Systemic sclerosis
A bird's eye review of the recent literature

edited by Chiara Tani

Pathogenesis and new therapeutical targets

Authors: Maurer B, Busch N, Jüngel A, Pileckyte M, Gay RE, Michel BA, Schett G, Gay S, Distler J, Distler O.
Title: Transcription factor Fos-related antigen-2 induces progressive peripheral vasculopathy in mice closely resembling human systemic sclerosis.
Circulation 2009; 120: 2367-76.
Summary: In this study the authors investigated the potential pathogenetic role of Fos-related antigen-2 (Fra-2) for the peripheral microangiopathy in Fra-2 transgenic (tg) mice and in human systemic sclerosis (SSc) patients. Fra-2 is a transcription factor of the activator protein-1 (AP-1) family involved in the control of stress response including cell proliferation, apoptosis, inflammation, wound healing and tumorigenesis. Fra-2 tg mice develop a proliferative vasculopathy of the lung followed by progressive lung fibrosis similar to lung manifestations in human SSc. By immunohistochemistry analysis, the authors found an over-expression of Fra-2 in skin section both in Fra-2 tg mice and in SSc patients with a significant vascular predominance (endothelial and vascular smooth muscle cells). Additionally, a significant decrease in capillary density over time and a progressive time-dependent increase in dermal thickness have been observed in Fra-2 tg mice suggesting that the onset of microangiopathy is paralleled by the development of skin fibrosis; interestingly this finding was anticipated by a significant increase in apoptotic endothelial cells as demonstrated *in vivo* in Fra-2 tg mice and *in vitro* by experiments on human microvascular endothelial cells.
In conclusion, two main messages could be extrapolated from this study: first, the authors provided the first evidence of a peripheral vasculopathy and skin fibrosis in Fra 2 tg mice that developed simultaneously with the lung involvement, proposing them as an excellent SSc preclinical model. Second, Fra-2 can play a central role in both vasculopathy and fibrosis in SSc and it could represent a potential therapeutic target.

Authors: Oga T, Matsuoka T, Yao C, Nonomura K, Kitaoka S, Sakata D, Kita Y, Tanizawa K, Taguchi Y, Chin K, Mishima M, Shimizu T, Narumiya S.
Title: Prostaglandin F_{2a} receptor signaling facilitates bleomycin- induced pulmonary fibrosis independently of transforming growth factor-β.
Nature Medicine 2009; 15 /12): 1426-30.
Summary: Transforming growth factor-β has been demonstrated to have a crucial but not exclusive role in the pathogenesis of idiopathic pulmonary fibrosis.
In this study, the authors investigated the potential pathogenetic role of the prostaglandin pathway in bleomycin-induced pulmonary fibrosis, an animal model of idiopathic pulmonary fibrosis. In this order, they studied knockout mice lacking receptors for the following prostaglandins: PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane A_2.
Among these, mice lacking $PGF_{2\alpha}$ receptor ($Ptgfr^{-/-}$) showed significantly less pulmonary fibrotic changes after bleomycin administration than wild type (WT) mice; interestingly, in these mice, the authors did not observe differences in inflammatory response by examining the cellular content of brochoalveolar lavage fluid (BALF), suggesting that the lack of $PGF_{2\alpha}$ receptor reduces fibrosis without changes in inflammation. By different approaches including gene expression analysis in the lungs of both $Ptgfr^{-/-}$ and WT mice, the authors found that the $PGF_{2\alpha}$-receptor pathway contributes to the fibrogenesis by enhancing the expression of fibrosis-related genes independently of the TGF-β pathway.
These interesting findings suggest that the inhibition of the $PGF_{2\alpha}$-receptor signaling could represent an alternative and additional therapeutic target in pulmonary fibrosis.

Authors: Hecker L, Vittal R, Jones T, Jagirdar R, Luckhartd TR, Horowitz JC, Pennathur S, Martinez FJ, Thannickal VJ.
Title: NADPH oxidase-4 mediates myofibroblast activation and fibrogenic responses to lung injury
Nature Medicine 2009; 15: 1077-81
Summary: In this study, the authors investigated the potential role of the NOX4 isoform (one of the members of the NADPH oxidase- NOX- family of enzymes) in tissue repair functions of myofibroblasts and fibrogenesis. By *ex-vivo* and *in-vivo* experiments, the authors identified in NOX- 4 the enzymatic source of extracellular H_2O_2 production by myofibroblasts and their capability in mediating myofibroblast differentiation and contractility. Moreover, NOX- 4 resulted to be upregulated in the lungs of human subjects with idiopathic pulmonary fibrosis supporting a role for this NOX isoform in myofobroblast activation. To further confirm this observation genetic or pharmacologic inihibition of NOX-4 expression in bleomycin-induced lung injury in mice ameliorated pulmonary fibrosis.
In conclusion, the NOX-4 pathway could have an important pathogenetic role in different fibrotic diseases and it could represent a novel potential therapeutic target.

Clinical aspects

Authors: Savarino E, Bazzica M, Zentilin P, Pohl D, Parodi A, Cittadini G, Negrini S, Indiveri F, Tutuian R, Savarino V, Ghio M.
Title: Gastroesophageal Reflux and Pulmonary Fibrosis in Scleroderma: a study using pH-impedance monitoring.
Am J Respir Crit Care Med 2009; 179: 408-13.

Summary: The mechanism leading to interstitial lung disease (ILD) in Systemic sclerosis is poorly understood; recent studies postulated a possible pathogenetic role of chronic microaspiration of gastric content as observed in patients with gastroesophageal reflux (GER). In this cross- sectional study, the authors evaluated 40 consecutive SSc outpatients and 48 healthy controls for the presence of acidic and non acidic GER by esophageal manometric evaluation and esophageal 24- hour impedance- pH monitoring. SSc patients were also investigated for ILD by a complete pulmonary evaluation including pulmonary high resolution computed tomography scan which provided a quantitative ILD score. The authors observed a more extensive esophageal involvement as expressed by lower resting pressures, lower esophageal contraction amplitudes, higher frequency of GER episodes (both acidic and non acidic) up to the proximal esophagus in SSc patients with ILD compared with SSc patients without ILD; in addition, a very good correlation between the extent of ILD and total number of reflux episodes were observed.
These findings suggest the possible pathogenetic role of non-acidic GER (as well as acidic reflux) for the development and/or progression of ILD and postulated that, if confirmed in further studies, a reflux- reducing therapy could represent a targeted preventive therapy for both esophageal and pulmonary involvement in SSc. One new and important finding is that non-acidic reflux correlates with lung fibrosis. This is important because the usual PPI strategies would not be expected to work to prevent non-acidic reflux.

Treatment

Authors: Khanna D, Clements PJ, Furst DE, Korn JH, Ellman M, Rothfield N, Wigley FM, Moreland LW, Silver R, Kim YH, Steen VD, Firestein GS, Kavanaugh AF, Weisman M, Mayes MD, Collier D, Csuka ME, Simms R, Merkel PA, Medsger TA, Sanders ME, Maranian P and Seibold JR for the Relaxin Investigator and the Scleroderma Clinical Trial Consortium.
Title: Recombinant human relaxin in the treatment of systemic sclerosis with diffuse cutaneous involvement: a randomized, double-blind, placebo-controlled trial.
Arthritis Rheum 2009; 60: 1102-11.
Summary: In previous pre-clinical and phase I- II studies, relaxin demonstrated antifibrotic properties and resulted safe and clinically efficacious both in improving skin manifestation and reducing functional disability in SSc patients.
This is a phase III randomised, double-bind, placebo controlled trial to evaluate efficacy and safety of recombinant human relaxin (10 μg/Kg/day or 25 μg/kg/day) as a continuous subcutaneous infusion given for 24 weeks in patients with stable diffuse moderate to severe SSc.
One hundred and five SSc patients completed the 24-week study; as far as efficacy outcome measures are concerned, no differences were observed between the three groups in terms of skin involvement (MRSS), change in DLCO % predicted, HAQ DI score or physician's global assessment. As expected according to the physiological effect of relaxin on the renovascular system, increase in creatinine clearance, lowering of blood pressure and decrease in hemoglobin levels were observed in the treatment groups with respect to the placebo group. Additionally, menorrhagia was more frequently reported in the relaxin groups and, surprisingly, after treatment discontinuation, serious renal adverse events in both relaxin groups were observed (for a total of 7 renal event in the treatment group *vs*. none event in the placebo group).
In conclusion, recombinant human relaxin did not show significant clinical efficacy in diffuse SSc patients and did, whenit was abruptly interrupted or stopped, resulted in elevated blood pressures and failing renal function in 7 SSc patients. The message is that patients who discontinue Relaxin infusions must be followed closely for several weeks with daily blood pressure readings and if need be serum creatinine levels.

Authors: J.R. Seibold, C.P. Denton, D.E. Furst, L. Guillevin, L.J. Rubin, A. Wells, M. Matucci-Cerinic, G. Riemekasten, P. Emery, H. Chadha-Boreham, P. Charef, S. Roux, J. Korn, C.M. Black.
Title: Randomized, prospective, placebo-controlled trial of bosentan in interstitial lung disease secondary to systemic sclerosis
Ann Rheum Dis (in press)
Summary: Recent findings on the pathophysiological role of Endothelin-1 (ET-1) in SSc-related lung fibrosis ILD) suggested a possible benefit from drugs targeting the ET-1 pathway in ILD-SSc.
This is a double-blind, randomised, placebo-controlled trial designed to evaluate whether a 12-month treatment with bosentan (a non-selective endothelin receptor antagonist) could interfere with the ILD progression and therefore with the exercise capacity in SSc patients with active and progressive ILD without significant pulmonary hypertension.
One hundred and sixty three patients were randomised (77 to bosentan and 86 to placebo); at 12 months no significant differences were observed between the bosentan and the placebo groups in terms of six-minute walk distance; additionally, no effect on time to death or on worsening of pulmonary function tests were observed in the bosentan group over the course of the 12-month trial. No deaths were registered during the study and the overall incidence of adverse events was similar for both groups; the most common adverse event leading to discontinuation of treatment was worsening of pulmonary function tests.
Overall, this study did not demonstrate the efficacy of bosentan in reducing clinically important worsening in SSc related-ILD, thus discouraging the use of endothelin receptor antagonists in this clinical setting.