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THU0351 LOW ERA EXPRESSION MIGHT BE IMPLICATED IN THE DEVELOPMENT OF PULMONARY HYPERTENSION IN FEMALE MICE LACKING PSGL-1

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Background: Pulmonary arterial hypertension (PAH) is a rare disease with unknown etiopathogenesis and no curative treatment [1]. PAH is one of the major complications of connective tissue diseases, and 7-15% of patients with systemic sclerosis (SSc) develop PAH [2]. Mice deficient for the leukocytic receptor P-selectin glycoprotein ligand-1 (PSGL-1^{-/-}) spontaneously develop a SSc-like autoimmune syndrome with ageing [3].

Objectives: To check whether PSGL-1^{-/-} mice may develop PAH and the molecular mechanisms that might be implicated in the initiation and establishment of the disease.

Methods: Doppler pulse echocardiography was used to evaluate pulmonary artery flow acceleration time/ejection time (PAAT/ET) ratio in WT and PSGL-1^{-/-} C57BL/6 mice. Isolated pulmonary artery rings were incubated with acetylcholine and responses were registered with a wire myograph coupled to an isometric force transducer. Expression levels of the NO-sensing probe DAR-4M AM by fluorescence microscopy and flow cytometry. Angiotensin II lung concentration was quantified by ELISA. eNOS, p-ENOS, AT1R and AT2R expression was evaluated by western blot. In all cases, data are expressed as the mean±SD.

Results: Aged PSGL-1^{-/-} females showed reduced flow PAAT/ET ratio indicating PAH. Moreover, pulmonary arterial rings from aged PSGL-1^{-/-} females presented ROS-independent reduced vasodilation response to acetylcholine. Importantly, eNOS phosphorylation was impaired and NO production by lung EC was reduced in aged PSGL-1^{-/-} females. Vascular remodeling and reduced expression of AT2R were observed in lungs of PSGL-1^{-/-} females from a younger age. With ageing, the levels of angiotensin II and the percentages of IFN γ -producing interstitial macrophages, T and B lymphocytes were increased in PSGL-1^{-/-} females. The differences in the gender-biased genotype could be explained by the reduced expression of ER α in the lungs of aged PSGL-1^{-/-} females while WT and PSGL-1^{-/-} males showed similar expression.

Conclusion: PSGL-1 deficiency leads to pulmonary hypertension in >18-months-old female mice, involving various mechanisms:

1. Lung vessel wall remodeling and reduced AT2R expression.
2. Reduced eNOS phosphorylation and reduced NO production with the subsequent specific lung endothelial dysfunction in PSGL-1^{-/-} females. Importantly, ROS production is not increased nor help to NO reduction.
3. Increased pulmonary AngII levels with ageing in PSGL-1^{-/-} females.
4. Increased Th1 polarization, reduced Treg population and increased IFN- γ production by interstitial macrophages.

Impaired ageing up-regulation of ER α expression in the lungs of PSGL-1^{-/-} females.

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THU0352 THE ROLE OF PRURITOGENIC MEDIATORS IN DERMATOMYOSITIS RELATED ITCH

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Background: Pruritus is a common symptom in systemic autoimmune diseases like dermatomyositis (DM). Recent researches have indicated that interleukin-31 (IL-31), IL-33, IL-6, or inflammatory cytokines, such as tumor necrosis factor (TNF α), peroxisome proliferator-activated receptor γ (PPAR γ) and ion channels belonging to the transient receptor potential (TRP) family are involved in pruriception.

Objectives: We examined targeted gene expression analysis of lesional versus non-lesional skin samples of patients affected with active DM. We looked for correlations between the examined pruriceptive signaling molecules, disease activity and itching sensation of DM patients.

Methods: Gene expression of TNF α , PPAR γ , IL-33, IL-6 and TRPV channels in lesional DM skin was evaluated by RT-qPCR and was compared with non-lesional DM skin samples. Pruritus and disease activity of DM was evaluated by the 5-d itch scale and Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), respectively. Statistical analysis was performed with IBM SPSS 20.0 software.

Results: Skin samples of 17 active DM patients were analyzed. We could show, that itching index in DM was positively correlated with CDASI score with a correlation coefficient of 0.82 ($p < 0.001$). TNF α gene expression was significantly higher (34.87%) in lesional DM skin than non-lesional DM skin ($p = 0.03$). The normalized TNF α mRNA expression was positively correlated with itch scale ($R = 0.605$, $p = 0.022$) and its level was significantly higher in skin samples of patients with severe itch (itching score: 15-20) versus mild itch (itching score: 5-10) (2.02 ± 0.38 vs. 1.12 ± 0.20 ; $p < 0.01$). The level of PPAR γ was decreased in lesional DM skin, but this was statistically not significant. The mRNA expression of normalized PPAR γ was negatively correlated with itch scale ($R = -0.618$, $p = 0.019$), and its level was significantly lower in skin samples of patients with severe itch versus mild itch (0.28 ± 0.36 vs. 1.53 ± 0.98 ; $p = 0.038$). Lesional IL-6 mRNA levels were associated with CDASI activity score ($R = 0.619$, $p = 0.018$). The mRNA levels of TRPV1-4 channels were not associated with 5-D itch score, but normalized TRPV1 and TRPV4 mRNA expressions were positively correlated with CDASI damage score ($R = 0.699$, $p = 0.008$; $R = 0.789$, $p = 0.001$). Interestingly, itching sensation of DM patients was not correlated with IL-33 mRNA levels measured in skin samples.

Conclusion: Our results argue for that higher cutaneous disease activity generate pruritus. TNF α and PPAR γ might play a determining, but opposite role in DM-associated itch. Furthermore IL-6, TRPV1 and TRPV4 channels might participate in pathomechanism of cutaneous manifestation of the disease.

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THU0353 AN ORALLY AVAILABLE HIGHLY SELECTIVE 5-HYDROXYTRYPTAMINE 2B (5-HT_{2B}) RECEPTOR ANTAGONIST AMELIORATING PULMONARY AND DERMAL FIBROSIS IN PRECLINICAL MODELS OF SYSTEMIC SCLEROSIS

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Background: Serotonin or 5-hydroxytryptamine (5-HT) is well known as a stimulator of tissue fibrosis and a significant role of peripheral 5-HT_{2B} receptors in fibrosis has been suggested with the receptor being upregulated in fibrotic tissues. In addition, agonism of the 5-HT_{2B} receptor has been implicated in human tissue fibrosis caused by drugs known to activate the receptor. Pharmacologic inhibition of 5-HT_{2B} receptor signalling consequently represents a promising treatment strategy for fibrotic disorders including systemic sclerosis. 5-HT is released from platelets activated upon vascular damage, one of the first pathological events in systemic sclerosis. The local 5-HT concentration is increased and leads to activation of 5-HT_{2B} receptors on e.g. fibroblasts. The pro-fibrotic effects of 5-HT and the 5-HT_{2B} receptor are believed to be mediated through activation of the TGF- β /Smad signaling pathway.

Objectives: The objective of the present study was to evaluate a novel highly selective orally available 5-HT_{2B} receptor antagonist, AM1476, for its ability to reduce pulmonary and dermal fibrosis in the sclerodermatous