Career situation of first and presenting author Student for a master or a PhD.

Introduction Endothelial cells (EC) are important contributors to inflammation via expression of inflammatory mediators, including chemokines and adhesion molecules. Production of these inflammatory mediators can be induced via canonical and NF- κ B-inducing kinase (NIK)-dependent noncanonical NF- κ B signalling. The ligands activating these pathways are well studied, but less is known about the cells producing ligands that can activate NF- κ B signalling in EC.

Objectives To study the effects of soluble factors produced by activated memory T (T_m) cells on NF- κ B dependent inflammatory activation of EC.

Methods CD4⁺CD45RO⁺ Memory T cells were isolated from healthy PBMC using MACS sorting and cultured in medium containing anti-CD3 and anti-CD28 for 72 hour, after which supernatant was harvest. Human umbilical cord EC (HUVEC) were stimulated with 50% T_m supernatant (T_m sup). After 72 hour of T_m sup stimulation HUVEC protein and RNA was harvest and NF- κ B signalling and downstream expression of inflammatory mediators was analysed using qPCR and Western Blot. Culture supernatant was analysed by ELISA to detect presence of inflammatory mediators. To repress canonical NF- κ B signalling an inhibitor of IKK β (iIKK β) was used and to repress NIK-dependent NF- κ B signaling an inhibitor of NIK (iNIK) was used.

Results Stimulation with T_m sup led to activation of both canonical NF- κ B signalling, indicated by increased levels of phosphorylated (p)-I κ B α , and noncanonical NF- κ B signalling, indicated by increased p100 to p52 processing. HUVEC stimulated with T_m sup had increased mRNA levels of all tested inflammatory mediators compared to non-treated cells. Gene expression of chemokines (CXCL1, CXCL5, IL6, IL8 and GM-CSF) after T_m sup stimulation was significantly reduced after treatment with iIKK β and to a lesser, but still significant, extent after treatment with iNIK. Interestingly, treatment with iIKK β also led to a reduction in mRNA levels of the adhesion molecules VCAM-1 and ICAM-1, while this effect was minimal after iNIK treatment. In addition, treatment with either IKK β or iNIK led to a significant reduction in CXCL5 in the culture supernatant of HUVEC stimulated with T_m sup.

Conclusions This study provides new insights into the cellular interactions leading to production of inflammatory mediators by EC. Our findings demonstrate that activated T_m cells factors produce factors that can cause NF- κ B-dependent inflammatory activation of EC. Targeting canonical NF- κ B signaling and, although to a lesser extent, NIK-dependent NF- κ B signaling reduces inflammatory activation of the endothelium.

Disclosure of Interest None declared.

P086

SYSTEMIC OVEREXPRESSION OF INTERLEUKIN-22 INDUCES EXPRESSION OF THE NEGATIVE IMMUNE-REGULATOR SOCS3 AND POTENTLY REDUCES COLLAGEN-INDUCED ARTHRITIS IN MICE

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Career situation of first and presenting author Student for a master or a PhD.

Introduction High interleukin-22 (IL-22) levels are detected in serum and synovial fluid of rheumatoid arthritis (RA) patients

and have been shown to positively correlate with disease activity markers and more erosive disease. The role of IL-22 in autoimmunity and inflammation appears to be greatly contradictory, being both pro- and anti-inflammatory. Especially the anti-inflammatory properties of IL-22 are not well understood. We aimed to investigate the anti-inflammatory and immune-suppressive effect of IL-22 during experimental arthritis.

Methods Collagen-induced arthritis was induced in DBA1 mice by immunization and booster with bovine collagen type II (CII). After booster, but before arthritis onset, IL-22 was overexpressed either locally or systemically using an adenoviral construct (AdIL-22) or Luciferase as control (AdLuc). 1×10^7 plaque-forming units (PFU) of the adenoviruses were injected intra-articularly for local overexpression, or 3×10^8 PFU was injected intravenously for systemic overexpression in immunized mice, and mice were sacrificed 10 days later. Macroscopic scoring and histological analysis was performed, and mRNA expression and protein production of various pro- and anti-inflammatory mediators was determined in synovial tissue, spleen, and serum.

Results Local overexpression of IL-22 by injection of AdIL-22 in the knee joint of CII-immunized mice resulted in an unaltered arthritis incidence and severity as compared to the control virus AdLuc. Accordingly, no changes in mRNA expression or protein production were observed in CIA mice locally overexpressing IL-22. In contrast, systemic overexpression of IL-22 potently reduced disease incidence and severity, which was also confirmed by histological analysis. Systemic levels of IL-1 β , IL-17, GM-CSF and MCP1 were unaltered in mice overexpressing IL-22 systemically. However, these mice showed significantly lower serum levels of IFN γ , TNF α , MIP1 α , and IL-10. Interestingly, the significantly enhanced splenic SOCS3 expression was found to negatively correlate to serum TNF α and MIP1 α levels, which is in line with our hypothesis that that the observed reduction in the cytokine levels is mediated in a SOCS3-dependent manner.

Conclusions With this study, we revealed clear anti-inflammatory effects of IL-22 overexpression during collagen-induced arthritis, which are completely dependent on the systemic route of administration. Additionally, we were the first to show that this protective effect of IL-22 during experimental arthritis is likely orchestrated via up-regulation of the negative regulator SOCS3.

Disclosure of Interest None declared.

P087

THE ANTI-INFLAMMATORY CYTOKINE INTERLEUKIN 37 IS AN ENDOGENOUS INHIBITOR OF TRAINED IMMUNITY

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Career situation of first and presenting author Assistant.

Introduction Trained immunity (TI) is a *de-facto* innate immune memory program induced in monocytes/macrophages

by exposure to pathogens or vaccines, which evolved as a protective mechanism against infections. TI is characterized by rewiring of functional, epigenetic and metabolic programs of innate immune cells such as monocytes and macrophages, which sustain enhanced production of pro-inflammatory cytokines. Since aberrant activation of TI is implicated in inflammatory diseases, tight regulatory mechanisms are likely in place, but the mechanisms responsible for this modulation remain elusive.

Objectives Scope of this study was to evaluate the role of IL-37, an anti-inflammatory cytokine that curbs inflammation as well as modulates metabolic pathways, as an endogenous regulator of trained immunity.

Methods The effects of recombinant IL-37 were evaluated in a mouse model of TI induced by the administration of beta-glucan *in vivo* (survival to a lethal inoculum of infectious agents, production of inflammatory cytokines, recruitment of inflammatory cells at the sites of infection). Subsequently, the effects of IL-37 were evaluated *ex vivo* on splenic and bone marrow monocytes (production of inflammatory cytokines, metabolomic analysis of the activation status of the main pathways of cellular energy metabolism). Finally, we evaluated the association between IL-37 gene polymorphisms and the induction of TI in monocytes of healthy donors with *in vitro* functional studies.

Results The exogenous administration of IL-37 abrogates the pro-inflammatory effects of TI, significantly reducing the production of pro-inflammatory cytokines and the survival of experimental animals subjected to a disseminated infection model. The inhibitory effects of IL-37 on TI are also associated with reduced recruitment of neutrophils at sites of inflammation. IL-37 and TI programs have differential and opposite effects on the modulation of cellular energy metabolism of monocytes. In humans, polymorphisms in the IL-37 gene are associated with reduced activation of TI programs and reduced production of inflammatory cytokines by healthy donor monocytes.

Conclusions In conclusion, IL-37 emerges as an endogenous regulator of TI, which makes this cytokine a potential therapeutic target in immune-mediated pathologies.

Disclosure of Interest None declared.

P088

CHARACTERIZATION OF NOVEL HUMANIZED IL-17 MOUSE PRECLINICAL PLATFORMS FOR THE EFFICACY EVALUATION OF ANTI-HUMAN IL17 THERAPEUTICS

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Career situation of first and presenting author Post-doctoral fellow.

Introduction As the IL17/IL23 axis has proven pathogenic for many inflammatory conditions like rheumatoid arthritis, psoriasis, IBD, multiple sclerosis (MS) and others, IL17 inhibition is an attractive target for the treatment of these diseases. Indeed, biologics targeting human IL17 (hIL17) have recently proven a successful treatment for psoriasis with similar therapeutics being currently under development for this and other diseases.

Objectives To describe novel preclinical platforms based on a hIL17A transgenic mouse model for the efficacy evaluation of human therapeutics, targeting psoriasis and MS.

Methods Human IL17A transgenic mice were generated using as transgene a 170 kb genomic DNA fragment comprising hIL17A intron exon sequences flanked by extended 5' and 3' regulatory regions. These mice were further crossed with IL17AKO¹ resulting in a mouse line (TghIL17) that exclusively expresses hIL17A. We standardized IMQ-induced psoriasis and MOG-induced Experimental Autoimmune Encephalomyelitis (EAE) induction protocols in these mice and characterized their response to anti hIL17 treatment. Disease severity was evaluated using established clinical and histopathological scoring scales.

Results TghIL17 mice have no overt pathology, and express hIL17A upon induction. IMQ-induced psoriasis induction in TghIL17 mice resulted in the development of skin pathology characterized clinically by skin erythema, thickening and scaling and histopathologically by acanthosis, hyperkeratosis and lymphocytic infiltration. Treatment with secukinumab resulted in alleviation of both clinical and histopathological psoriasis hallmarks to levels comparable to those observed in the IL17KO mice. MOG-induced EAE in TghIL17 mice resulted in clinical symptoms comparable to the ones observed in WT mice that involved, at the peak of the disease, paraplegia with forelimb weakness or paralysis. Treatment of EAE-affected TghIL17 mice with secukinumab ameliorated the pathological findings to a level similar to the one observed in IL17KO mice.

Conclusions TghIL17 mice upon induction develop pathologies similar to WT animals demonstrating that human IL17A efficiently replaces its mouse counterpart. Using these mice with standardized IMQ-induced psoriasis and MOG-induced EAE protocols we established and validated with commercially approved anti-hIL17 biologics, preclinical platforms that allow the efficient and reproducible evaluation of anti-hIL17 therapeutics.

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Disclosure of Interest None declared.

P089

MUCOSAL-ASSOCIATED INVARIANT T (MAIT)-CELL-DERIVED IL-17A AND IL-17F PRODUCTION IS IL-23-INDEPENDENT AND BIASED TOWARDS IL-17F

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Career situation of first and presenting author Young investigator.

Introduction The requirement for IL-23 in driving IL-17A and IL-17F production in humans is incompletely understood. Pre-clinical data support IL-17F, together with IL-17A, as a key driver of chronic tissue inflammation.¹ MAIT cells, an innate T-cell population, uniformly express RORγt but only a minority have been shown to produce IL-17A.² Dysregulation in frequency and function of MAIT cells has been associated with IL-17A-mediated inflammatory diseases, including PsA and AS.³⁻⁴ IL-17F production in MAIT cells remains largely unexplored.