SAT0316 ANGII INVOLVEMENT IN LUNG ENDOTHELIAL DYSFUNCTION AND PAH DEVELOPMENT IN PSGL-1 DEFICIENT FEMALE MICE

R. González-Tajuelo[1], M. de la Fuente-Fernández[1], D. Morales-Cano[2], B. Barreira[2], J. Silván[1], C. Gamallo[1], S. Castañeda[3], E. Vicente-Rabaneda[3], F. Pérez-Vizcaíno[2], Á. Cogolludo[2], L.J. Jiménez-Borreguero[4], A. Urzainqui[1]. *[1]Servicio de Inmunología, Fundación de Investigación Biomédica, Instituto de Investigación Sanitaria-Princesa, Hospital de la Princesa; [2]Departamento de Farmacología, Facultad de Medicina, Universidad Compluentense de Madrid; [3]Servicio de Reumatología, Fundación de Investigación Biomédica, Instituto de Investigación Sanitaria-Princesa, Hospital de la Princesa; [4]Servicio de Cardiología, Hospital de la Princesa, Madrid, Spain*

Background: Pulmonary arterial hypertension (PAH) is a rare disease whose etiopathogenesis is poorly understood, and existing treatments are neither curative nor sufficient for stopping disease progression [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*$^{-/-}$ mice may develop PAH and which mechanisms might be implicated in the initiation and progression of the disease.
Methods: Vascular remodeling was assessed by immunohistochemistry on lung sections of WT and *PSGL-1*$^{-/-}$ C57BL/6 mice. Doppler pulse echochardiography was used to evaluate pulmonary artery flow acceleration time/ ejection time (TPV/ET) ratio. Isolated pulmonary artery rings were incubated with KCL, serotonin or acetylcholine and responses were registrated with a wire myograph coupled to an isometric force transducer. Angiotensin II lung concentration was quantified by ELISA. ACE, ACE2, AT1R and AT2R expression was evaluated by western blot. Expression levels of the NO-sensing probe DAR-4M AM and IFN-γ were measured by flow cytometry.
Results: *PSGL-1*$^{-/-}$ mice presented vascular remodeling of distal lung blood vessels. Aged *PSGL-1*$^{-/-}$ females showed reduced flow TPV/ET ratio in the pulmonary artery and RV remodeling, indicating PAH. Moreover, pulmonary arterial rings from aged *PSGL-1*$^{-/-}$ females presented increased vasoconstriction response to KCL and reduced vasodilation response to acetylcholine. Importantly, NO production by lung EC was reduced in aged *PSGL-1*$^{-/-}$ females. Expression of AT2R was reduced in lungs of *PSGL-1*$^{-/-}$ females from a young 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.
Conclusions: Together, these studies implicate leukocyte-endothelium interactions for the maintenance of vascular homeostasis and protection against PAH in PSGL-1 deficient female mice.
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SAT0317 TYPE VI COLLAGEN FORMATION: A NEW OBJECTIVE BLOOD-BASED MARKER REFLECTING FIBROSIS OF THE SKIN IN SYSTEMIC SCLEROSIS

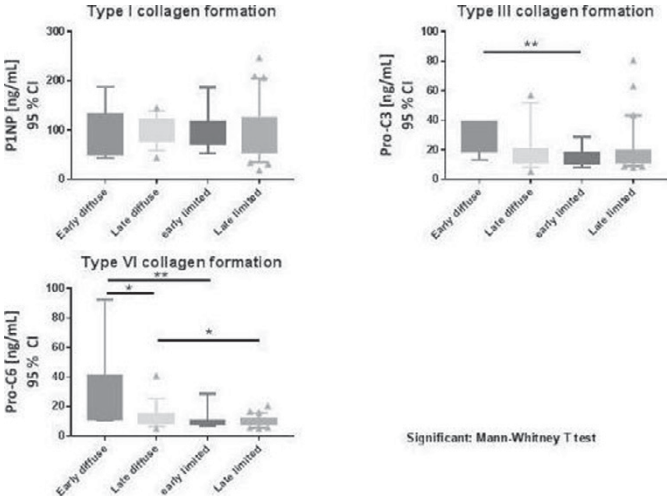
P. Juhl[1], L. Iversen[2], T. Karlsmark[2], M. Karsdal[1], A.-C. Bay-Jensen[1], M. Mogensen[2], A.S. Siebuhr[2]. *[1]Nordic Bioscience, Herlev; [2]Department of dermatology, Bispebjerg Hospital, Copenhagen, Denmark*

Background: Systemic sclerosis (SSc) is characterized by fibrosis of the skin. The dermis of the skin is rich in type I and III collagen, but other collagens as type VI collagen are present in the skin and play a key role in the organization of type I and III collagen. There is a lack of objective disease activity markers in SSc for frequent assessment of patients. The only measurement of disease activity currently is the subjective modified Rodnan skin score (mRSS).
Objectives: The objective is to examine blood-based markers of type I, III, and VI collagen formation as surrogates of disease activity and fibrosis in SSc.
Methods: SSc patients fulfilling the ACR criteria (n=121) were included. The study included both limited SSc (lSSc, n=79) and diffuse SSc (dSSc, n=42) (approval number H-B-2008–131). Markers of type I, III and VI collagen formation (P1NP, PRO-C3 and PRO-C6, respectively) were measured in serum by ELISA. Difference in the markers between groups were tested by Mann-Whitney T test and correlations were assessed by multiple linear regression adjusting for age, gender and BMI. Discriminative power of the markers was analyzed by ROC AUC on tertiles of mRSS.
Results: There were no significant difference in gender, BMI or disease duration between lSSc and dSSc. The mean age of the population was 57.4 (SD 11.6) years, 84% were female, mean disease duration was 11.7 (SD 8.9) years and mean mRSS was 11.2 (SD 8.6).
PRO-C3 and PRO-C6 were significantly higher early (<4 years) dSSc compared to early lSSc patients (both p=0.006). PRO-C6 was significantly elevated in early dSSc compared to late dSSc (p=0.04) and increased in late dSSc compared to late lSSc (p=0.02; Figure). Both PRO-C3 and PRO-C6 correlated with mRSS when adjusted for age, gender, and BMI with R-partial of 0.36 (p=0.0001) and 0.29 (p=0.002), respectively.
Both PRO-C3, and PRO-C6 could separate the patient group having the highest tertile of mRSS from the rest with an AUC (95% CI) of 0.73 (0.62–0.82), and 0.74 (0.63–0.83), respectively. Together, PRO-C3 and PRO-C6 could separate the groups with an AUC (95% CI) of 0.77 (0.67–0.86) (Table 1).
PRO-C3 and PRO-C6 performed equally well for identification of patients with the highest skin score (highest tertile vs. the middle and lower tertile) with a relative risk of 2.3 (1.4–3.8) (Table 2). The risk of being in the highest tertile of mRSS compared to the lowest were significantly higher with a high PRO-C6 (relative risk 2.6, 95% CI: 1.3–5.2) compared to PRO-C3 (relative risk: 2.2, 95% CI: 1.2–3.8) (Table 2).

Table 1

Skin (highest vs lowest tertile)	AUC (95% CI)	P-value
P1NP	0.56 (0.44–0.67)	
PRO-C3	0.73 (0.62–0.82)	<0.0001
PRO-C6	0.74 (0.63–0.83)	<0.0001
PRO-C3, PRO-C6	0.77 (0.67–0.86)	<0.0001

Analyzed by ROC curve.



Conclusions: Markers reflecting fibrosis (measures of type III and VI collagen formation) could be novel objective, and potentially predictive, biomarkers of disease activity and severity.
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SAT0318 EPIGENETIC REGULATION OF FRA2 BY JMJD3 REGULATES FIBROBLAST ACTIVATION IN SYSTEMIC SCLEROSIS

C. Bergmann[1], A. Brandt[1], C. Dees[1], T. Wohlfahrt[1], Y. Zhang[2], C.-W. Chen[1], T. Mallano[1], R. Liang[1], R. Kagwiria[1], P.-S. Kam[1], A. Bozec[1], D. Abraham[3], R. Rieker[4], A. Ramming[5], O. Distler[6], G. Schett[1], J. Distler[1]. *[1]Internal Medicine III-Rheumatology; [2]University Clinic Erlangen-Nuremberg, Erlangen, Germany; [3]Centre for Rheumatology and Connective Tissue, UCL School of Life and Medical Sciences, London, United Kingdom; [4]Department of Pathology; [5]Centre for Rheumatology and Connective Tissue, University Clinic Erlangen-Nuremberg, Erlangen, Germany; [6]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland*

Background: Chronic and exaggerated fibroblast activation is a central hallmark of Systemic Sclerosis (SSc) fibrotic disease and results in a high morbidity and

Abstract SAT0317 – Table 2

	Highest tertile of skin score vs rest				Highest vs low tertile of skin score			
	OR (95% CI)	P-value	RR (95% CI)	P-value	OR (95% CI)	P-value	RR (95% CI)	P-value
P1NP	1.1 (0.5–2.6)		1.1 (0.6–1.9)		2.3 (0.7–6.9)		1.6 (0.8–3.2)	
PRO-C3	3.7 (1.6–8.3)	p=0.002	2.3 (1.4–3.8)	p=0.001	5.7 (1.7–18.4)	p=0.004	2.2 (1.2–3.8)	p=0.008
PRO-C6	3.7 (1.6–8.3)	p=0.002	2.3 (1.4–3.8)	p=0.001	6.0 (1.9–18.8)	p=0.002	2.6 (1.3–5.2)	p=0.006

OR: odds ratio, RR: relative risk.