Looking for a SLE Signature on Peripheral B Cell Subsets: Does a Preponderant CD38+ Plasmablast-Subpopulation Lack CD73 as a Sign of a Disturbed Adenosine Axis?

M. Siekerka-Harms, M. Schroeder, G. Chehab, J. Richter, M. Schneider, G. Pongratz. Rheumatology, Heinrich-Heine University Duesseldorf, Medical Faculty, Duesseldorf, Germany

Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disorder characterised by polyclonal Bcell activation, production of dsDNA-autoantibodies and cytokines. Subsets of Bcells play a central role in SLE-pathogenesis. The inflammatory milieu is characterised by the accumulation of adenosine, which confers immunosuppressive effects.

Objectives: In SLE, the role of CD73, an enzyme involved in the extracellular generation of adenosine from ATP, is not well characterised. This study aimed to characterise expression of CD73 Bcell subsets of SLE-patients as compared to healthy controls (HC).

Methods: Bcell subsets were characterised from peripheral blood of 23 SLE patients attending the outpatient clinic at the Rheumatology Unit of University Hospital Düsseldorf and of 15 HC by FACS. All patients fulfilled the revised SLE-criteria of ACR and were randomly collected in clinical remission state (SLEDAI 1±1.1).

Results: By comparison of Bcell subsets between SLE and HC, CD38 was dominantly expressed by SLE-patients (SLE 74.2±12.9% vs. HC 64.2±12.2%; p(MWU)=0.018). Furthermore, SLE-patients showed an increased frequency of CD19+IgD-CD727+CD38+ high plasmablasts (SLE 2.1±3.4% vs HC 0.4±0.4%, p(MWU)=0.001). Furthermore, SLE-plasmablasts showed decreased CD73 expression as compared to HC (SLE 2.1±1.9% vs HC 3.5±2.2%; p(MWU)=0.034). SLE-Bcells revealed a trend towards an augmented CD38highCD138+ plasmacellular fraction (SLE 0.4±0.5% vs HC 0.08±0.07%; p=0.07), without any difference in CD73 expression. On the other hand, exhausted-memory B cell fraction (CD19+IgD-CD27-CD21-CD138-) showed an increased CD73 expression in SLE (SLE 13.7%±9.2% vs HC 6.2%±0.4%, p(MWU)<0.001). Furthermore, SLE-plasmablasts showed decreased CD19+IgD-CD727+CD38+ high plasmablasts (SLE 0.40%±0.5% vs HC 0.08%±0.4%, p(MWU)=0.006). CD19+IgD-CD27-CD21-CD138- showed an increased CD73 expression in SLE (SLE 13.7%±9.2% vs HC 6.2%±0.4%, p=0.004).

Conclusions: Our study confirms CD38+ plasmablasts as being increased in peripheral blood from SLE patients as compared to HC. Furthermore, the data reveal a deficiency for CD73 on SLE plasmablasts, which suggests a decreased anti-inflammatory capacity of SLE plasmablasts as compared to HC, supporting the notion of a disturbed adenosine axis in SLE. On the other hand, the enlarged CD73+ exhausted memory pool in SLE could point to an accelerated flow of CD73+ B cells into an exhausted B cell fraction. These findings support the hypothesis of dysregulation of the adenosine axis in SLE even in inactive SLE patients.

References:


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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 HIBE cytokoty 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, HIBE apoptosis was relatively more in PD-1+ CD8+ T cells co-clture group. These effects could be antagonised by anti-PD-1 antibody and enhanced by PD-L1.

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 HIBE 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 HIBE. PD-1/PD-L1 pathway functions as an important pathway in the immunological mechanism of PBC.

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Innate immunity in rheumatic diseases

**AB0037**

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

Z. Yin1, W. He1, X. Chen1, X. Luo1, Y. Zhang2, Z. Ye1. Shenzhen Futian Hospital for Rheumatic Diseases, Shenzhen; *Rheumatology and Immunology, First Clinical College of Harbin Medical University, Harbin, China

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 lentivirus mediated miR-155 (LV-miR-155) infection and silencing of miR-155 expression by lentivirus-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 determined by flow cytometry (FCM). The expressions of some key autoimmune-response genes including RORgt, IFN-γ, Ets-1, IL-17, IL-23, and Stat3 were further examined by 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, Ets-1, IL-17, IL-23, and Stat3 but it significantly inhibited Ets-1 gene expression. Secondly, 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 averse 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 averse 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

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**AB0038**

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

E. Huisinga1, I. Bodewes1, C. van Helden-Mrouwes1, L. Tas1, R. Huizinga1, V. Dalm1, M. van Hagen1, N. Groot3, S. Kamphuis3, P. van Dale2, M. Versnel1.

1Immunoology; 2Internal Medicine; 3Pediatric Rheumatology, Erasmus MC, Rotterdam, Netherlands

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