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

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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-7Rα), 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 MIP1α by mDCs (TARC; from 4 to 89, MIP1α; 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.