$p=0.03$), and to both lcSSc (OR 2.80, 95% CI 1.16 to 6.84, $p=0.02$) and dcSSc (OR 3.42, 95% CI 1.20 to 9.72, $p=0.02$) subtypes. The *SRP55* rs2235611 A minor allele and AA genotype showed a significant risk association with susceptibility to SSc-related pulmonary fibrosis (A allele: OR 1.39, 95% CI 1.00 to 1.93, $p=0.046$; AA genotype: OR 3.95, 95% CI 1.48 to 10.54, $p=0.006$). A trend toward an association between the AA genotype and anti-Scl70 antibody-positive SSc was also found (OR 2.82, 95% CI 0.95 to 8.37, $p=0.06$). Both rs2235611 A allele and AA genotype were significantly associated with the SSc subset without digital ulcers (A allele: OR 1.33, 95% CI 1.01 to 1.75, $p=0.04$; AA genotype: OR 3.26, 95% CI 1.32 to 8.03, $p=0.01$).

Conclusion: The *SRP55* rs2235611 polymorphism is associated with susceptibility to SSc and, in particular, with SSc-related pulmonary fibrosis and peripheral vascular phenotype, consistent with a role of VEGF-A pre-mRNA alternative splicing in the development of pulmonary fibrosis and impairment of angiogenesis. Further replication studies are warranted to confirm our findings in independent SSc cohorts.

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SAT0283

SOLUBLE GUANYLATE CYCLASE REDUCED THE GASTROINTESTINAL FIBROSIS IN BLEOMYCIN-INDUCED MOUSE MODEL OF SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) is a chronic autoimmune-mediated connective tissue disorder. Although the etiology of the disease remains undetermined, SSc is characterized by fibrosis and proliferative vascular lesions of the skin and internal organs. SSc involves the gastrointestinal tract in more than 90% of patients¹. Soluble guanylate cyclase (sGC) is used to treat pulmonary artery hypertension (PAH), and has been shown to inhibit experimental skin fibrosis².

Objectives: The aim of this study is to investigate whether bleomycin (BLM)-treated mice show gastrointestinal fibrosis, and find a therapeutic strategy to the lesion.

Methods: Female C57BL/6J mice were treated with BLM or normal saline by subcutaneous implantation of osmotic minipump. These mice were sacrificed on day 28 or day 42. Gastrointestinal pathologies were examined by Masson Trichrome staining. The expression of fibrosis-related genes in gastrointestinal tract were analyzed by real-time PCR, and the levels of collagen in the tissue was measured by Sircol collagen assay. To evaluate peristaltic movement, the small intestinal transport (ITR%) was calculated as [Dyeing distance × (Duodenum - Appendix)] - 1 × 100 (%). We treated BLM-treated mice with soluble guanylate cyclase (sGC) or DMSO orally and analyzed them on day 42.

Results: Histological examination revealed that fibrosis from lamina propria to muscularis mucosa in the esophagus was significantly increased in BLM-treated mice, suggesting that BLM induces esophageal fibrosis in C57BL/6J mice. In addition, the levels of Col3a1 and CTGF were significantly increased in BLM-treated mice. More severe fibrosis was observed in the mice sacrificed on day 42 than the mice sacrificed on day 28. The ITR% was found to be significantly lower in BLM-treated mice, suggesting that gastrointestinal peristaltic movement was reduced in BLM-treated mice. Furthermore, we demonstrated that sGC treatment significantly reduced fibrosis of esophagus and intestine in BLM-treated mice, by histological examination and Sircol collagen assay.

Esophagus (Masson's trichrome stain×100)

* One way ANOVA Newman-Keuls

Conclusion: These findings suggest that BLM induces gastrointestinal fibrosis in C57BL/6J mice, and treatment with sGC improves the BLM-induced gastrointestinal lesion.

References:

- [1] Anton Emmanuel. Current management of the gastrointestinal complications of systemic sclerosis. *Nat Rev Gastroenterol Hepatol*. 2016; 13: 461-472.
- [2] Clara Dees, et al. Stimulators of Soluble Guanylate Cyclase (sGC) Inhibit experimental Skin Fibrosis of Different Aetiologies. *Ann Rheum Dis*. 2015;74 (8): 1621-5.

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SAT0284

EPIGENETIC DEREGLATION OF AUTOPHAGY PROMOTES FIBROSIS IN SYSTEMIC SCLEROSIS

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Background: Autophagy is catabolic process allowing cells to degrade unnecessary or dysfunctional cellular organelles. Failure of appropriate regulation of autophagy, however, can severely perturb tissue homeostasis. Several stimuli present in fibrosis such as pro-fibrotic cytokines are known to activate autophagy.

Objectives: The objective of this work was to characterize the regulation of autophagy in systemic sclerosis (SSc) and to decipher its role in the pathogenesis of SSc.

Methods: Activation of autophagy in SSc skin and matched tissue samples from healthy individuals was assessed by immunofluorescence staining for ATG7, BECLIN1 and P62. We generated *Atg7^{fl/fl} × Col1a2; CreER* mice to selectively disable autophagy in fibroblasts. The role of the autophagy was investigated in the model of bleomycin- and TβRIact-induced dermal and pulmonary fibrosis. Overexpression of *Myst1* was achieved by adenovirus encoding for *Myst1*. Collagen release and protein expression were measured by Western blot. Target genes were analyzed by RT-PCR. Co-immunoprecipitation and reporter assay were performed to study physical and functional interactions between MYST1 and SMAD3. To monitor the autophagic flux *in vitro* and *in vivo* we generated adenoviral vectors encoding for tandem fluorescent-tagged LC3 (mRFP-EGFP-LC3).

Results: Transforming growth factor-β (TGFβ) activates autophagy by an epigenetic mechanism to amplify its profibrotic effects. TGFβ induces autophagy in fibrotic diseases by SMAD3-dependent downregulation of the H4K16 histone acetyltransferase MYST1, which regulates the expression of core components of the autophagy machinery such as ATG7 and BECLIN1. Activation of autophagy in fibroblasts promotes collagen release and is both, sufficient and required, to induce tissue fibrosis. Forced expression of MYST1 abrogates the stimulatory effects of TGFβ on autophagy and re-establishes the epigenetic control of autophagy in fibrotic conditions. Interference with the aberrant activation of autophagy inhibits TGFβ-induced fibroblast activation and ameliorates experimental dermal and pulmonary fibrosis. These findings link uncontrolled TGFβ signaling to aberrant autophagy, deregulated epigenetics in fibrotic diseases and may open new avenues for therapeutic intervention in fibrotic diseases.

Conclusion: We demonstrate that the epigenetic control of autophagy is disturbed by a TGFβ-dependent downregulation of the H4K16 histone acetyltransferase MYST1. The increased activation of autophagy induces fibroblast-to-myofibroblast transition and promotes fibrotic tissue remodeling. Re-expression of MYST1 prevents aberrant autophagy, limits the profibrotic effects of TGFβ and ameliorates experimental fibrosis. Restoration of the