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 leukocyte 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 ERα 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 AngI 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 ERα expression in the lungs of PSGL-1−/− females.

REFERENCES

Disclosure of Interests: None declared.

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

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 pruripetic signaling molecules, disease activity and itching sensation of DM patients.

Methods: Gene expression of TNFα, PPARγ, IL-33, IL-6 and TRPV channel genes 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 (CDSAI), 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 and IL-6 mRNA levels (R=0.60, p=0.001) and it 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 PPARγ was decreased in lesional DM skin, but this was statistically not significant. The mRNA expression of normalized PPARγ was negatively correlated with itch scale (R= -0.518, 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 CDASAI 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 CDASAI 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. TNFα and PPARγ might play a determining, but opposite site role in DM-associated itch. Furthermore IL-6, TRPV1 and TRPV4 channels might participate in pathomechanism of cutaneous manifestation of the disease.

DISCLOSURE OF INTERESTS: None declared.

Background: Serotonin or 5-hydroxytryptamine 2B (5-HT2B) receptor antagonist ameliorates pulmonary and dermal fibrosis in preclinical models of systemic sclerosis.

Objectives: We evaluated a novel highly selective orally available 5-HT2B receptor antagonist, AM1476, for its ability to reduce pulmonary and dermal fibrosis in the scleroderma-like models.

Methods: Pulmonary fibrosis (PFTs) and skin fibrosis (SF) were evaluated in the 5/6 nephrectomized (5/6Nx) rat model of experimental pulmonary fibrosis. SF was assessed by measuring skin thickness and skin hydroxyproline content. PFTs were assessed by measuring forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and diffusion capacity for carbon monoxide (DLCO).

Results: AM1476 significantly reduced PFTs and SF in the 5/6Nx model compared to vehicle. Treatment with AM1476 resulted in a significant improvement in FVC, FEV1, and DLCO. AM1476 significantly reduced skin thickness and skin hydroxyproline content. Treatment with AM1476 resulted in a significant improvement in FVC, FEV1, and DLCO. AM1476 significantly reduced skin thickness and skin hydroxyproline content.

Conclusion: AM1476 is a novel highly selective orally available 5-HT2B receptor antagonist with potential therapeutic applications in the treatment of pulmonary and dermal fibrosis in the 5/6Nx model of experimental pulmonary fibrosis.