against targets not tested for in clinic. In this study, we aimed at extending the detection of autoantibodies by including all cytoplasmic aaRSs in the analysis of patients with IIM. We hypothesized the existence of new potential autoantigens with small protein size. 

Methods: The presence of anti-aaRS autoantibodies was determined using a multiplex suspension bead array assay on 242 IIM patients from the Karolinska University Hospital myositis cohort. A panel of 186 recombinant constructs, representing 57 proteins that included full-length or partial sequence overlaps between constructs of all cytoplasmic aaRSs as well as other myositis related proteins, were coupled to magnetic color-coded beads and each plasma sample was tested against the complete antigen panel.

Results: By the use of this multiplex method we identified patients with autoantibodies against many of the tested aaRS. Autoantibodies binding to HisRS have previously been shown to bind with higher reactivity to the WHEP domain of HisRS and this was also confirmed in this study. We confirmed reactivity against three of the other aaRS tested for in the clinic (PL-12, PL-7, and EJ). In addition, we identified patients positing for anti-Zo, -KS and -HA, autoantibodies usually not screened for in routine. Finally, our data indicates that there are autoantibodies binding to other aaRS than the previously known eight autoantigens, which will be presented.

Conclusion: In this study, we could detect autoantibodies in plasma from patients with IIM, both against the most common aaRS autoantigens, but also against other aaRS that are usually not tested for in clinic. We conclude that it is important to continue the studies of anti-aaRS autoantibodies, and their correlation to clinical manifestations, and in the long run also include more aaRS autoantigens in clinical practice.

References:

Disclosure of Interests: Charlotte Pregler: None declared, Antonella Notarnicola: None declared, Cecilia Hellström: None declared, Edward Wignen: None declared, Catia Cerqueira: None declared, Peter Nilsson: None declared, Ingrid E. Lundberg: None declared, Catia Cerqueira: None declared, Peter Nilsson: None declared, Ingrid E. Lundberg: None declared, Cinzia Raspoll: None declared, Anna Maria Gauthier: None declared, Pern-Johan Jakobsen Shareholder of: Gesynta Pharma, Grant/research support from: Bristol-Myers Squibb, Corbus Pharmaceuticals, Inc.

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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 (TGFβ) 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 antibiotic 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 shown to interact in a functional manner with several pathways involved in actin organization and focal adhesion (NEXN, FRMD5, ANTXR1, DYSF, SMAD, LMOD1, ANKRD1, SULF1, JPH2, CAVIN4, OXTR, DYSF, SMA). XIAP-expression was analyzed by qPCR, IF and Western blot. XIAP inhibition may thus be a novel approach to target aberrant WNT/β-catenin signaling in dermal fibrosis.

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 analyzed 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 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-like graft versus host disease, the model of bleomycin induced skin fibrosis and Toposomerase I induced fibrosis (Topol) mice. TGFβ induces the expression of XIAP in vitro and in vivo and treatment with the TGFβ1 receptor antagonist SD208 reverses the TGFβ1-induced expression of XIAP. Inhibition of XIAP with embelin or siRNA reduces the TGFβ1-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 αSMA. 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 thickness, 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 TGFβ-dependent manner and promotes fibroblast activation by fostering canonical WNT signaling. Our data suggest that XIAP mediates an amplification loop between TGFβ and WNT/β-catenin signaling. Inhibition of XIAP may thus be a novel approach to target aberrant WNT/β-catenin signaling in fibrotic diseases.

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