EVIDENCE FOR INCREASED RESPONSIVENESS TO INTERFERON TYPE I IN CD8+ T CELLS IN PATIENTS WITH GIANT CELL ARTERITIS

Keywords: Innate immunity, Cytokines and chemokines, Vasculitis

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Background: Giant cell arteritis (GCA) is a vasculitis which can lead to severe complications when not timely recognized and treated. There is a need for the discovery of biomarkers to expedite the diagnostic process. Interferon type I (IFN-I) is increasingly recognized as a key player in a range of autoimmune diseases and might play a role in GCA pathogenesis [1]. However, evidence for IFN-I potentially linking innate and adaptive immune responses in GCA is limited. IFN-I activates the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway, leading to an increased expression of interferon stimulated genes (ISGs).

Objectives: In this study, IFN-I involvement in GCA pathogenesis is explored.

Methods: Phospho-STAT1 (pSTAT1) expression was investigated in IFN-I-stimulated peripheral mononuclear cells (PBMCs) gated separately for CD8+ T-cells of patients with GCA (n=18), healthy controls (HC, n=15) and infection controls (n=11) by fluorescent cell barcoding and flow cytometry. Also, in 3 GCA patients and 3 HCs, single cell RNA sequencing was performed on PBMCs focusing on ISG expression. Furthermore, IFN-I induced myxovirus-resistance protein A (MxA) and CD8+ expression was investigated in temporal artery biopsies (TAB) of GCA patients (n=20) and GCA mimics (n=20) by immunohistochemistry.

Results: pSTAT1 expression was increased in IFN-I stimulated CD8+ T-cells from patients with GCA compared to both HC (p<0.05) and infection controls. Furthermore, Interferon Induced Transmembrane Protein 1 (IFITM1) mRNA expression was upregulated in peripheral blood CD8+ T cells (p=0.001). MxA was present in TABs of 13/20 GCA patients compared to 2/20 mimics and MxA location co-localized with CD8+ expression in the tissue.

Conclusion: Our results provide evidence for IFN-I involvement in GCA pathogenesis, with CD8+ T cells as IFN-I responding effector cells. Increased pSTAT1, IFITM1 and MxA expression may reflect increased IFN-I responsiveness in CD8+ T-cells of GCA patients, both locally and systemically. These findings warrant further investigation regarding IFN-I induced biomarkers and IFN-I related novel therapeutic options.

REFERENCE:

Figure 1 MxA expression (brown staining) in temporal artery biopsy of A) a non-GCA patient and B) a biopsy-proven GCA patient.

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AMELIORATION OF IGA VASCULITIS BY SUPPRESSION OF THE PATHOLOGICAL EXPANSION OF Tfh17 CELLS

Keywords: Vasculitis, Animal models, Treat to target

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Background: Immunoglobulin A vasculitis (IgAV), also named Henoch–Schönlein purpura, is a systemic vasculitis characterized by the deposition of IgA-dominant immune complexes in small vessels that often involves the skin, joints, gastrointestinal tract, and kidney [1-3]. Research indicated increased frequencies of circulating activated B cells and plasmablasts in IgAV, which may serve as the source of the rising IgA levels [4]. T follicular helper (Tfh) cells are considered to support the activation of B cells and help germinal center (GC) B cells switch to high-affinity IgA production. In human, Tfh17 cells prompt naive B cells to produce higher concentrations of IgA [5]. T cell-deficient mice that receive an adoptive transfer of Tfh17 cells show induced development of IgA-expressing GC B cells from BD uveitis subjects with scRNA seq.

Objectives: To evaluate the pathological role of Tfh17 cells in IgAV patients and IgAV rats and explore how to ameliorate IgAV condition.

Methods: Peripheral blood mononuclear cells from IgAV patients were analyzed by flow cytometry. In vitro culture was performed to assess the modulation of

Ocular and Periferal Blood Immune Phenotypes Suggest Transmigration of CD4+ Monocytes to an Important Effectore Site in Behçet’s Disease

Keywords: Cell biology, Behçet’s disease, -Oomics

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Background: Cellular immunity of Behçet’s Disease (BD) remains poorly understood. Previous work has provided clues pointing to most innate and adaptive immune cell types in BD, but strong signals from non-immunogenetic studies are rare and often inconclusive.

Objectives: Here we aimed to identify BD/HD discriminant single immune cell profiles in semi-biased and targeted approaches and determine their significance at a BD relevant effector site.

Methods: We utilized multi-parametric flow cytometry to dissect cellular phenotypes in PBMC of untreated BD patients (n=27) and HD (n=22) constituting predominantly of active ocular and major vascular BD subjects. Data were subjected to supervised machine learning (CITRUS) and results verified with targeted gating. We also analyzed anterior chamber (AC) fluid cells and autologous PBMC from BD uveitis subjects with scRNA seq.

Results: CITRUS identified CD16+, CD14low, CD4low, CD3+, CD19- cells as a BD/HD distinguishing cellular expression pattern at an FDR of >0.05. Targeted gating confirmed highly significant differences with large effect sizes in PBMC of BD vs HD for “non-classical” (CD14lowCD16hi) and “intermediate” (CD14+CD16+) monocytes at decreased frequencies compared to peripheral blood “classical” (CD14++CD16+) monocytes were more abundant in BD PBMC than in HD. CD16+ dendritic cells (DC) were significantly decreased in BD PBMC. CD14+ cells showed high abundance in the AC during BD uveitis and co-expressed CD16 far more frequently than CD14+ cells in autologous peripheral blood.

Conclusion: Significantly lower frequencies of CD16+ monocytes and DC subsets in PBMC of untreated active BD vs HD strongly point to their importance in BD. The high abundance of CD14+ cells with CD16 co-expression in the eye during uveitis relative to their frequency in autologous peripheral blood, suggests their transmigration or post-migrational interconversion within the eye during BD uveitis rather than a stochastic process.

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cytokine-induced phenotypes. IgAV rat model was established by intragastric administration of mixed solution, intraperitoneal injection of ovalbumin and Freund’s adjuvant. IgAV rats were used to explore the therapeutic effects of IL-6 blockade and the regulatory functions of IL-6 and TGF-β-producing dendritic cells in Th17 cells. Serum cytokine and IgA levels were measured by ELISA while histopathological changes were evaluated by H&E and PAS staining. Flow cytometry and immunofluorescence staining were used to detect T cell and GC B cell phenotypes in circulation and tissues of IgAV rats.

**Results:** Frequency of CD4+CXCR5+CCR6+ Th17 cells were increased in IgAV patients and associated with disease severity. IL-6 promoted the dendritic cell production of TGF-β and Th17 differentiation. Blockade of IL-6 signaling using tocilizumab inhibited Th17 differentiation, resulting in a reduction of the germinal center and IgA production. Suppression of Th17 cells using IL-6 blockade greatly ameliorated clinical symptoms such as hemorrhagic rash and bloody stool and decreased IgA deposition and mesangial proliferation in the kidney in IgAV rats.

**Conclusion:** Our findings suggest that suppression of Th17 differentiation can alleviate IgA-mediated vasculitis and may permit the development of tailored medicines for treating IgAV.

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**SLE, Sjögren’s and APS - clinical aspects (other than treatment)**

**PO51443 CORRELATION BETWEEN SAXON TEST AND UNSTIMULATED SALIVARY FLOW RATE IN PATIENTS WITH SUSPECTED SJÖGREN’S SYNDROME**

**Keywords:** Sjögren syndrome, Diagnostic tests

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**Background:** Sjögren syndrome (SS) is a chronic systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands, which alters their function producing dryness of the mouth, eyes and other mucous membranes. The method used to quantify glandular hypofunction is by whole saliva flow stimulated and unstimulated (UWSF) [1], which takes between 5 and 15 minutes (min). The Saxon test (St) [2], is another tool with the same objective but requires less time: 2 minutes. In the literature, we only have found one study that compared the Saxon test with other diagnostic methods although it is developed in patients without SS [3].

**Objectives:** To compare the Saxon test and UWSF in a cohort of patients with suspected SS.

**Methods:** In a consecutive cohort of patients who attended the rheumatology department for suspected SS, UWSF was measured (mL/5min) and the Saxon test (gr/2min) was performed. The index Reported by Patients with SS of the EULAR (ESSPRI) was collected too. This is a patient-reported index designed to assess the severity of patients’ symptoms (dryness, pain, somatic and mental fatigue) in SS through an average of single 0–10 numerical scale for each domain. To measure the UWSF, patients were asked to swallow their saliva before the start of the test and then to spit into a container for 5 min. The St was performed by calculating the difference in the weight of two pieces of sterile gauze that the patient chewed for two minutes. A UWSF >0.25 mL/min and a St >2.75g/2min were considered normal, as well as and ESSPRI<5. Spearman’s rank correlation coefficient (rs) was used to determine the correlation between both quantitative variables. The Chi-square test and the Gamma test were used in the comparisons between the groups (altered and normal) and the Mann-Whitney U in the comparisons of the quantitative variables based on the groups (altered and normal) previously defined. P values <0.05 were considered statistically significant.

**Results:** We enrolled 199 patients (166 women), with a mean age ± standard deviation of 55.1±13.7 years. The medians (Me) and interquartile ranges (IQR) obtained were 1.50 (0.70 – 2.50) mL/5min for the UWSF, 2.31 (1.60-2.10) g/2min for the St, 6.33 (3.67- 7.67) for ESSPRI and 700 (5.00-8.00) for ESSPRI-dryness score. A direct and significant correlation between the St and the UWSF (rs=0.391; P=2.236x10³) was observed; 76 patients (38.2 %) presented an altered UWSF and 107 patients (56.2 %) had an altered St. When we analysed the intensity of the association between the different groups (altered/normal) of both variables, we observed a direct and significant association (Gamma value=0.4, P<0.019) between both tools. We also detected differences in the St between patients with altered UWSF (Me: 1.72gr/2min; IQR: 1.04-2.50) and those with normal UWSF (Me: 2.62 gr/2min; IQR: 1.95-3.54) (P=3.9x10⁻²). Similarly, we observed significant differences in UWSF values between patients with altered St (Me: 1.50/mL/5min IQR: 0.60-2.50) and those with a normal St (Me: 2.00/mL/5min IQR: 1.00-3.00) (P<0.014). Regarding the ESSPRI, 129 (65.8 %) patients presented an altered ESSPRI and 153 (78.1%) had an altered ESSPRI-dryness score. The group patients with ESSPRI-dryness score≥5 obtained significantly lower scores on the St (Me: 2.10g/2min IQR: 1.39-3.01), on the UWSF (Me: 1.5/mL/5min IQR: 0.6-2.0), and on the ESSPRI (Me:700 IQR:5,33-8,00) than the normal ESSPRI-dryness score group:Me:2.98g/2min, IQR:2.22-3.75, on St (P>0,001), Me:2.45/mL/5min, IQR:1.50-3.50, on UWSF (P=6.5x10⁻²); Me:9.17, IQR:1.04-4.08, on the ESSPRI (P=4.17x10⁻²).

**Conclusion:** In patients with suspected SS, there is a direct and significant correlation between the St and the UWSF. Therefore, the St could be useful in the initial assessment of oral gland dysfunction, to save time and/or to select patients who require performing the UWSF.

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