Conclusion The development of CIA and autoimmune responses in MRL/lpr mice were markedly suppressed by SX-5452 via inhibition of anti-CII/anti-DNA antibodies formation. Since SX-5452 exerts no overt toxicity after repeated administration in mice, it is an interesting candidate for therapeutic use in rheumatoid arthritis.

THU0089 INHIBITION OF RHEUMATOID ARTHRITIS SYNOVIOCYTES GROWTH BY TAURINE CHLORAMINE

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Background Hyperplasia of synovial membrane, a characteristic feature of rheumatoid arthritis (RA), is proposed to result from either the enhanced proliferation of fibroblast-like synoviocytes (FLS) or the resistance of these cells to apoptotic death. Therapeutic approaches to inhibit an excessive growth of RA FLS are not satisfactory. We have previously shown that taurine chloramine (Tau-Cl), a chlorinated derivative of a dominant free amino acid taurine (Tau), formed by neutrophils during respiratory burst, inhibits FGF-triggered proliferation of RA FLS (Arthritis Rheum 1999;42:2552).

Objectives The aim of present study was to investigate the mechanism of Tau-Cl inhibition of RA FLS growth.

Methods FLS, isolated from the synovial membrane of RA patients, were stimulated *in vitro* for 18–72 h with 10 ng/ml of either rhPDGF or rhTNF- α . Tau or Tau-Cl were added (at 100–500 μ M concentration) together with the stimuli. Cell proliferation was determined by incorporation of 3H-TdR. To evaluate the cytotoxicity of tested compounds, and to estimate the recovery of the cells from the cultures, the lactate dehydrogenase (LDH) activity was measured in culture supernatants and in cell lysates, respectively. The expression of proteins regulating the cell-cycle progression or apoptosis, was estimated by Western blotting.

Results The rate of spontaneous proliferation of FLS ranged from 176 to 4639 cpm. Both, PDGF and TNF- α raised it significantly by 6 and 2 times, respectively. Tau was neither cytotoxic nor affected the recovery/proliferation of RA FLS. In contrast, Tau-Cl inhibited both the proliferation and the cell recovery in a dose-dependent manner. Independent of the type of stimulus, both responses were reduced by 70% in the presence of 250 μ M, and were almost completely blocked (by 90%) in the presence of 500 μ M concentration of Tau-Cl. At the same concentrations (250 and 500 μ M) Tau-Cl inhibited PDGF- and TNF- α - triggered expression of PCNA (proliferating cell nuclear antigen) but has no effect on the expression of either the Cdk-4 (the cyclin-dependent kinase-4), Cdk-inhibitors (p16, p21, p27) or the anti-apoptotic, Bcl-2, protein. At the late time points (48–72 hrs) only the higher (500 μ M) concentration of Tau-Cl exerted cytotoxic (50%) effect.

Conclusion We report that Tau-Cl, a physiologic factor originated from activated neutrophils, blocks proliferation of RA FLS by affecting the common event critical for the cell cycle progression: the expression of PCNA protein, known to act as a cofactor for DNA polymerase δ . Thus, Tau-Cl might be promising therapeutic agent for RA. Whether Tau-Cl triggers apoptosis of RA FLS is under investigation.

THU0090 TAP1 AND TAP2 GENE POLYMORPHISM IN RHEUMATOID ARTHRITIS IN EASTERN FRENCH POPULATION

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Background The Transporter associated with antigen processing (TAP) gene products are involved in the processing of endogenous peptides that bind to human leukocyte antigen (HLA) class I molecules and polymorphism within these genes could alter the immune responses, the phenomenon relevant to the development of autoimmune diseases.

Objectives In this study, we examined the polymorphism of TAP1 and TAP2 genes in patients with rheumatoid arthritis (RA).

Methods TAP1 and TAP2 typing was performed in 138 white RA patients and 100 healthy controls, all of them originating from Eastern France. TAP1 polymorphic residues at position 333 and 637 and amino acid variants 379, 565, 651 and 665 in TAP2 gene were determined using amplification refractory mutation system (ARMS)-PCR. This method enabled us to determine 4 TAP1 alleles (TAP1A to TAP1D) and 8 TAP2 alleles (TAP2A to TAP2H). All patients and controls had been HLA DRB1* genotyped.

Results The polymorphic residues TAP1/333 and TAP1/637 did not show any difference in their distribution between patients and controls.

Similar findings were observed for TAP2/379 and TAP2/665. However, we found an increased frequency of Thr homozygosity and heterozygosity at position 565 in TAP2 gene (RA vs Controls: 25.3% vs 14%; p: 0.032; OR: 2.09; CI: 1.01–4.38). Similarly, the prevalence of subjects who were homozygote and heterozygote for Cys/651 was increased in the RA group (RA vs Controls: 22.4% vs 11%; p: 0.02). The frequency of TAP2F was higher in RA patients (24.5%) as compared with controls (11.3%), without significance after correction (p: 0.029; p corr: 0.17).

Finally, we found no linkage disequilibrium between DRB1* associated -alleles and amino acid substitution Thr/665 whereas Cys/651 was not independent of DRB1*04, a strongly RA-linked allele.

Only a few patients expressing Thr at position 565 in TAP2 gene were associated with severe clinical manifestations.

Conclusion We evidenced in this study an association between a particular amino acid residue, namely Thr/665 in TAP2 gene, and RA.

This association was found to be weak and did not seem to be a predictor for the severity of the disease.

THU0091 IL-8 PRODUCTION INDUCED BY PROTEIN I/II, A MODULIN FROM ORAL STREPTOCOCCI, IN SYNOVIOCYTES FROM RHEUMATOID ARTHRITIS (RA) PATIENTS INVOLVES THE MAPKS AND FAK SIGNALLING PATHWAYS AND NF-KB

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