AB0158 TAUROURSODEOXYCHOLIC ACID DECREASES THE EXPRESSION OF ERAD COMPONENTS AND THE ACCUMULATION OF SALIVARY MUCINS INDUCED BY PRO-INFLAMMATORY CYTOKINES

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Background: The salivary glands of Sjögren's syndrome patients show endoplasmic reticulum (ER) stress characterized by intracellular accumulation of secretory products such as MUC1[1], dilated ER cisternae[2] and high levels of pro-inflammatory cytokines. Previous results from our laboratory revealed an increase of the ATF6α pathway of the UPR[3] and activation of ER-associated protein degradation (ERAD)[3]. Increased expression of proteins involved in ERAD (SEL1L and EDEM1) has been reproduced *in vitro* in human submandibular gland (HSG) cells treated with TNF-α or IFN-γ[2]. Tauroursodeoxycholic acid (TUDCA) is a chemical chaperone utilized for alleviate ER stress by enhancing the folding of proteins[3].
Objectives: The aim of this study was to evaluate if TUDCA decreases EDEM1, SEL1L, and MUC1 expression induced by pro-inflammatory cytokines in salivary gland epithelial cells.
Methods: HSG-cells were incubated with 10 ng/mL of IFN-γ or TNF-α for 24h. Alternatively, cells were incubated with cytokines for 6h and then co-incubated with TUDCA (150 and 250 μM) up to 24h. EDEM1, SEL1L and MUC1 protein and mRNA levels were determined by Western-blot and RT-qPCR, respectively. EDEM1 and SEL1L localization was determined by immunofluorescence.
Results: HSG cells stimulated with IFN-γ or TNF-α showed a significant increase of EDEM1 and SEL1L protein and mRNA levels. Importantly, TUDCA co-incubation caused a significant decreased expression of both molecules. Treatment with both cytokines induced a cytoplasmic increase of staining intensity of EDEM1 and SEL1L, which was suppressed by TUDCA. HSG cells stimulated with cytokines showed a significant increase of MUC1 protein and mRNA levels, which was also suppressed by TUDCA.
Conclusions: Decreased expression of MUC1, SEL1L and EDEM1 in the presence of TUDCA suggests that this chemical chaperone promotes folding of proteins in the ER, by decreasing ERAD activity and ER stress induced by pro-inflammatory cytokines in HSG cells. These results enable us to propose that TUDCA might alleviate the ER stress of salivary glands from Sjögren's syndrome patients.
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AB0159 AUTOIMMUNE REACTIVITY TO MALONDIALDEHYDE ADDUCTS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by recurrent disease activity flares, multiple organ involvement, and often with a presentation of nephritis. Malondialdehyde (MDA) post-translational modification of proteins occurs upon inflammation and oxidative stress. Natural IgM anti-MDA autoreactivity is present from birth and may be beneficial. However, both IgM and IgG anti-MDA can also be increased in autoimmune disease. Yet, the role for potentially pro-inflammatory autoreactive IgG anti-MDA in SLE remains elusive.
Objectives: Here, we study the association between serum IgG anti-MDA and clinical features of SLE.
Methods: This cross-sectional study included 398 SLE patients at the Karolinska University Hospital fulfilling at least four of the 1982 ACR criteria. Data was compared to the previously reported combined US east coast cohorts (1, 2). Disease activity was assessed by SLEDAI-2K. Total IgG and ANA IgGs were assessed in the clinical laboratory and sTNFR by ELISA. IgG anti-MDA was measured by a quantitative ELISA using modified BSA. As a comparison, we measured IgG anti-phosphorylcholine (PC), another oxidation-associated natural IgG. Cutoff for positivity was based on highest control quartile. Specific IgGs were normalized for total IgG levels in the analysis. Means were compared with Mann-Whitney test, correlations with Spearman's analysis, and meta-analysis used Mantel-Haenszel fixed effect model.
Results: Serum IgG anti-MDA significantly correlated with SLE-associated auto-IgG (e.g. anti-dsDNA, n=398 R=0.42 $p<0.0001$). IgG anti-MDA correlated with higher disease activity by SLEDAI in two independent cohorts (Sweden KS, n=397 R=0.33 $p<0.0001$; US east coast, n=219 R=0.34 $p<0.0001$) and was confirmed in meta-analysis of dichotomized data showing an Odds Ratio of 3.9 (CI 2.6–5.8 $p<0.0001$) for IgG anti-MDA positivity in patients with active disease (SLEDAI≥6). Association of anti-MDA with disease activity was supported by an inverse correlation of IgG anti-MDA normalized for total IgG with complement (C2, n=304 R=-0.24 $p<0.0001$, C3 and C4, n=385 R=-0.24 $p<0.0001$). Furthermore, we observed elevated IgG anti-MDA/total IgG reactivity in SLE patients with current or history of nephritis compared to no history of nephritis (n=389 4.5+/-4.0 vs 3.4+/-3.3 $p<0.0001$) and inverse weak correlation of IgG anti-MDA/total IgG with markers of kidney function (serum cystatin C, n=283 R=0.20 p=0.0008, urine albumin, n=373 R=0.23 $p<0.0001$). Anti-MDA IgG/total IgG also directly correlated with serum soluble TNF receptors (sTNFR1, n=286 R=0.21 p=0.0003, sTNFR2, n=287 R=0.35, $p<0.0001$). IgG anti-PC either did not correlate or inversely correlated with disease measurements, consistent with its previously reported more protective properties.
Conclusions: IgG to MDA-modifications correlates with other autoreactivities, disease activity and nephritis in SLE, and should be further evaluated for its potential prognostic utility. Yet, it remains unclear, if IgG anti-MDA directly contributes to pathogenesis in SLE.
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AB0160 INTERFERON-Γ-INDUCIBLE KYNURENINES INFLAMMATION PATHWAY: THE MISSING LINK BETWEEN DISEASE ACTIVITY AND SYMPTOMS IN SJÖGREN'S SYNDROME

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Background: Tryptophan (TRYP) can be converted to kynurenine (KYN) by indoleamine 2,3-dioxygenase (IDO) drived by interferon-γ. Recent studies have suggested that the KYN pathway reflects an important interface between the immune and nervous system modulation.
Objectives: The aim was to study KYN pathway and their correlation to clinical and immunological parameters in primary Sjögren's syndrome (pSS).
Methods: We included 97 pSS (AECG) and 63 healthy controls matched to age, sex, ethnicity, and body mass index (BMI). KYN metabolites and TRYP were analysed by liquid chromatography mass spectrometry.
Results: Patients aged 50±11 years showed anti-SSA-Ro of 63%, anti-SSB-La 31%, anti-nuclear antibody 81%, rheumatoid factor 24%, and systemic manifestations 67%. Most (68%) showed low disease activity measured by Eular Sjögren's Syndrome Disease Activity Index (ESSDAI), 22% moderate and 10% high ESSDAI. The kynurenine:tryptophan ratio (KTR) was (0.031±0.014 vs. 0.024±0.007, p=0.001), KYN (1.890±0.580 vs. 1.652±0.426, p=0.005), quinolinic acid (QA) (477.82±251.55 vs. 382.05±128.06, p=0.018), hydroxikynurenine (3HK) (53.45±52.05 vs. 39.15±9.67, p=0.056), anthranilic acid (AA) (19.86±6.26 vs. 16.78±4.71, p=0.001) were higher while xanthurenic acid (XA) (11.52±7.88 vs.13.00±5.68, p=0.019), and TRYP (64.90±13.43 vs. 71.02±8.88, p=0.012) were lower in pSS compared to controls. Higher KTR was associated with disease duration (r=0.211,p=0.042), CRP (r=0.254,p=0.029), lower hemoglobin (r=-0.219, p=0.34), creatinine (r=0.588, p=0.000), hypergammaglobulinemia (r=0.254, p=0.014), hyper IgG (r=0.354, p=0.004), lower C3 (r=0.262, p=0.011) and C4 (r=-0.294, p=0.004). Higher KTR was observed in those with Biological ESSDAI domain involvement (0.033±0.016 vs. 0.029±0.013, p=0.003), glandular manifestation (0.037±0.014 vs.0.029±0.013, p=0.007), in the other hand lower KTR in those with presence of musculoskeletal pain (0.029±0.011 vs. 0.032±0.015, p=0.003). ESSDAI showed a tendency to correlate with KTR (r=0.177, p=0.091) and ESSPRI inversely correlated with AA (r=-0.233, p=0.071). Either patient with pain showed lower AA (20.66±6.66 vs. 17.22±5.07, p=0.021).
Conclusions: TRYP is decreased and KYN metabolites pathway is increased in pSS. IDO activity expressed like KTR was positively correlated with disease activity and glandular manifestations but negatively with pain. A better understanding of the KYN pathway can clear the dissociation of symptoms and disease activity in pSS.
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