A101 **TSLP: A NOVEL POTENT PROINFLAMMATORY MEDIATOR THAT ACTIVATES MYELOID DENDRITIC CELLS TO STIMULATE TH1 AND TH17 ACTIVITY IN RHEUMATOID ARTHRITIS**

Frederique M Moret, C Erik Hack, Kim MG van der Wurff-Jacobs, Floris PJG Lafeber, Joel AG van Roon *Rheumatology and Clinical Immunology, University Medical Center Utrecht, The Netherlands*

10.1136/ard.2010.148981.4

Background Thymic stromal lymphopoietin (TSLP) is well known for its potent activation of myeloid dendritic

cells (mDCs) resulting in Th2-mediated immune responses. TSLP signals cells via the interleukin (IL)-7 receptor- α chain (IL-7R α), shared with IL-7, together with the TSLP receptor (TSLPR) subunit. Recently, the authors have demonstrated that prevention of TSLPR signalling strongly reduces Th17-driven experimental arthritis and immunopathology. Furthermore, the authors have shown that administration of TSLP enhances severity of inflammation and joint destruction in collagen induced arthritis.

Objective To determine the levels of TSLP and TSLPR in joints of rheumatoid arthritis (RA) patients and the capacity of TSLP to induce mDC-dependent T cell activation.

Methods TSLP was measured in synovial fluid (SF) of RA (n=44) and osteoarthritis (OA) patients (n=20). CD1c⁺ mDC numbers and TSLPR expression on these cells were assessed by FACS analysis in paired samples of SF and peripheral blood (PB) from RA patients (n=7). mDCs, isolated from PB of RA patients (n=10) were stimulated with TSLP for 24 h and cytokine production was measured. Washed TSLP-activated mDCs were added to autologous CD4 T cells from PB in the absence of additional stimuli, cultured for 6 days and subsequently proliferation was measured. T cell cytokine production was measured upon restimulation with ionomycin/PMA.

Results TSLP levels in SF of RA patients were increased compared to OA patients (460 vs 75 pg/ml, respectively, $p<0.01$). CD1c⁺ mDC numbers from SF were increased compared to PB (3.8% vs 0.7%, respectively, $p<0.02$). mDCs from SF and PB expressed substantial levels of TSLPR (SF: 76% positive cells, MFI 19; PB: 70% positive cells, MFI 15).

TSLP significantly stimulated production of chemokines TARC and MIP1 α by mDCs (TARC; from 4 to 89, MIP1 α ; from 1545 to 6293 pg/ml, $p<0.02$). Upon incubation with TSLP, TSLPR-expressing mDCs potently stimulated proliferation of autologous CD4 T cells compared to unstimulated mDCs (ratio T cell: DC 5:1; from 1537 to 18903 cpm). Upon restimulation, TSLP-mDC-activated CD4 T cells produced increased levels of tumour necrosis factor (TNF)- α (4737 vs 12125 pg/ml, $p<0.02$), IFN- γ (163 vs 818 pg/ml, $p<0.02$) and IL-17 (50 vs 592 pg/ml, $p<0.05$) in addition to IL-4 (24 vs 300 pg/ml, $p<0.03$). Induction of TNF- α and IL-17 was significantly higher in RA patients compared to healthy controls ($p<0.05$).

Conclusion The authors' data indicate that increased intra-articular TSLP concentrations in RA potently activate TSLPR-expressing mDCs from RA patients to cause chemotaxis and activation of arthritogenic T cells. This suggests that TSLP and its receptor are novel therapeutic targets for RA.