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AB0196 ENDOPLASMIC RETICULUM STRESS IN SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis is an autoimmune connective tissue disease in which their is inflammation and skin fibrosis. Currently there is no disease modifiying treatment due to the limited understanding of the pathogenesis of the disease. Endoplasmic recticulum (ER) stress, characterised by misfolded proteins, can be induced by a variety of stressors such as redox imbalanace and calcium depletion. This activation of ER stress by whatever trigger results in activation of an evolutionary conserved cell sensors and a resulting signalling cascade to help restore homeostasis. It is suggested in other fibrotic diseases that ER stress is prominent.
Objectives: The aim of this study is to determine the role of ER stress in Systemic Sclerosis.
Methods: Healthy dermal fibroblasts where cultured *in vitro* and stimulated with the ER stress inducer thaspigargin and in some experiments with small interfering RNA to X-Box binding protein-1 or scramble controls at the matched concentration. Cell were then lysed and subjected to western blotting of XBP-1, IRE-alpha, ATF-6, collagen-1 and alpha tubulin for a loading control. In some experiments the dermal fibroblasts were treated with ER stress and 4-phenylbutric acid to inhibit ER stress and makers measured. q-RT-PCR was performed for Fli-1 and 18S using specific primers and subjected to real time with SYBR green and normalised to 18S.
Results: ER stress mediated by thaspigargin results in activation of classical ER stress pathways. Inhibition of these pathways through small interfering RNA results in attenuation of collagen expression in dermal fibroblasts. This was also the case with dermal fibroblasts treated with the chemical inhibitor 4-phenylbutric acid. The epigenetic modifier Fli-1 is reduced after ER stress. This is known to act as a brake on collagen regulation.
Conclusions: ER stress induced collagen accumulation and could be blocked by chemical and genetic reduction of XBP-1. Mechanistically this could be due to reduced Fli-1 therby releasing the brake on collagen1 expression. Modulation of ER stress via chemical inhibitors could be a promising new treatment in SS.
Disclosure of Interest: None declared
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AB0197 METALLOPROTEINASE-7 AS AN EARLY MARKER OF LUNG DAMAGE AMONG POLYMYOSITIS AND DERMATOMYOSITIS PATIENTS

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Background: Interstitial lung disease (ILD) can complicate the course of polymyositis/dermatomyositis (PM/DM) almost in the half of patients and represents as a high risk factor of mortality among such cohort of patients from chronic pulmonary insufficiency. Lung function monitoring and chest high resolution computer tomography (HRCT) are obligatory methods of investigation among PM/DM patients. However, these methods allow to determine already formed interstitial changes in the lungs. Therefore, there is a need for biomarkers to seek early changes of lung tissue, what allows to prescribe basic treatment in time, encountering its side effects.
Metalloproteinase 7 (MMP-7) reflect lung damage and can also be an early biomarker of ILD which complicates PM/DM. It was early reported that −181A/G (rs11568818) polymorphism in MMP-7 promoter modulates gene expression and plays pivotal role in the MMP-7 upregulation in that way affects ILD progression. Here, we evaluated the impact of −181A/G polymorphism in MMP-7 promoter activity and its association with MMP-7 elevation.
Objectives: Our study was aimed to analyse the level of MMP-7 as an early marker of lung damage among PM/DM patients and also probable influence of rs11568818 on the MMP-7 elevation.
Methods: 17 patients with PM/DM have been observed in the rheumatology department with primary established diagnosis, 9 patients among them has proved diagnosis of ILD with HRCT. All patients have been examined according to the recommended EULAR standards and paraneoplastic reaction have been excluded. Patients have been divided into 2 groups, 1st group include 9 patients with PM/DM complicated with ILD, 2nd – 8 patients with isolated PM/DM. Control group included 17 healthy volunteers. MMP-7 level was assayed by the enzyme immunoassay system in the blood serum. −181A/G (rs11568818) polymorphism was genotyped by polymerase chain reaction restriction fragment length polymorphism (PCR–RFLP) method. All statistical calculations were done using SPSS software 21.0.
Results: Results. Mean age of patients of the 1st group – 48,44±2,74, 2nd – 54,25±2,55, control group – 49,0±2,4 (p=0,33). DM have been established in 7 patients and PM – 10. Mean level of MMP−7 in the 1st group was 4,02±1,58 (CI 95% 2,81–5,24), 2nd – 1,43±0,2(CI 95% 0,93–1,92), control group – 1,3±0,75 (F=30,87, p <0,001). It was determined that the level of MMP-7 was positively correlated with Anti-Jo1 antibodies (r=0,82, p=0,007) and it was higher among PM/DM patients complicated with ILD (p=0,001). Analysis of genotypes frequency AA/AG/GG with regard to rs11568818 polymorphism, shows no significant distribution(p=0,984) and is following in the 1st group – 66,7%/22,2%/11,1% and 62,5%/25%/12,5% – in the 2nd, in the control group – 70,6%/17,6%/11,8% respectively. The analysis of the connexion between studied genetic polymorphism with the level of MMP-7 didn't show any interdependence (p=0,771).
Conclusions: The level of MMP-7 is higher among the 1st group, in comparison with 2nd and control groups. Positive correlation connexion between the level of MMP-7 and Anti-Jo1 antibodies among PM/DM patients with ILD was found. The difference between genotypes distribution according to the rs11568818 gen polymorphism depending on existence of ILD and MMP-7 level is absent. Taking into account the results, we can admit that MMP-7 is a perspective marker of lung tissue damage among PM/DM patients.
Disclosure of Interest: None declared
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AB0198 BIOLOGICAL PROPERTIES OF URINE-STEM CELLS AND THERAPEUTIC EFFECT ON SYSTEMIC SCLEROSIS FIBROSIS

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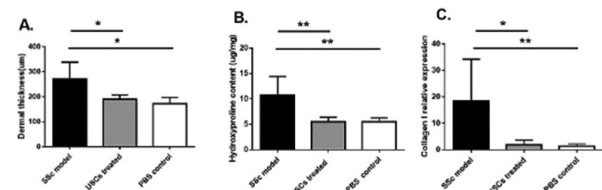
Background: Because of the lack of effective treatment of systemic sclerosis (SSc), cellular therapy is considered as a salvage option.[1–4] Mesenchymal stem cells (MSCs) are gaining attentions in the field of cell therapy of SSc. However, current isolation methods of MSCs are all invasive and challenging.[5] Some studies have reported the isolation from urine recently, and definition of urine-derived stem cells (USCs).[6] The collection of USCs is noninvasive that could be a desired resource of MSC. So far, the information of therapeutic effect on SSc is limited.
Objectives: We aimed to explore the biological characterizations of USCs and investigate the therapeutic effect on murine SSc model.
Methods: USCs were isolated and cultivated from sterile urine samples of healthy adult individuals. The related cell markers were examined by flow cytometry. The differentiation potentials were observed in adipogenic, osteogenic and chondrogenic medium, respectively. SSc murine models were conducted by daily intradermal injections of bleomycin and were further divided as treated and untreated group. Also, the healthy control group was conducted by daily injection of phosphate buffered saline (PBS). Treated group received an infusion of 2.5 × 10^5 USCs in the tail vein twice in one week after the 3 week modelling. Skin samples were obtained one week after the treatment. Hematoxylin-eosin and Masson staining were accomplished to observe the skin thickness and the hydroxyproline content was detected by hydroxyproline kit. The relative expression of collagen type I alpha 1 chain (Col1-a1), alpha-smooth muscle actin (α-SMA), and fibronectin 1(Fn-1) were detected by real-time quantitative PCR.
Results: The morphology of USCs was spindle-shaped. They express CD73, CD90, and CD105 but CD34, CD45, CD19, CD11b, or HLA-DR. USCs possessed the abilities to differentiate into adipocytes, osteoblasts, and chondrocytes. In USCs treated group, the skin thickness(p=0.031) (Figure1A), the deposition of collagen in HE and Masson trichrome-staining (p=0.007) (Figure1B), and Col1-a1 gene expression(p=0.010) (Figure1C) were significantly reduced in comparison with untreated group and were close to healthy controls.



Abstract AB0198 – Figure 1