Figure 1. Serum Myostatin levels in IIM as compared with healthy controls (A) and disease controls (B). Levels in juvenile myositis as compared with adult IIM (C) and in various subsets of IIM (D). Serum Myostatin levels in active and inactive disease (E).

Although Follistatin was lower in IIM than HC (198.4 vs 243.6, $p < 0.0001$), the neither Follistatin nor Myostatin: Follistatin ratios differ between subsets, and in active versus inactive disease Figure 2 A-D). On follow-up, the serial Myostatin estimation paralleled change in disease activity.

Figure 2. Serum Follistatin levels in IIM as compared with healthy controls (A) and disease controls (C). Levels in juvenile and adult IIM (D) and in various subsets of IIM (D).

Conclusion: Elevated serum Myostatin levels in active myositis raise the possibility of accelerated senescence in the inflamed muscle tissues which need further investigation.

Acknowledgments: : Partly funded by APLAR and IRA research grants awarded to LG.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.5641

SAT0291 THE ROLE OF X-LINKED INHIBITOR OF APOPTOSIS PROTEIN (XIAP) IN SYSTEMIC SCLEROSIS

C. Bergmann¹, L. Hallenberger¹, B. Merlevede¹, C. Dees¹, C. W. Chen¹, O. Distler², G. Schett¹, J. Distler¹. ¹Department Internal Medicine III- Rheumatology, Erlangen, Germany; ²University Hospital of Zürich, Zürich, Switzerland

Background: Pathologic activation of fibroblasts is a central feature of fibrotic tissue disease in Systemic Sclerosis (SSc). Although individual key signaling pathways of fibroblast activation such as transforming growth factor β (TGF β) and WNT/ β -catenin signaling have been identified, the consequences of the concomitant upregulation of these pathways and their crosstalk are incompletely characterized. Given the high medical need, the identification of mutual activation and amplification loops of profibrotic signals is essential to identify novel candidates for antifibrotic therapies. XIAP (X-linked inhibitor of apoptosis protein) is a ubiquitously expressed member of the IAP protein family which are implicated in the regulation of various cellular functions and tissue turnover. XIAP was recently described to be implicated in WNT/ β -catenin signaling and TGF β signaling.

Objectives: The aim of this study is to characterize the role of XIAP in fibrotic disease.

Methods: XIAP-expression was analyzed by qPCR, IF and Western blot. XIAP was targeted pharmacologically and with siRNA. The activation of WNT/ β -catenin signaling was assessed by analyses of WNT target genes, by TOPflash/FOPflash luciferase reporter assay and in reporter mice. *In vivo*, XIAP inhibition was analysed in two different models of fibrosis.

Results: The expression of XIAP is increased in the skin of SSc patients compared to matched healthy individuals with a particular prominent expression in fibroblasts. The overexpression of XIAP is more pronounced in SSc patients with diffuse and active skin fibrosis compared to SSc patients with limited and inactive disease. The overexpression of XIAP is also reflected in several experimental fibrosis models: the model of scleroderma graft versus host disease, the model of bleomycin induced skin fibrosis and Topoisomerase I induced fibrosis (Topol) mice. TGF β induces the expression of XIAP *in vitro* and *in vivo* and treatment with the TGF β 1 receptor antagonist SD208 reverses the TGF β induced expression of XIAP. Inhibition of XIAP with embelin or siRNA reduces the TGF β induced activation of fibroblasts with reduced collagen release and reduced expression of myofibroblast markers. In addition, XIAP inhibition reverted the activated fibroblast phenotype in SSc fibroblasts with reduced expression of stress fibers and

α SMA. The antifibrotic effects of XIAP inhibition occurred in non-toxic doses as demonstrated by MTT and by TUNEL staining. *In vivo*, inhibition of XIAP reduced skin fibrosis in the models of bleomycin induced skin fibrosis and in Topol-induced skin and lung fibrosis as demonstrated by analysis of dermal thickening, dermal hydroxyproline content and by analysis of myofibroblast differentiation. Mechanistically, XIAP inhibition reduced the activation of WNT/ β -catenin signaling as demonstrated by TOPflash reporter assays and by the analysis of WNT target genes.

Conclusion: XIAP is upregulated in SSc fibroblasts and murine SSc models in a TGF β -dependent manner and promotes fibroblast activation by fostering canonical WNT signaling. Our data suggest that XIAP mediates an amplification loop between TGF β and WNT/ β -catenin signaling. Inhibition of XIAP may thus be a novel approach to target aberrant WNT/ β -catenin signaling in fibrotic diseases.

Disclosure of Interests: Christina Bergmann: None declared, Ludwig Hallenberger: None declared, Benita Merlevede: None declared, Clara Dees: None declared, Chih-Wei Chen: None declared, Oliver Distler Grant/research support from: Grants/Research support from Actelion, Bayer, Boehringer Ingelheim, Competitive Drug Development International Ltd. and Mitsubishi Tanabe; he also holds the issued Patent on mir-29 for the treatment of systemic sclerosis (US8247389, EP2331143)., Consultant of: Consultancy fees from Actelion, Acceleron Pharma, AnaMar, Bayer, Baecon Discovery, Blade Therapeutics, Boehringer, CSL Behring, Catenion, ChemomAb, Curzion Pharmaceuticals, Ergonex, Galapagos NV, GSK, Glenmark Pharmaceuticals, Inventiva, Ialtfarmaco, IQvia, medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Roche, Sanofi and UCB, Speakers bureau: Speaker fees from Actelion, Bayer, Boehringer Ingelheim, Medscape, Pfizer and Roche, Georg Schett Speakers bureau: AbbVie, BMS, Celgene, Janssen, Eli Lilly, Novartis, Roche and UCB, Jörg Distler Grant/research support from: Boehringer Ingelheim, Consultant of: Boehringer Ingelheim, Paid instructor for: Boehringer Ingelheim, Speakers bureau: Boehringer Ingelheim

DOI: 10.1136/annrheumdis-2020-eular.3265

SAT0292

INTEGRATIVE TRANSCRIPTOMIC AND FUNCTIONAL ANALYSIS REVEALS A ROLE OF DIMETHYL-A-KETOGLUTARATE IN TGF β -DRIVEN CYTOSKELETON REGULATION AND MYOFIBROBLAST DIFFERENTIATION

B. Burja^{1,2}, G. Kania², M. Tomsic¹, S. Sodin-Semrl¹, O. Distler², K. Lakota¹, M. Frank-Bertoncelj². ¹University Medical Centre Ljubljana, Department of Rheumatology, Ljubljana, Slovenia; ²Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland

Background: Myofibroblasts are the orchestrators of aberrant extracellular matrix (ECM) remodelling in fibrosis. Actin cytoskeleton is a central hub that integrates mechanical signals to promote myofibroblast differentiation and ECM remodelling. Targeting these pathways could represent a novel antifibrotic strategy. We have recently shown that metabolic intermediate dimethyl- α -ketoglutarate (dm- α KG) blocks TGF β -driven myofibroblast differentiation in dermal fibroblasts (DF).

Objectives: To investigate the mechanisms by which dm- α KG regulates TGF β -driven myofibroblast differentiation and inflammatory responses in DF.

Methods: DF from healthy controls and patients with systemic sclerosis (SSc) were treated with TGF β (10 ng/ml) and/or dm- α KG (6 mM) for 24h, 48h and 72h. RNA sequencing (Illumina 2000, n=3 per experimental group) was followed by the analysis of differentially expressed genes (DESeq2, log2 fold ≥ 10.5 , $p_{adj} < 0.01$), pathway enrichment analysis (GO terms) and supervised PCA analysis (ClustVis). Protein amounts (fibronectin, α SMA, IL-6), cell contraction and apoptosis were measured with Western blot (n=6), ELISA (n=4), collagen gel contraction assay (n=4) and real time Annexin V assay (n=6). Significance ($p < 0.05$) was determined by one-sample t-test or ANOVA with Tukey's correction for multiple comparisons.

Results: TGF β (24h) altered the expression of 4076 genes in DF as determined by RNA-seq, among which 1864 genes were upregulated. The upregulated genes were enriched in GO biological processes/molecular functions/cellular compartments related to ECM organization ($p=1e-07$), Wnt signalling ($p=5e-06$), actin binding ($p=3e-07$), focal adhesion ($p=1e-10$), stress fibers ($p=3e-07$) and actin cytoskeleton ($p=3e-06$). Dm- α KG altered the expression of 589 genes in TGF β -treated DF compared to TGF β only. The most downregulated pathways in DF treated with dm- α KG + TGF β compared to TGF β only included actin binding ($p=5e-05$), muscle contraction ($p=0.001$), ECM organization ($p=0.008$), focal adhesion ($p=0.01$), Z disk ($p=0.01$) and stress fibers ($p=0.03$). Specifically, dm- α KG significantly ($p < 0.01$, log2 > -0.5) decreased the expression of many TGF β -induced genes involved in actin organization and focal adhesion (NEXN, FRMD5, ANTXR1, ACTC1, LIMCH1, SORBS2, TGM2, CSRP2, CAP2, LMO7, FZD2), muscle contraction (SNTB1, LMOD1, ANKRD1, SULF1, JPH2, CAVINA, OXTR, DYSF, FBXO32) and ECM organization (COL10A1, COL11A1, HAPLN1, MMP14,