Abstracts

P015 AUTOPHAGY CONTROLS TREGS TO TH17 CONVERSION AND SHAPES THE SEVERITY OF ARTHRITIS

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Introduction Macroautophagy is an important contributor of cellular homeostasis, and therefore is active and up regulated in various conditions of cellular stress and inflammation. The pathway has been implicated in shaping the innate and adaptive immune responses by acting at multiple and diverse levels including cytokine secretion and antigen presentation.

Objectives Our aim is to analyse the contribution of macroautophagy in antigen presenting cells to the adaptive immune response in the context of arthritis. We analysed the autophagy induced arthritis model in mice that are deficient in autophagy in their dendritic cells.

Methods CD11c-Cre mice (C57BL/6), (Jackson Laboratory) were crossed with Atg5+/− mice (C57BL/6) provided by Dr. Noboru Mizushima (Japan). ATG5 is an essential autophagy gene, its targeted deletion in dendritic cells completely abolished a functional autophagy pathway in these cells (DC/ATG5−). For the targeted deletion in dendritic cells completely abolished a functional autophagy pathway in these cells (DC/ATG5−). The targeted deletion in dendritic cells completely abolished a functional autophagy pathway in these cells (DC/ATG5−). For the targeted deletion in dendritic cells completely abolished a functional autophagy pathway in these cells (DC/ATG5−).

Results Mice lacking autophagy in their dendritic cells (DC/ATG5−) showed enhanced cartilage destruction and bone erosion. Interestingly, the Th1/Th17 response in DC/ATG5− mice was significantly increased. In parallel this phenotype was linked to a decreased Foxp3 expression in the regulatory T cell (Treg) population. Using Treg transfer upon AIA we could demonstrate that regulatory T cells switch to Th17 cells in the context of inflammation.

Conclusions Autophagy deficiency in dendritic cells exacerbates the Th1/Th17 inflammatory response in the AIA model, resulting in increased cartilage destruction and bone erosion. This phenotype is linked to Tregs instability upon inflammation.

Disclosure of interest None declared

P016 BASELINE LEVELS OF IL-17-PRODUCING CD4+ T CELLS PREDICT CLINICAL RESPONSE TO ABATACEPT IN RHEUMATOID ARTHRITIS PATIENTS

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Introduction Rheumatoid arthritis (RA) develops upon aberrant activation of the immune system mainly due to failure of self-tolerance mechanisms.1 Abatacept, approved for RA treatment, is a recombinant fusion protein of the extracellular domain of human cytotoxic T lymphocyte antigen 4 (CTLA4), restricts T cell activation by blocking interaction of CD80/CD86 on dendritic cells (DCs) to CD28 on T cells.2 In clinical practice, approximately 40–50% of RA patients treated with abatacept, respond to therapy in the first 6 months.3 Development of a predictor of response is of clinical and immunological significance.

Objectives Herein, we sought to investigate for early biomarkers of response to abatacept, based on a detailed immunological profile of peripheral blood cells and cytokines.

Methods RA patients (ACR/EULAR 2010 criteria) who started abatacept due to highly active disease, were recruited to perform immunological studies at baseline, 3 and 6 months of therapy. Peripheral blood mononuclear cells (PBMCs) were isolated and pathogenic IL-17 and IFN-γ producing CD4+ T cells (Th1, Th17), regulatory (Tregs) T cell subsets as well as myeloid cell populations, like DCs and myeloid derived suppressor cells (MDSCs) were characterized using flow cytometry. Response to therapy (remission or low disease activity) was assessed based on the “Swollen joints” value.

Results We studied 21 patients (mean age 60 years, 86% women, 48% rheumatoid factor or anti-citrullinated protein antibody positive). After 6 months of treatment, 45% of them attained remission or low disease activity. Notably, baseline levels of Th17 were statistically significant decreased in peripheral blood of patients in remission or low disease activity compared to those with active disease at 6 months of treatment (1.29±0.18% versus 2.44±0.41%, p=0.0482). Baseline levels of Th1 and Foxp3+ Tregs were comparable between responders and non-responders. No significant differences in CD14+CD15+CD33+ MDSCs or CD3+HLADR+ DCs were observed.

Conclusions In this cohort of RA patients treated with abatacept (CTLA4Ig), low levels of IL-17 producing CD4+ T cells at baseline are associated with a better response to abatacept at 6 months. This novel finding (validation to a larger cohort in progress) may be used as an early biomarker to predict clinical responses to abatacept.

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P017 RANK/RANK-LIGAND INTERACTION REGULATES PATHOGENIC T CELL RECRUITMENT IN SJÖGREN’S SYNDROME

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Introduction The RANKL (ligand)-RANK-OPG triad, members of the TNF(R) superfamily, is implicated in lymphoid organ...
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PROTEASE ACTIVATED RECEPTOR 2 (PAR2) EXPRESSION IN THE MYELOID COMPARTMENT IMPACTS OSTEOCLASTGENESIS

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Introduction Protease activated receptor 2 (PAR2) is a G protein coupled receptor responsive to serine proteases, which plays a key role in inflammation and pain reception. Rheumatoid arthritis (RA) patients have up-regulated surface expression of PAR2 in circulating monocytes which correlates with disease activity. We have previously demonstrated that Par2-/- mice are protected from inflammation, bone erosion, and cartilage destruction in a Freund’s Complete Adjuvant (FCA) induced arthritis model. However, it is unclear how PAR2 affects the composition of the myeloid compartment and osteoclastogenesis.

Objectives The aim of this study was to evaluate the impact of loss of PAR2 on the myeloid compartment and osteoclastogenesis.

Methods Bone marrow (BM) from 6–10 week old Par2-/- and control C57BL/6 mice was cultured in pro-osteoclastogenic media for 5 days and the generated mature osteoclasts, tartrate-resistant acid phosphatase positive (TRAP) multinucleated cells, were counted. The resorption potential of these cells was assessed using osteolysis plates and the total osteo-resorption quantified after 7–14 days of culture. BM was also collected for flow cytometric analysis of the haematopoietic cellular composition (with the following markers: CD11b, Ly6C, Ly6G, CD115, and CD117) and assessed for osteoclast precursors.

Results In vitro osteoclastogenesis revealed an increase in numbers of mature osteoclasts from Par2-/- BM compared to WT, corresponding with increased levels of resorption. Flow cytometry of BM from both WT and Par2-/- mice showed 3 distinct monocyte populations defined by the cell surface expression levels of CD11b and Ly6C. The overall ratio of these populations was not altered in Par2-/- animals.

Conclusions BM from Par2-/- mice has increased osteoclastogenic potential and overall resorptive activity. We propose that this is not due to differences in bone marrow residing osteoclast pre-curursors. This study indicates a potential role for PAR2 in osteoclast differentiation and bone remodelling.

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ULTRASOUND DETECTED TENOSYNOVITIS AS A MARKER OF SUBCLINICAL INFLAMMATION PRIOR TO ARTHRITIS ONSET

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Introduction Prospective studies of individuals at increased risk of developing rheumatoid arthritis (RA) will further improve the understanding of disease development. Ultrasound emerges clinically useful in detecting suble infer inflammatory changes in rheumatic diseases.

Objectives To investigate ultrasound (US) detected changes as markers for future arthritis development.

Methods Patients presenting with musculoskeletal complaints and a positive Anti-Citrullinated Protein Antibody (ACPA) test at primary care, were referred to Karolinska rheumatology clinic for further rheumatic joint disease assessments. Those lacking arthritis by clinical and US examination (defined as synovial hypertrophy with Doppler activity) were recruited...