

antigen presenting cells and are therefore implicated in the initiation of chronic autoimmune diseases, including rheumatoid arthritis. Using the K/BxN serum transfer arthritis, a model of human rheumatoid arthritis, which depends only on the innate immune system, allowed us to investigate the innate role of dendritic cells in inflammatory arthritis.

**Methods** KBxN serum transfer arthritis was induced in CD11c-diphtheria toxin receptor (DTR) transgenic mice, which express the human diphtheria-toxin receptor under the CD11c promoter. This allows for specific depletion of CD11c+ cells by administration of diphtheria toxin (DT). DT or PBS were given on day -1, 3, 6 and 9 and the severity of arthritis was determined clinically and histologically. In addition, serum transfer arthritis was induced in wild type animals who also received DT.

**Results** Efficient depletion of DCs from the spleen after injection of DT was confirmed by flow cytometry and histological analysis. Clinical scores of arthritis showed that CD11c-DTR transgenic mice had significantly reduced paw swelling and loss of grip strength compared to PBS treated animals. In contrast, wild type animals receiving DT showed identical clinical signs of arthritis as PBS treated animals, excluding unspecific effects of DT in mice. Histological analysis found that CD11c-DTR transgenic mice that had received DT displayed decreased synovial inflammation and a trend towards reduced local bone destruction.

**Conclusions** These data show that dendritic cells are involved in innate reactions leading to inflammatory arthritis and suggest that dendritic cells could be an important target for rheumatoid arthritis therapy.

#### A2.6 CELL-SPECIFIC TYPE I IFN SIGNATURES IN AUTOIMMUNITY AND VIRAL INFECTION: WHAT MAKES THE DIFFERENCE?

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**Background** Gene expression profiling experiments using peripheral blood mononuclear cells (PBMCs) revealed a crucial role of type I interferon (IFN) in the pathogenesis of systemic lupus erythematosus (SLE). However, it is almost unknown how particular leukocyte subsets contribute to the overall type I IFN signature described for PBMCs. Furthermore, a detailed analysis of how IFN signatures differ in autoimmune disease from that observed after viral infection is missing so far. Therefore, we compared expression levels of 2442 IFN signature genes in peripheral CD4+ T helper cells and monocyte (Mo) subsets isolated from patients with SLE, healthy donors (ND) and ND vaccinated against yellow fever by global gene expression profiling.

**Materials and Methods** Peripheral blood from 8 patients with SLE and 4 ND were recruited. Same ND were examined before and after immunisation by yellow fever vaccine. After sorting cells, isolated RNA were applied to Affymetrix Human Genome U133 Plus 2.0 Array. Data analysis was done using BioRetis database, Genesis Software and Ingenuity Pathway Analysis (IPA).

**Results** 98/165/173 probe sets (CD4+ T cells/CD16- inflammatory Mo/CD16+ resident Mo, respectively, fold change  $\geq 2$ ,  $\leq -2$ ) were detected as a “common” IFN signature observed both in autoimmunity and in immunised ND. 111/164/120 probe sets were detected as an “autoimmune-specific” IFN signature, whereas only 0/8/5 probe sets were detected to be specific for the “virus-induced” IFN signature. Expression pattern of these IFN signature genes clearly distinguished patients with SLE from immunised ND by hierarchical cluster analysis. Although major IFN signature genes

were commonly expressed in CD4+ T cells and Mo of patients with SLE and immunised ND, expression magnitudes of them were higher in patients with SLE compared to immunised ND. In SLE, in addition to the typical “viral-induced” IFN signature, genes that are involved in apoptosis signalling, antiviral PKR signalling, Fc $\gamma$  receptor-mediated phagocytosis and IL-10-/IL-9-/IL-15-mediated JAK/Stat signalling pathways were identified by IPA.

**Conclusions** This study demonstrated that IFN signature in autoimmunity and that in viral infection are quite different in the number of IFN-related genes activated and their expression magnitudes. Autoimmunity is characterised by a much stronger expression of IFN signature genes and is obviously modulated by a separate set of co-regulated genes defining the “autoimmune-specific” IFN signature. “Common” and “autoimmune-specific” IFN signature genes can be applied as a clinical biomarker to diagnose SLE flare discriminating from viral infection.

#### A2.7 EFFECTS OF VAGUS NERVE STIMULATION ON THE CENTRAL PROSTAGLANDIN SYSTEM AND SUBSTANCE P FOLLOWING PERIPHERAL INFLAMMATION

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**Background and Objectives** Activation of cholinergic anti-inflammatory pathway (CAP) has shown to be important for regulation of arthritis, and ongoing trials show promising effects of vagus nerve stimulation (VNS) in RA. While peripheral mechanisms have been thoroughly investigated, central effects remain elusive. We showed recently that central nervous inflammation is a feature of RA (Lampa *et al*, PNAS 2012), and also coupled to autonomic activity. Moreover, prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) may act as an important neuromediator in this context and we have earlier shown impaired CAP in knockout mice for the PGE<sub>2</sub> inducing enzyme mPGES (Le Maître *et al*, EWRR 2012). Here, we aimed to study the effects of VNS on central prostaglandin system and neuropeptides associated with inflammation.

**Materials and Methods** After VN isolation, we injected lipopolysaccharide (2 mg/kg) intraperitoneally. The VN was either electrically stimulated for 5 minutes (VNS) or left unstimulated (SHAM). After 6 hours, mice were sacrificed and brains were collected. Expression of the inducible enzymes COX2 and mPGES-1 in frozen brain sections was quantified by immunohistochemistry. mRNA levels of c-FOS and substance P (SP), a key central neuropeptide, were analysed by in situ hybridisation. Investigated areas include Hippocampus (Hi), Hypothalamus (Hy), periaqueductal grey (PAG), Cingulate Cortex (CC) and Dorsal raphe nuclei (DRN).

**Results** c-FOS mRNA level significantly increased in vagus related areas such as Hi (75.3  $\pm$  5.7 (mean grey value; SHAM) versus 105.0  $\pm$  1.7 (VNS);  $p < 0.001$ ) and Hy (73.8  $\pm$  9.4 versus 102.2  $\pm$  6.7;  $p < 0.05$ ). Hi and Hy as well as all other regions displayed a strong trend to VNS-induced increase in mPGES-1 protein, (Hi 0.66  $\pm$  0.29 versus 0.88  $\pm$  0.25 and Hy 0.72  $\pm$  0.44 versus 1.49  $\pm$  0.57). COX2 protein tended to decrease in all areas except CC. Interestingly, VNS exhibited strong inhibitory effects on the SP mRNA expression (Hi 119.9  $\pm$  4.9 versus 98.0  $\pm$  4.2  $p < 0.05$ ; Hy 114.0  $\pm$  6.5 versus 83.1  $\pm$  8.2;  $p < 0.05$ ).

**Conclusions** These data indicate a role for prostaglandins and mPGES in central mechanisms of the CAP. The decreased brain COX2 expression may be related to the suppression of systemic inflammation caused by peripheral CAP action, while the up regulation of mPGES-1 in vagus-related brain areas seems to be directly related to central CAP action. These effects may be of clinical importance both in the coming VNS RA trials as well as in the