cells were observed to be increased in the peripheral blood of SSc pts compared to HSs, suggesting their possible role in the pathogenesis of the disease.

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FRI0405

A NOVEL ANIMAL MODEL FOR SYSTEMIC SCLEROSIS INDUCED BY IMMUNISATION OF ANGIOTENSIN II RECEPTOR 1

X. Yue¹, F. Petersen¹, X. Wang¹, H. Heidecke², G. Riemekasten³, X. Yu¹.

¹Research center borstel, Borstel; ²Celltrend GmbH, Luckenwalde; ³Department of Rheumatology, University hospital lübeck, lübeck, Germany

Background: Systemic sclerosis (SSc) is a complex connective tissue disease which is characterised by autoimmunity, vasculopathy and fibrosis¹. Our recent study showed that the progression of SSc was strongly associated with the autoantibodies against angiotensin II receptor I (AT1R), suggesting a role of autoimmunity to AT1R in the pathogenesis of the disease².

Objectives: In this study, we aimed to investigate the role of AT1R in the pathogenesis of SSc in mice.

Methods: C57BL/6J mice were immunised with membrane extract (ME) of CHO cell overexpressing human AT1R or with ME of CHO cells as control. Serum, lung and skin samples were collected and assessed 63 days after immunisation for autoantibody production, inflammation and fibrosis, which are hallmarks for SSc.

Results: Immunisation with hAT1R induced the production of autoantibodies against the receptor in mice, and autoantibody deposition was found in the lung. Histologically, mice immunised with hAT1R showed a SSc-like disease, including perivascular infiltrates and fibrosis in the skin as well as pulmonary inflammation. The inflammation in the skin and the lung were characterised by infiltration of T- and B-cells. Furthermore, transfer of immune cells from hAT1R-immunised mice into C57BL/6J mice induced inflammation in the lung.

Conclusions: This study demonstrates that immunisation with hAT1R can induce a SSc-like disease, thus showing a pathogenic role of autoimmunity to AT1R and providing a novel mouse model for the diseases. Furthermore, this study also introduces a new immunisation strategy to generate functional autoantibodies against receptors on the cell membrane.

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FRI0406

INCREASED FREQUENCY OF CIRCULATING CD163+ NON-CLASSICAL MONOCYTES IN SCLERODERMA AND ENHANCED DUAL POLARISATION TOWARDS M1 AND M2-LIKE PHENOTYPES IN MONOCYTE-DERIVED MACROPHAGES

A. Tam¹, L. Reinke-Breen², G. Trujillo², S. Xu¹, C. P. Denton¹, D. J. Abraham¹, G. Jarait², V. H. Ong¹. ¹Centre for Rheumatology and Connective Tissue Disease, UCL, London, United Kingdom, ²Discovery Biology, Fibrotic Diseases, Bristol-Myers Squibb, Pennington, United States

Background: Scleroderma (SSc) is an autoimmune connective tissue disease involving complex interactions between various cell types leading to organ-based tissue fibrosis. Emergence of the monocytes (Mo)/macrophages (Mφ) lineage(s) as key contributors to inflammation, vascular dysfunction and scarring in scleroderma^{1,2} have led to increased scrutiny of their phenotype and function.

Objectives: To determine the circulating Mo subpopulations and phenotypes of Mφ in SSc.

Methods: PBMC were collected from healthy (HC) and SSc donors, and analysed by flow cytometry using Mo phenotypic antibodies or purified and cultured *in vitro*. For flow cytometry immunophenotyping, Mo were gated on

CD3⁺CD19⁺CD56⁺HLA-DR⁺ populations, and subsets defined by CD14, CD16, CD163 and CD206 expression. For Mφ cultures, Mo were negatively selected from PBMCs, cultured for 7 days, and treated with IFN-γ (5 ng/ml) or IL-4 (20 ng/ml) for 24 hours. Cytokine levels in the conditioned media were evaluated by MSD analyses and normalised to total protein levels.

Results: The frequency of circulating CD163⁺ non-classical Mo (CD14^{lo}CD16^{hi}) was 2-fold higher in SSc patients than in HC (unpaired t-test, p=0.026). No difference was found in the frequency of CD206⁺ monocyte subsets between HC and SSc. *In vitro*, unstimulated SSc Mφ (M0) secreted higher levels of classically-activated pro-inflammatory (M1) and alternatively-activated pro-regenerative (M2) cytokines. Compared to HC cells, SSc Mφ were more readily polarised towards an M1 phenotype or an M2 phenotype, when cultured in the presence of IFN-γ or IL-4, respectively. Th17 markers and MMPs were significantly increased in SSc Mφ (table 2).

Abstract FRI0406 – Table 1. Demographics.

	Mo (flow cytometry)		Mφ supernatant (cytokine assay)	
n	HC n=9	SSc n=10	HC n=13	SSc n=27
Age (years)	56.7±14.3	50.7±5.7	60.6±16.7	52.1±13.0
Female : Male	7:2	8:2	6:7	26:5
SSc subtype	-	dcSSc ⁽¹⁰⁾	-	dcSSc ⁽²⁷⁾
Disease duration	-	≤5 years ⁽¹⁰⁾	-	≤5 years ⁽¹⁵⁾ >5 year ⁽¹²⁾

Abstract FRI0406 – Table 2. Cytokines significantly increased in SSc vs control. Unpaired t-tests, *p<0.05, **P<0.01.

Cell Population	M1 Markers	M2 Markers	Th17 Cytokines and MMP's
M0	CCL-3, CCL-4, IL-6, IL-18, IL-12, IL-15, TNF-α	CCL-1, CCL-17, CCL-20, CCL-24, IL-1Rα, YKL-40	IL-21, IL-22, IL-31, MMP1, MMP3
M0 + IFN-γ	CCL-3, CCL-4, CCL-11, CXCL8, IL-1β, IL-6, IL-18, TNF-α	CCL-1, CCL-22, CCL-24, CCL-26, IL-1Rα, YKL-40	IL-21
M0 + IL-4	CCL-3, CCL-4, IL-12, IL-18, TNF-α	CCL-17, CCL-22, CCL-24, IL-1Rα, YKL-40	IL-21, MMP3

Conclusions: Studies exploring Mo have revealed distinct populations with selective biological functions. Our observation of an increased number of CD163⁺ non-classical Mo in SSc suggests that this subpopulation may play a key role in inflammatory-driven fibrosis and act as an important source of pro-fibrotic cytokines. This data is consistent with previous reports of elevated serum levels of CD163 and increased CD163 secretion by SSc PBMCs³. SSc Mφ showed a pronounced and enhanced dual M1 and M2 polarisation basally compared to HC, indicating cells were 'primed' to undergo phenotypic polarisation. Our studies support the notion that Mφ cytokine secretion generates a pro-fibrotic milieu in scleroderma tissues, playing a prominent role in dysregulated tissue repair in fibrosis.

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FRI0407

DIPEPTIDYL-PEPTIDASE-4 (DPP4) IS A POTENTIAL NEW MOLECULAR TARGET FOR TREATMENT OF FIBROSIS

A.M. Soare, H. Györfy, A. Matei, C. Dees, Y. Zhang, T. Wohlfahrt, C.-W. Chen, A. Ramming, G. Schett, J. Distler. *Department of Internal Medicine 3 – Rheumatology and Immunology, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Universitätsklinikum Erlangen, Erlangen, Germany*

Background: Dipeptidyl-peptidase-4 (DPP4) plays a role in tissue scarring and its inhibition leads to reduced scar formation. Its function in tissue fibrosis, however, is unknown.

Objectives: The aim of the study was to investigate the expression of DPP4 in fibrotic tissue of systemic sclerosis (SSc) patients, to characterise DPP4 positive cells, to study the mechanism of action of DPP4 in fibroblasts and to evaluate the antifibrotic effect of pharmacological and genetically inhibition of DPP4 in different preclinical models of SSc.

Methods: Expression of DPP4 in human and murine skin was analysed. Mouse fibroblasts were isolated and DPP4 positive cells properties were assessed.