A>G were determined by PCR-RFPL using *HhaI* and *MspI* restriction enzymes.

Results: There was no difference in genotypes distribution of LEP -2548 G>A and *LEPR* 668 A>G between RA and control. *LEPR* 668 G allele was associated with higher anti-CCP titers and disease activity score compared to *LEPR* 668A/A homozygotes, 4.2±1.7 vs. 3.46±1.2 *P*=0.012. *LEP* -2548A allele was associated with younger age of RA diagnosis vs. G/G homozygotes, 35.9±11.5 vs. 41.8±13.9 years old (*P* =0.045). OR for diagnosis before 40 years old was 2.7 (CI95% 1.04 – 7.45).

Conclusions: *LEP* -2548 G>A is related with a younger age at diagnosis of RA and *LEPR* 668 G/G was associated with increased anti-CCP titers and disease activity. This suggests that there is an additive effect between chronic inflammation of RA and obesity were leptin may favor humoral immune response against citrullinated proteins and influence the severity of RA.

In preobese and obese patients with RA anti-CCP (+) there is an increased sLep production. *LEP* -2548 G>A is related with a younger age at diagnosis of RA and *LEPR* 668 G/G was associated with increased anti-CCP titers and disease activity. These suggests that there is an additive effect between chronic inflammation of RA and obesity were leptin may favors humoral immune response against citrullinated proteins and influence the severity of RA.

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