the “Slow Progressor” (3303 ± 6065 pg/ml vs 13300 ± 10308 pg/ml, p=0.052) without reaching a significant value, due probably to the low number of cases.

**Conclusion:** Our study confirms that the presence of specific autoantibodies and capillaroscopic abnormalities correlate to an increased risk of developing SSc in patients with UCTD [6]. Beside we found significantly higher levels of CXCL4 in our 27 VEDOSS patients respect to controls, in agreement with other authors showing the association of this chemokine with early stages and specific organ involvement [4][5][7]. The finding of CXCL4 lower levels in “fast progressor” cases is consistent with our recent report of anti-CXCL4 antibodies in patients with early SSc, determining lower levels of this antigen [7]. We need deeper investigations to better evaluate the role of CXCL4 in the different stages of SSc.

**REFERENCES:**

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**Disclosure of Interests:** None declared

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**OP0247**

**IN MYOSITIS MUSCLE FIBRE PLAYS A DIRECT AND CRITICAL ROLE IN THERAPEUTIC RESPONSE TO GLUCOCORTICOIDs**

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**Background:** Myositis are rare autoimmune diseases, affecting more women than men, characterized by chronic inflammation of skeletal muscle causing muscle weakness, decreased quality of life and increased mortality. Glucocorticoids (GC) are potent anti-inflammatory drugs, and are the first line treatment of myositis. They improve muscle strength of myositis patients (therapeutic effect), yet muscle recovery is generally only partial. Moreover, GC have an iatrogenic effect on skeletal muscle fibre leading to steroid myopathy. Thus myositis care has been improved. Despite the autoimmune terrain of myositis, our team has recently shown that muscle fibres themselves develop immuno-meta-bollic modifications that participate to muscle weakness and perpetuation of the disease. GC effects are mediated by the glucocorticoid receptor (GR), which is expressed in various cell types including immune cells and myofibres, but the muscle fibres mediating therapeutic responses remain to be determined.

**Objectives:** Unravel the mechanisms underlying the therapeutic effect of GC in myositis, particularly elucidate the role of skeletal muscle fibres.

**Methods:** Experimental myositis was induced in eight to ten week-old C57BL/6J female mice by a single intradermal injection of part of skeletal muscle fast-type (HSA-CreERT2/GR L2/L2). Tamoxifen (1 mg/ml) was administered for 5 days by IP injection. The mice were euthanized 21 days after myositis induction. Muscle strength was assessed by grip test at D 0, before the 1st PDN administration (D 14) and the day before sacrifice (D 20). To investigate whether the PDN effects are mediated by myofi-bre, we generated transgenic mice carrying two LoxP sites within the GR gene in skeletal muscle fiber (GR(i)skm-/- mice). Similar treatments were applied to GR L2/L2 that do not express Cre-ERT2, and served as controls.

We compared 4 groups of myositis mice, GR L2/L2 treated by PDN (n=9) or vehicle (n=8) and GR(i)skm-/- treated by PDN (n=10) or vehicle (n=10), by grip test and at the histological level (hematoxylin eosin (HE) and Gomori trichrome (GT) staining). Moreover, LC3 expression was studied by RtpQPCR and western blot.

**Results:** Muscle strength was decreased in both GR L2/L2 and GR(i)skm-/- myositis mice from D 14 to D 20. GR L2/L2 myositis mice recovered muscle strength after PDN treatment; no significant difference compared to D 0 was detected. In contrast, PDN did not improve muscle strength in GR(i)skm myosi-tis mice (Figure 1).

HE and GT staining did not reveal quantitative differences in inflammatory infiltrate. Necrotic and degenerative fibres were detected in the 4 groups. At RTqPCR, LC3, an autophagy marker, was upregulated in PDN-treated GR L2/ L2 myositis mice compared to untreated GR L2/L2 myositis mice; moreover it was 2-fold more expressed in PDN-treated GR L2/L2 myositis mice compared to PDN-treated GR(i)skm-/- mice.

**Conclusion:** GR in skeletal muscle fibre is crucial to mediate the therapeutic response to GC in a murine model of myositis. Autophagy is one of the candidate pathways controlled by myofibre GR underlying this effect.

**REFERENCES:**

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**OP0248**

**DEVELOPMENT OF A 3D SKIN MICROTISSUE MODEL FOR FIBROTIC DISEASES**

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**Background:** Traditional preclinical approaches, such as two-dimensional cell culture and animal models, are often inadequate to mimic the pathophysiological features of complex diseases such as systemic sclerosis (SSc). Human specific targets, such as the recently described pro-fibrotic long non coding RNA (lncRNA) H19X1, are becoming increasingly relevant in preclinical research, creating the need of new strategies and tools in translational medicine. The employment of novel three-dimensional (3D) culture systems, where multiple cell types are included, is filling an important gap left by the traditional preclinical methods.

**Objectives:** To develop an easy to produce 3D fibrotic skin microtissues model for translational proof of concept studies.

**Methods:** Two thousand five hundred dermal fibroblasts isolated from skin of SSc patients were seeded in ultra-low attachment 96-well plates. Fibroblast were let to aggregate into spheres for 48h. Two thousand five hundred primary normal human keratinocytes were added to the culture and let to layer onto the fibroblast spheres for 72h. H19X1 silencing experiments were used as proof of concept studies. H19X1 silencing with antisenese oligonucleotides or transfections with a scrambled control were performed in fibroblasts prior to the sphere formation for 24h. TGFi (10ng/ml) was added to microtissue to exacerbate the fibrogenic phenotype. Haematoxylin eosin staining as well as immunohistochemistry staining for vimentin and cytokeratin 10 was performed. Skin microtissues were processed for RNA and protein isolation. Pro-collagen I and fibronectin were quantified in the supernatants with ELISA. Can I further assist you with this information?
Results: The microtissues presented a core of SSc fibroblast as revealed by vimentin staining and an external layer of keratinocytes as revealed by cytokeratin 10 staining, mimicking the human skin architecture. Gene expression analysis following TGFβ stimulation displayed induced expression of extracellular matrix gene COL1A1 (p=0.044) and the myofibroblast marker ACTA2 (p=0.018), indicating that microtissues were able to develop a fibrotic response. Microtissues, where H19X was silenced, displayed reduced gene expression of COL1A1 and ACTA2 after TGFβ stimulation (COL1A1 p=0.007, ACTA2 p=0.045). Additionally, H19X silencing led to lower levels of TGFβ protein expression (p=0.009) and pro-collagen1 secretion (p=0.039) in the supernatant of the microtissue cultures as revealed by Western Blot and ELISA, respectively. FN1 expression and fibronectin protein levels were not significantly reduced in the microtissues after H19X silencing.

Conclusion: We were able to produce a 3D microtissue resembling skin architecture that can respond to fibrotic stimuli. Knockdown experiments of pro-fibrotic IncRNA H19X confirmed the potential of the model as screening platform for novel pro-fibrotic effectors. A future aim will be to optimize the model for high-throughput automated screening platforms.


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Table 1. Significantly altered proteins at serum proteome analysis of systemic sclerosis (SSc) with or without interstitial lung disease (ILD) and healthy controls (HC)

<table>
<thead>
<tr>
<th>SSc versus healthy controls</th>
<th>SSc with ILD versus SSc without ILD and healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>Reduced</td>
</tr>
<tr>
<td>Adolase A</td>
<td>Adrenomedullin</td>
</tr>
<tr>
<td>Angiopoietin-2</td>
<td>ASGR1</td>
</tr>
<tr>
<td>C1QR1</td>
<td>C1s</td>
</tr>
<tr>
<td>Calpain</td>
<td>C5</td>
</tr>
<tr>
<td>COLEC12 Eotaxin</td>
<td>Calgranulin B</td>
</tr>
<tr>
<td>EphA5</td>
<td>CD177</td>
</tr>
<tr>
<td>Fractalkine/CXCL-1</td>
<td>Desmoglein-1</td>
</tr>
<tr>
<td>Granulins</td>
<td>Fit-3 Igand</td>
</tr>
<tr>
<td>IDS Kininogen, HMV</td>
<td>G-CSF-R</td>
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<tr>
<td>LAG-3</td>
<td>IL1Ra</td>
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<tr>
<td>Lamin-B1</td>
<td>Leptin</td>
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<tr>
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<td>Lypd3</td>
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<tr>
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<td>SH21A</td>
</tr>
<tr>
<td>MMP-12</td>
<td>SNPS2</td>
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<tr>
<td>STAT1 TMR4</td>
<td>TPSBS2</td>
</tr>
</tbody>
</table>

*significantly increased also at ELISA** significantly increased at ELISA only in SSc with ILD versus HC

The majority of proteins with higher levels in SSc with ILD compared to SSc without ILD were involved in intracellular signaling and cell cycle (FCRL3, PDE11, Statratin), along with higher MCP-3, a monocyte chemoattractant, and siCAM-5, a ligand for the leukocyte adhesion protein LFA-1. Of note, we found that increased IL-2BBP, antagonist of IL-22, and decreased BAFF levels characterized SSc with ILD.

Conclusion: Aptamer proteomic analysis allowed to define serum profiles differentiating SSc cases from healthy controls and SSc with ILD from SSc without ILD; the proteins identified are involved in SSc pathogenic pathways and after further investigation on larger cohorts they can be used as reliable biomarkers.

Characters from table content including title and footnote: 631

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Imaging in axial spondyloarthritis – what is new?

**OP0250**

MRI VERTEBRAL CORNER INFLAMMATION AND FAT DEPOSITION ARE ASSOCIATED WITH WHOLE SPINE LOW DOSE CT DETECTED SYNDYMOSPHYES: A MULTILEVEL ANALYSIS

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Background: A few studies have shown an association between vertebral corner inflammation (VCI) and vertebral corner fat deposition (VCFD) on MRI and syndysmophyte formation on cervical and lumbar conventional radiography.

Objectives: To investigate whether magnetic resonance imaging (MRI) patterns of VCI, VCFD and a combination of both are associated with the development of new or grown syndysmophyes as detected by whole spine low dose computed tomography (ldCT), thereby studying these associations also in the thoracic spine.

Methods: Patients in the Sensitive Imaging in Ankylosing Spondylitis cohort underwent MRI at baseline, 1 year and 2 years, and ldCT at baseline and 2 years. MRI lesions were scored by 3 central readers, using the SPARCC method for VCI, VCFD and a combination of both are associated with the development of new or grown syndysmophyes as detected by whole spine low dose computed tomography (ldCT), thereby studying these associations also in the thoracic spine.

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