in PBC group ($n=21$) (0.82 ± 0.76 vs 3.03 ± 4.23 , $p=0.028$). Immunofluorescence co-localization revealed that increased PD-1 positive cells in early PBC stage than late one, and less PD-L1 positive cells as well as PD-L1 and CK19 co-localised ones in PBC patients compared to HC. In the CTL and HiBEC co-culture system *in vitro*, the cytotoxicity of PD-1⁺ CD8⁺ T cells was weaker, with less proliferation and tendency of decreased production of IFN- γ and TGF- β compared to PD-1⁻ CD8⁺ T cells. Meanwhile, HiBEC apoptosis was relatively more in PD-1⁻ CD8⁺ T cells co-culture group. These effects could be antagonised by anti-PD-1 antibody and enhanced by PD-L1.

Abstract AB0036 – Figure 1

Conclusions: In PBC, the expression of Tbet is up-regulated in CD8⁺ T cells, which leads to the down-regulated expression of PD-1 on. Meanwhile, the expression of PD-L1 in HiBEC may be down-regulated. The silenced PD-1/PD-L1 pathway caused more CD8⁺ T cells proliferation, more related cytokines production and the enhanced CTL cytotoxic effects on HiBEC. PD-1/PD-L1 pathway functions as an important pathway in the immunological mechanism of PBC.

REFERENCES:

- [1] Kaplan MM. N Engl J Med, 1996;335(21):1570–1580.
- [2] Kita H, et al. J Clin Invest, 2002;109(9):1231–1240.
- [3] Yang GX, et al. J Immunol, 2011;186(2):1259–1267.
- [4] Keir ME, et al. Annu Rev Immunol, 2008;26:677–704.
- [5] Mataka N, et al. Am J Gastroenterol, 2007;102(2):302–312.

Acknowledgements: This work was supported in part by a grant from Capital Youth Medical Research and Development Fund (No. 2016–4–40111), National Natural Science Foundation (Outstanding Youth Foundation) (No. 81501414) and a grant from The National Key Research and Development Program of China^{No. 2016YFA010100}.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.1859

AB0037

MIR-155 PROMOTES THE DIFFERENTIATION OF TH17 CELL BY TARGETING ETS-1 IN RHEUMATOID ARTHRITIS

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Background: MicroRNAs play important roles in arthritis. MiR-155 emerges as a central regulator of the immune response, but its function in autoimmune arthritis is poorly understood.

Objectives: To clarify the role of miR-155 in the balance of CD4⁺Th17 and Treg cell differentiations as well as how their mechanisms function in autoimmune arthritis.

Methods: CD4⁺ T cells were *in vitro* isolated from DBA1 mice. The transfections of miR-155 mimics and miR-155 inhibitors in CD4⁺ T cells were performed for

enhanced or knockdowns of miR-155 expression and RNA interference was applied to silence Ets-1 gene expression. In addition, we carried out *in vivo* experiments of enhanced miR-155 expression by lenti-virus mediated miR-155 (LV-miR-155) infection and silencing of miR-155 expression by lenti-virus-anti-miR-155 (LV-anti-miR-155) within our well-established type II collagen (CII)-induced arthritis (CIA) mice model. The ratios of IL-17⁺ TH17 cells were analysed using flow cytometry (FCM). The expressions of some key autoimmune-response of genes including RORgt, IFN- γ , Ets-1, IL-17, IL-23, and Stat3 were further determined by (Taqman) Quantitative Real-time PCR and Western blotting. Initially $n=6$ per group if not indicated further; totally 6 groups in parallel per experiment. * $p<0.05$, considered as significantly; ** $p<0.01$, considered as highly significantly.

Results: For the first time we showed that miR-155 may promote Th17 cell differentiation in RA pathogenesis. Firstly, we observed that miR-155 may significantly induce the expressions of some key autoimmune-response genes including RORgt, IFN- γ , IL-17, IL-23, and Stat3 but it significantly inhibited Ets-1 gene expression. 2ndly, miR-155 may in part modulates Th17 cell differentiation by targeting Ets-1 in that indeed the expression of miR-155 significantly co-related with disease index in CIA mice. Furthermore, the CIA mice with *in vivo* forced expression of miR-155 have significantly more Th17 cells (i.e. high ratio) and severe CIA disease index compared to their control CIA mice; strikingly, they also have a significantly higher expression of aforementioned autoimmune-response genes compared to their corresponding controls along with the response of Ets-1 exactly in a verse direction. Consistently, the CIA mice with *in vivo* knockdown of miR-155 expression resulted in significantly less Th17 cells and lesser severe CIA disease index compared to their control CIA mice. However, they have a significantly lower expression of above-mentioned autoimmune-response genes compared to their corresponding controls along with a response of Ets-1 in a verse direction (the data in part shown in Figure 1; sham=CIA treated with LV-nonspecific sequence).

Conclusions: For the first time our data show miR-155 has a critical role in Th17 differentiation and the RA pathogenesis via targeting the Ets-1. Although it warrants further investigations, miR-155 might be a promising therapeutic target for autoimmune diseases, esp. RA.

Abstract AB0037 – Figure 1

Acknowledgements: This work was supported by National Natural Science Foundation of China #81102266. All authors listed were either involved in conception and design, or acquisition, analysis and interpretation of data, and/or writing. Each author gave their final approval of this version.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.3877

Innate immunity in rheumatic diseases

AB0038

TBK1: A KEY REGULATOR AND POTENTIAL TREATMENT TARGET FOR INTERFERON POSITIVE SYSTEMIC LUPUS ERYTHEMATOSUS AND SYSTEMIC SCLEROSIS

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Background: Upregulation of type I interferons (IFN-I) is a hallmark of systemic autoimmune diseases like systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). Three different receptor families are implicated in the induction of IFN-I production: Toll-like receptors (TLRs), RIG-like receptors (RLRs) and DNA-sensing receptors (DSRs). TANK-binding kinase (TBK1), is an important signalling hub downstream of RLRs and DSRs. TBK1 activates IRF3 and IRF7, leading

to IFN-I production and subsequent induction of interferon-stimulated genes (ISGs).

Objectives: To explore the potential of TBK1 inhibitors to downregulate IFN-I activation in SLE and SSc.

Methods: TBK1, IRF3, IRF7 and STAT1 were determined by qPCR in PAXgene samples and phosphorylated-TBK1 (pTBK1) was analysed by flowcytometry in plasmacytoid dendritic cells (pDCs) from IFN-I positive (IFNpos) patients. Peripheral blood mononuclear cells (PBMCs) from SLE and SSc patients and TLR7-stimulated PBMCs from healthy controls (HCs) were cultured with the TBK1 inhibitors BX795 followed by analysis of ISGs.

Results: Increased expression of TBK1, IRF3, IRF7 and STAT1 in whole blood and pTBK1 in pDCs was observed in IFNpos pSS, SLE and SSc patients compared to HCs. Upon treatment with BX795, PBMCs from IFNpos pSS, SLE, SSc and TLR7-stimulated HCs downregulated the expression of the ISGs MxA, IFI44, IFI44L, IFIT1 and IFIT3. The TBK1 inhibitor inhibited the secretion of IFN-I by TLR7-stimulated PBMCs from HCs.

Conclusions: TBK1 inhibition reduced expression of ISGs in PBMCs from IFNpos SLE and SSc patients indicating TBK1 as a potential treatment target.

Acknowledgements: The research for this manuscript was (partly) performed within the framework of the Erasmus Postgraduate School Molecular Medicine. The authors thank patients and healthy volunteers for taking part in this study.

Disclosure of Interest: E. Huijser: None declared, I. Bodewes: None declared, C. van Helden-Meeuwsen: None declared, L. Tas: None declared, R. Huizinga: None declared, V. Dalm: None declared, M. van Hagen: None declared, N. Groot: None declared, S. Kamphuis: None declared, P. van Daele: None declared, M. Versnel Grant/research support from: Research funding Domainex

DOI: 10.1136/annrheumdis-2018-eular.6367

AB0039 IMMUNOSUPPRESSIVE EFFECT OF MESENCHYMAL STEM CELLS ON MONOCYTES DERIVED FROM PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Mesenchymal stem cells (MSCs) are a heterogeneous population of fibroblast-like progenitor cells that may be isolated and expanded from bone marrow, umbilical cord and other tissues. Moreover, MSCs display the capacity to self-renew and differentiate into various mesodermal cell lineages. They also have drawn considerable attention for their regenerative and immunosuppressive effects in a range of autoimmune diseases, which raises the question for their potential use as therapeutic tool in rheumatoid arthritis.

Objectives: In line with aforementioned and taking in mind that monocytes playing pivotal role in orchestrating immunological tolerance, we aimed to study the immunosuppressive effects of adipose tissue derived mesenchymal stem cells (AT-MSC) on monocytes derived from patients with rheumatoid arthritis (RA).

Methods: We enrolled 12 patients matching the ACR/EULAR 2010 criteria for RA. AT-MSC were isolated and cultured according to well established protocols. ELISA was performed for testing the cytokines produced by AT-MSC (IL-1, IL-10, IL-4, IFN- γ , IL-6, IL-8, CCL-5, RANTES, IL-17). Peripheral blood mononuclear cells (PBMCs) isolated from RA patients' samples were cultured in AT-MSC conditioned media and in control media. Flow cytometry was used for detection of monocytes markers (CD14, CD80, CD86, HLA-DR).

Results: Our results revealed considerable increase in number of cells expressing the myeloid lineage surface marker CD14 ($p=0.026$) under the influence of AT-MSC medium. We further demonstrated decrease in percentage values of monocytes expressing HLA-DR ($p=0.004$) and CD80/86 surface molecules ($p=0.47$). Moreover, significant reduction in mean fluorescent intensity of HLA-DR surface expression ($p=0.016$) was also demonstrated.

Conclusions: Our study unambiguously points out that under the impact of AT-MSC media monocyte development into dendritic cells was hampered and was also skewed into direction of accumulation of monocytes displaying more tolerogenic phenotype characterised by down regulation of HLA-DR and B7 complex (CD80/86) surface expression. Furthermore, antigen presentation alongside with expression of the co-stimulatory B7 complex and cytokine ambience forms a three-way signalling pathway responsible for T helper activation and proliferation and consequent antibody production by plasma cells. Hence, effects exerted by AT-MSC conditioned media on monocyte lineage development should not be neglected in the context of developing novel therapeutic approaches and strategies for treatment of RA.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.3201

AB0040 TOLL-LIKE RECEPTOR 9 INFLUENCES INFLAMMATORY ARTHRITIS AND OSTEOCLASTOGENESIS

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Background: Release and insufficient removal of endogenous nucleic acids may be involved in triggering autoimmune reactions important in the initiation of systemic autoimmune diseases including rheumatoid arthritis (RA). Nucleic acid sensing molecules, such as the endosomal Toll-like receptors (TLRs) 7 and 9, have been linked to pathogenic autoimmune processes, but their role in RA is less clear. Data obtained in rats with pristane-induced arthritis (PIA) suggested involvement of TLR9 in the pathogenesis of this arthritis model¹.

Objectives: To gain more insight into the role of TLR9 in autoimmune arthritis, TLR9 inhibition with specific oligodeoxynucleotide sequences (ODN)² was investigated in rats with PIA. To further investigate TLR9 involvement, streptococcal cell wall (SCW) arthritis was induced in TLR9^{-/-} mice.

Methods: Arthritis was induced in mice with SCW lysates and in rats with the mineral oil pristane. Rats were treated with a TLR9 antagonist, starting before disease induction. Arthritis was scored using established scoring systems, inflammation and bone erosion were quantified by histological analysis. Levels of α -1-acid-glycoprotein (AGP), rheumatoid factor (RF) and IL-6 in sera were analysed. The role of TLR9 in osteoclast differentiation and activation was investigated *in vitro*.

Results: In PIA, the TLR9 antagonist reduced arthritis severity by ~50%, which was accompanied by a reduction of AGP, IL-6 and RF. TLR9 inhibition led to reduced inflammation, bone erosion and cartilage degradation. Moreover, the T cell-dependent chronic phase of SCW arthritis was significantly suppressed in TLR9^{-/-} mice. Remarkably, TLR7 and TLR9 mRNA levels strongly differed in the course of *in vitro* osteoclastogenesis. Whereas TLR7 expression did not change throughout osteoclastogenesis, expression of TLR9 was higher in precursor cells than in mature osteoclasts and stimulation with a TLR9 agonist (CpG) completely inhibited osteoclastogenesis.

Conclusions: Taken together, the results suggest a role for TLR9 in the T cell-dependent phases of PIA and SCW arthritis thus an important involvement of the DNA (CpG) recognising TLR9 in the initiation of autoimmune arthritis and during osteoclastogenesis. The precise role(s) of TLR9 in the different stages of arthritis needs to be further elucidated in future experiments.

REFERENCES:

- [1] Hoffmann MH, et al. Nucleic acid-stimulated antigen-presenting cells trigger T cells to induce disease in a rat transfer model of inflammatory arthritis. *J Autoimmun*, 2011;36(3-4):288-300.
- [2] Duramad O, et al. Inhibitors of TLR-9 act on multiple cell subsets in mouse and man *in vitro* and prevent death *in vivo* from systemic inflammation. *J Immunol*, 2005;174(9):5193-200.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.4557

AB0041 HETEROGENEITY OF THE TYPE I INTERFERON SIGNATURE IN RHEUMATOID ARTHRITIS MAY ACCOUNT FOR DIFFERENCES IN ITS CLINICAL RELEVANCE

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Background: increased expression of interferon-responding genes (IRGs), the so-called IFN signature, has been reported in rheumatoid arthritis (RA) in peripheral blood and synovial tissue. However, some controversy exists concerning its clinical relevance, since longitudinal changes of the IFN signature have been reported upon different treatments and a physiological diversification of the type I IFN signature among different conditions has been recently described. Additionally, the relevance of the IFN signature in the very early stage of RA is unknown.