PS5:97 ROLE OF CD107A+ (LAMP-1) CYTOTOXIC CD8+ T-CELLS IN PATIENTS WITH SLE

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Objectives Cytotoxic T-cells are a thought to play a pivotal role in the pathogenesis of systemic lupus erythematosus (SLE) in particular in lupus nephritis. The aim of this study was to investigate the activation marker CD314 (NKG2D) and CD107a (LAMP-1) on cytotoxic CD8 +T cells in patients with systemic lupus erythematosus.

Methods Peripheral blood of patients with systemic lupus erythematosus (n=30) and healthy controls (n=21) was stained with anti-CD8 (PB), -CD3 (Chrom Orange), -CD45RO (FITC), -CD197 (PE), -CD314 (APC), -CD107a (APC) antibodies and analysed by flow cytometry. Kidney biopsies of lupus nephritis patients were investigated by immunohistochemistry and immunofluorescence for the presence of CD8 +CD107a+cells. Patients disease activity was assessed by systemic lupus erythematosus disease activity index (SLEDAI).

Results The percentages of CD314 +on CD8+T cells were not different between SLE-patients and healthy controls. The percentages of CD107a+on CD8+T cells were significantly decreased in SLE-patients as compared to healthy controls ($40.2\pm 18.5\%$ vs $47.9\pm 15.0\%$, $p=0.02$). This was even more significant in SLE-patients with inactive disease. The evaluation of lupus nephritis biopsies showed a significant number of CD107a+CD8+T cells mainly located in the peritubular infiltrates.

Conclusions These results demonstrate that CD8 +T cells of patients with systemic lupus erythematosus have an altered activation status which seems to be associated with disease activity. The proof of intrarenal CD107a+CD8+suggests a role in the pathogenesis of lupus nephritis.

PS5:98 TCR ZETA DIM LYMPHOCYTES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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T lymphocytes with low or absent expression of TCRzeta chain (TCR zeta -/dim cells) are supposed to have pathogenic effect in the development of autoaggression and chronic inflammation. Systemic lupus erythematosus (SLE) is a model of chronic inflammatory disease with autoimmune background.

In vitro studies have shown, that microenvironment rich in proinflammatory cytokines, such as TNF-alfa and IL-6, especially promotes the impairment of TCR zeta chain expression, what leads to the increase of the percentage of T cells with defects of the synthesis of that molecule.

Objective The aim of this study was to define the size of the population of autoreactive TCR zeta -/dim lymphocytes in the blood of patients with SLE and the functional characteristics of TCR zeta-/dim and TCR zeta bright cells based on the assessment of their

capacity to synthesize certain cytokines (IFN-gamma and IL-2) and to compare it with healthy controls.

Results Our study showed decreased percentage of CD4 +and CD8+lymphocytes with TCR zeta chain expression in patients with SLE. The significantly diminished TCRzeta chain expression in lymphocytes of patients with SLE which in addition was correlated with longer disease duration, renal involvement and higher level of serum anti-dsDNA antibodies confirms former studies indicating not only the association of this defect with disease development, but also with more active clinical course.

The *in vitro* stimulation of T lymphocytes in SLE patients lead to overproduction of IFN-gamma especially in the population of autoreactive TCR zeta -/dim lymphocytes.

On the other hand, T lymphocytes of SLE patients have lower capacity of the synthesis of IL-2, which is strongly correlated with TCR zeta chain expression and may be observed even in patients with very low clinical disease activity.

Conclusion SLE is characterised by the expansion of TCR zeta -/dim lymphocytes in peripheral blood, which are regarded as autoreactive cells, and is correlated with clinical course of SLE. The decreased expression of TCR zeta may be due to the presence of exogenous inhibiting factor in blood of SLE patients. Higher synthesis of INF-gamma and lower of IL-2 may contribute to chronic inflammation and autoimmune proces in SLE.

PS5:99 EXAMINING THE MODULATORY EFFECTS OF ANTI-SERINE PROTEASE ANTIBODIES UPON FACTOR XA, THROMBIN AND COMPLEMENT INTERACTIONS

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Purpose Serine protease (SP) enzymes play a critical role in both the coagulation and complement cascades. Anti-SP antibodies are found in approximately 40% of patients systemic lupus erythematosus (SLE) and antiphospholipid Syndrome (APS). Complement activation is important in SLE and APS. However, little is known about the effects of anti-SP antibodies on complement activation in these diseases. We sought to investigate whether affinity-purified antibodies to the SP Factor(F)Xa and Thrombin (Thr) alter the effects of these SP on complement cleavage in the presence or absence of the physiological inhibitor anti-thrombin (AT).

Methods Serum was obtained by informed consent from patients with SLE (n=10) and/or APS (n=2) under long-term follow-up at University College London Hospital. A novel method was developed to affinity purify anti-FXa and anti-Thr IgG separately. We incubated FXa (2 µM) and Thr (2.7 µM) separately with complement component C3 to determine baseline C3 cleavage. We then repeated the experiment in the presence of AT3, the appropriate anti-SP (anti-FXa or anti-Thr) or both. Finally we reviewed medical records of 40 patients with SLE to determine whether low C3 was associated with seropositivity for anti-FXa and/or anti-Thr in these patients.

Results Both FXa and Thr cleaved C3 into C3a/C3 b. This was inhibited by AT, though both cleavage and inhibition by AT were stronger for Thr than FXa. Conversely anti-SP antibodies enhanced C3 cleavage by SP. Anti-FXa IgG (n=3) increased FXa-mediated cleavage of C3 by 1.3-fold. Anti-Thr IgG (n=8) increased Thr-mediated C3 cleavage by 1.8-fold. AT mediated inhibition was prevented by addition of anti-FXa

Abstract PS5:99 Figure 1 Data showing relative C3 cleavage of Thr and Fxa in the presence and absence of antibodies and inhibitors

IgG (n=2) but not anti-Thr IgG. Analysis of clinical serology records for the last 10 consecutive clinic visits of 28 anti-SP-positive patients showed a lower level of C3 (0.92 g/L) in the patients double positive for anti-Fxa and anti-Thr than for anti-Thr alone (1.12 g/L) or anti-Fxa alone (1.16 g/L).

Conclusions Anti-Fxa and anti-Thr enhance cleavage of C3 by Fxa and Thr respectively. Presence of these antibodies *in-vivo* in patients with SLE and/or APS may promote increased complement activation and disease activity. This finding may have potential translational implications for future treatment of these diseases.

PS5:100 PATOPHYSIOLOGICAL ROLE OF TYPE I AND III INTERFERONS IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Systemic Lupus erythematosus (SLE) is an autoimmune disease characterised by activated autoreactive lymphocytes and autoantibodies, resulting in tissue damage in multiple organs. An important factor for the disease's mortality is the development of Lupus nephritis (LN). Type I and III interferons, which are both part of the antiviral defense, have both been associated with the disease's activity. In sera and urine of SLE patients an enhanced level of IL28/29 was described, but their distinct functional role in the course of disease need to be further investigated.

To determine the role of type I and III interferons during onset and progression of autoimmunity – with focus on the development of LN – the expression of the IFNs and their specific receptors was observed in lupus prone MRL Faspr mice. These mice develop SLE like symptoms and immuno-complex glomerulonephritis. So far we could confirm the expression of IL28 and it's receptor by tubular epithelial cells

(TEC) in the kidney of MRL Faspr mice. The overall IL28 mRNA expression increased with disease activity in renal tissue, and a positive correlation to the IFN α and IFN β expression could be observed. Further the mRNA expression of the IFN receptor mRNA in the spleen accelerated with increasing disease activity.

Furthermore MRL Faspr mice deficient of the IL28R and/or IFN α R were generated and the progression of autoimmunity and LN was monitored. In preliminary studies with MRL Faspr IL28R^{-/-} mice, a less extenuated lymphadenopathy and less severe LN at the age of 3 month was observed, compared to their wild-type littermates. Similar observations according the Lymphadenopathy were made in MRL Faspr IFN α R^{-/-} mice.

Our results suggest a participation of type III IFNs in the development of Lupus nephritis in MRL Faspr mice. In upcoming experiments the effect of the IL28R knockout will be compared to the effect of the IFN α R knockout and the combined IL28R-IFN α R knockout. The subsequent aim is to transfer the results obtained in the murine model to human SLE and to evaluate IL28 as disease activity marker.

PS5:101 NUCLEAR ANTIGEN-REACTIVE CD4+ T CELLS ARE EXPANDED IN ACTIVE SLE, CORRELATE WITH DISEASE ACTIVITY, INVADE TARGET ORGANS SUCH AS THE KIDNEYS, AND OUTNUMBER THEIR REGULATORY COUNTERPARTS

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