survival and proliferation of B cells and mTOR inhibition has been shown to be effective in immune B cell suppression in transplant patients and in treatment of B cell lymphomas. Interestingly, in a pSS mouse model mTOR targeting inhibited lymphocytic infiltration in the lacrimal gland. However, mTOR activation in B cells has not been studied in pSS patients.
Objectives: To study the mTOR pathway in B cells of pSS patients as a potential therapeutic target to inhibit B cell hyperactivity.
Methods: Expression of mTOR pathway genes (MTOR, RPTOR, RICTOR, DEPTOR, AKT1, IGF1R, IGF1, PTEN) were assessed on an OpenArray platform in purified peripheral blood B cells and monocytes from pSS patients (n=12), non-Sjögren's sicca patients (n=17) and healthy controls (HC, n=9). Correlations with clinical parameters including lymphocytic focus score, ESSDAI and serum IgG levels were assessed. Flow cytometry analysis for B cell subset distribution was performed to assess potential effects of B cell subset distribution on gene expression differences. Culture experiments were performed to study inhibition of the mTORC1 pathway (phosphorylated S6, kinase activity downstream of mTORC1) in association with inhibition of B cell proliferation and IgG production by mTOR inhibition.
Results: RPTOR and IGF1R expression were significantly increased in B cells from pSS patients (p=0.019 and p=0.018, respectively) and correlated with serum IgG levels (r=0.429, p=0.020, and r=0.462, p=0.012). Differences in expression of mTOR pathway genes were not found in monocytes. To indicate the mTOR signature a cumulative mTORC1 score was calculated consisting of Z scores (AKT1 + IGF1R + IGF1 + RPTOR + MTOR – PTEN – DEPTOR) which was significantly elevated in pSS (p=0.027), correlating with serum IgG levels (r=0.463, p=0.011). Frequencies of memory and naïve B cells did not differ between pSS patients and HC in this cohort (p=0.415). Activation of B cells in culture resulted in phosphorylation of S6, which indicates increased mTORC1 activity, in accordance with B cell proliferation and IgG production in both HC and pSS patients. Inhibition of mTOR by rapamycin decreased pS6 (n=4, n=2 HC, n=2 pSS, MFI 1400±335 vs 935±306, p=0.060), strongly reduced B cell proliferation (n=6, n=3 HC, n=3 pSS, 80.8±9.9 vs 19.1±15.8%, $p<0.001$), reduced IgG+ B cells (n=6, n=3 HC, n=3 pSS 39.5±15.5 vs 11.1±5.7%, p=0.001) and decreased IgG production (n=4, n=2 HC, n=2 pSS, 160±180 pg/mL vs 25.3±13.0 pg/mL p=0.060).
Conclusions: Presence of an mTORC1 signature in B cells from pSS patients correlating with B cell hyperactivity indicates a role for mTORC1 in B cell activation in this disease. The fact that B cell proliferation and IgG production is effectively inhibited by rapamycin suggests that mTOR inhibition represents a potential therapeutic strategy for pSS.
Disclosure of Interest: None declared
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THU0224 ASSOCIATION OF IRAK-M WITH NEUROPSYCHIATRIC SYMPTOMS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Background: Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease, where a breakdown in immune tolerance leads to sustained inflammation and tissue damage. Patients exhibit multi-organ involvement with a diverse range of symptoms that include arthritis, nephritis, neuropsychiatric events and dermatological complaints. Interleukin-1 receptor-associated kinase M (IRAK-M), a negative regulator of toll-like receptor (TLR) signalling has previously been associated with SLE in a murine study [1]. Deficiency of IRAK-M was observed to exacerbated disease in a SLE model in C57BL/6-lpr/lpr mice [2].
Objectives: This study aimed to investigate the expression of IRAK-M in monocytes from SLE patients compared with healthy control donors and measure downstream cytokine production upon TLR stimulation.
Methods: The study was approved by the Brighton East Research Ethics Committee and the *National Research Ethics Service* Committee North West – Lancaster. Whole venous blood was collected from 39 SLE patients and 19 healthy donors. Peripheral blood mononuclear cells were purified from whole blood after which monocytes were isolated using $CD14^+$ selection beads. Expression of IRAK-M was determined relative to the geometric mean of the housekeeping genes glyceraldehyde 3-phosphate dehydrogenase and hypoxanthine phosphoribosyltransferase 1 by quantitative polymerase chain reaction. Cultured monocytes were stimulated with TLR ligands. Cytokine production was measured by enzyme-linked immunosorbent assay.
Results: IRAK-M expression was increased in the SLE patient group, however many of the patients did not show elevated expression compared to healthy donors. When stratified by disease symptoms, a clear correlation was observed between low expression of IRAK-M and neuropsychiatric symptoms which was not evident when evaluating other SLE symptoms. Interestingly, TLR activation led to elevated cytokine production in SLE patient monocytes that correlated with the basal level of IRAK-M expression in individual donors. Further investigation revealed that SLE monocytes demonstrated a reduced upregulation of IRAK-M after TLR activation compared to healthy donors.
Conclusions: Increased expression of IRAK-M was not unexpected in the SLE group due to the systemic inflammatory nature of the disease. However, not all patients presented with increased levels of IRAK-M and upon activation were less able to upregulate IRAK-M compared to healthy donors, suggesting a reduced capacity to resolve inflammation. This was reflected in the elevated cytokine production observed from SLE monocytes. Thus, low expression of IRAK-M in SLE monocytes is linked to elevated inflammatory cytokine production and may be a biomarker for neuropsychiatric symptoms in SLE patients.
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THU0225 ROLE OF THE IL-12/IL-35 BALANCE IN SJÖGREN'S SYNDROME

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Background: An interferon (IFN) signature is involved in the pathogenesis of primary Sjögren's syndrome (pSS), but whether the signature is type 1 or 2 remains controversial. Mouse models and genetic studies suggested the involvement of T helper 1 and type 2 IFN pathways. Likewise, polymorphisms of interleukin 12A gene (*IL-12A*), which encodes for IL-12p35, have been associated with pSS. IL-12p35 subunit is shared by 2 heterodimers, IL-12 and IL-35.
Objectives: To confirm the genetic association of *IL-12A* polymorphism and pSS and elucidate the involvement of the IL-12/IL-35 balance in pSS by functional studies.
Methods: The genetic study involved 673 patients with pSS from 2 French pSS cohorts and 585 healthy French controls. Functional studies were performed on sorted monocytes, stimulated or not. IL-12A mRNA and IL-12 and IL-35 protein levels were assessed by qRT-PCR and by ELISA and a multiplex kit for IL-35 and IL-12, respectively.
Results: We confirmed the association of the *IL-12A* rs485497 polymorphism and pSS and found an increased serum protein level of IL-12p70 in pSS patients carrying the risk allele (p=0.016). Serum level of IL-12p70 was greater in patients than controls (p=0.0001), especially patients with more active disease (p=0.05); conversely IL-35 level was decreased in patients (p=0.0001) especially in patients with a more active disease (p=0.05).
Conclusions: Our findings emphasize the involvement of the IL-12/IL-35 balance in the pathogenesis of pSS. Serum IL-35 level was associated with low disease activity, in contrast to serum IL-12p70 level, which was rather associated with a more active disease.
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THU0226 DIFFERENTIAL SUSCEPTIBILITY OF TH17 AND T REGULATORY CELLS TO APOPTOSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS – THE MODULATORY EFFECTS OF STATIN

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Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder. Patients with SLE have accelerated cardiovascular disease. Recent studies show there are more Th17 while less T regulatory (Treg) cells in the SLE patients. Th17/Treg imbalance may contribute to the pathogenesis of SLE.
Objectives: To investigate the underlying mechanisms of Th17/Treg imbalance, we test the proportion and susceptibility of Th17 and Treg to apoptosis, and the modulatory effects of statin in the SLE patients.
Methods: Totally 17 SLE patients and 20 gender- and age-matched control subjects were enrolled for this study. Peripheral blood mononuclear cells were isolated, either analyzed ex vivo, or cultured in the conditions to induce Th17 and/or Treg polarization. The proportion of Th17/Treg cells and frequency responding to apoptosis were analyzed by multiple color flow cytometry. Cytokines in cell culture supernatants and plasma were tested by ELISA. T cell polarization-related transcription factors were detected by quantitative real time PCR.
Results: The proportion of Th17 ($CD4^+IL17^+$) cells were higher in SLE patients,