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

edited by C. Tani

Pathogenesis and new therapeutic targets

Title: Genome-wide association study of systemic sclerosis identifies CD247 as a new susceptibility locus.
Authors: Radstake TR, Gorlova O, Rueda B, Martin JE, Alizadeh BZ, Palomino-Morales R, Coenen MJ, Vonk MC, Voskuyl AE, Schuerwegh AJ, Broen JC, van Riel PL, van 't Slot R, Italiaander A, Ophoff RA, Riemekasten G, Hunzelmann N, Simeon CP, Ortego-Centeno N, González-Gay MA, González-Escribano MF; Spanish Scleroderma Group, Airo P, van Laar J, Herrick A, Worthington J, Hesselstrand R, Smith V, de Keyser F, Houssiau F, Chee MM, Madhok R, Shiels P, Westhovens R, Kreuter A, Kiener H, de Baere E, Witte T, Padykov L, Klareskog L, Beretta L, Scorza R, Lie BA, Hoffmann-Vold AM, Carreira P, Varga J, Hinchcliff M, Gregersen PK, Lee AT, Ying J, Han Y, Weng SF, Amos CI, Wigley FM, Hummers L, Nelson JL, Agarwal SK, Assassi S, Gourh P, Tan FK, Koeleman BP, Arnett FC, Martin J, Mayes MD.
Nat Genet 2010 May; 42(5): 426-9. Epub 2010 Apr 11.
Summary: Genetic susceptibility and environmental factors are considered the most important predisposing factors to Systemic Sclerosis development. In this paper, the authors report the results on the first genome- wide association study of SSc including a total of 2296 SSc patients and 5171 healthy controls from four case- control series of European ancestry. A total of 279621 autosomal SNPs were analysed founding a significant association for five loci; STAT-4 and TNPO3- IRF5 which were already known from previous studies as HLA- related generic predisposing factors, and three new loci: CD247, CDH7, EXOC2-IRF4. These results were subsequentially tested in an independent case- control set (2753 cases and 4569 controls) and the significant association was confirmed in this replication cohort for the locus CD247, while for CDH7, EXOC2-IRF4 it was not. Interestingly, the new susceptibility locus CD247 identified by the authors encodes a protein involved in the immune response: the T- cell receptor zeta subunit which is a component of the T- cell receptor- CD3 complex. Moreover, CD247 as well as STAT4 and IRF5 are also known to be predisposing factors for other autoimmune conditions reinforcing the idea of a shared common genetic and pathogenetic basis for different systemic autoimmune diseases.

Title: Epithelial cell cycle arrest in G2/M mediate kidney fibrosis after injury
Authors: Yang L, Besschetnova TY, Brooks CR, Shah JV e Bonventre JV.
Nat Med 2010 May; 16(5): 535-43, 1p following 143. Epub 2010 May 2.
Summary: Fibrosis is the common final result of different kinds of tissue injuries, and it is responsible for irreversible damage and loss of normal organ function. In the kidney, acute injury can result in incomplete repair and persistent tubulo-interstitial fibrosis which is actually considered the common final step to end-stage renal disease irrespectively of the starting cause. The molecular mechanism responsible for the fibrotic response to injury is still poorly understood. However, there is increasing evidence that cell cycle modulation can be involved in this process. In this study, the authors employed five mouse models of acute kidney injury to investigate the cell cycle profile of tubular epithelial cells *in vivo*. They found a strong correlation between G2/M cell cycle arrest in tubular cells and fibrotic results. In fact, they demonstrated that, after kidney injury, proximal tubular cells arrested in the cycle phase G2/M are able to initiate a fibrotic reaction through the up-regulation of profibrogenic growth factors (TGF-β1 and CTGF). On the other hand, a significant reduction of the G2/M arrest resulted in a dramatic reduction in fibrogenesis. They also demonstrated that the up-regulation of profibrotic genes expression and the collagen production is initiated by the JNK, a gene transcription promoter, which resulted in activation during G2/M arrest; on the contrary, an inhibition of JNK activity resulted in a protection against the kidney fibrosis.
These observations have highlighted the central role of the tubular cells in the kidney fibrotic process and suggest a new therapeutic target to prevent interstitial fibrosis and the progression to irreversible kidney dysfunction.

Clinical aspects

Title: Exercise pulmonary hypertension associated with systemic sclerosis: four distinct entities.
Authors: Saggar R, Khanna D, Furst DE, Shapiro S, Maranian P, Belperio JA, Chauhan N, Clements P, Gorn A, Weigt SS, Ross D, Linch JP, Saggar R.
Arthritis Rheum 2010 Aug 18. [Epub ahead of print]
Summary: Despite recent therapeutic advances, pulmonary arterial hypertension (PH) is still one of the major causes of morbidity and mortality in systemic sclerosis (SSc). Recent findings have shown that exercise pulmonary hypertension (ePH) (might) represent an intermediate phase between normal pulmonary haemodynamic evaluation and resting PH. Thus, exercise evaluation of PH in SSc patients might permit earlier diagnosis and earlier treatment. However, data on prevalence and clinical significance of ePH in SSc patients are still lacking. In this study, the authors retrospectively col-

lected data on right heart catheterisation (RHC) of 80 consecutive SSc- spectrum patients referred to haemodynamic evaluation because of dyspnea and echocardiographic estimation of PH or lung function test impairment. Fifty- seven patients (25 diffuse SSc, 22 limited SSc and 10 overlap syndrome) were shown to have normal resting PH on RHC and were further evaluated with exercise testing during RHC. Four different haemodynamic subgroups were identified on exercise: normal (NL, 15), pulmonary venous hypertension (ePVH, 12), out of proportion PH* (eoPH; 9) and exercise PH (ePH, 21). The mean pulmonary artery (mPA) and pulmonary vascular resistance (PVR) resulted as the variables at rest that best distinguished ePH and eoPH from ePVH and NL. Interestingly, the authors provided a decision tree based on resting haemodynamic values to be used to predict exercise PH and out of proportion PH; namely, according to the decision model proposed by the authors, a resting mPAP< 14 mmHg has a 100% chance of ruling out exercise abnormal response (ePVH, ePH and eoPH) while resting mPAP>20 mmHg has a 90% chance of predicting mPA>30 mmHg during exercise.
PH assessing and treatment in SSc patients represents a crucial clinical challenge for rheumatologists. If further validated, the decision tree proposed by the authors could represent an important tool for the SSc management in everyday clinical practice.
*Out of proportion means that both left ventricular failure (ePVH) and PAH (ePH) together were additive and resulted in higher elevations in mPAP than either alone.

Title: Characterisation of connective tissue disease associated pulmonary arterial hypertension from the REVEAL registry: identifying systemic sclerosis as a unique phenotype.
Authors: Chung L, Liu J, Parson L, Haussoun PM, McGoon M, Badesch D, Miller DP, Nicolls MR, Zamanian RT.
Chest 2010 May 27. [Epub ahead of print]
Summary: Pulmonary arterial hypertension (PAH) affects approximately 3% to 13% of patients with connective tissue diseases (CTD) and, in general, in these patients it usually has a worse prognosis with respect to the idiopathic form.
This study was aimed at evaluating clinical characteristics and prognosis of PAH in patients with different connective tissue disease and at investigating eventual distinguishing features from the idiopathic PAH (IPAH). With this purpose, the REVEAL registry, the largest U.S. multicentre observational registry of patients with right heart cathetersation – confirmed PAH, was used as data source.
A total of 1892 patients were included in the analyses. Of these, 1251 were diagnosed with IPAH and 641 with CTD-PAH (589 with a known diagnosis: 339 SSc, 110 SLE, 52 MCTD, 28 RA). Overall, CTD- PAH patients demonstrated a better haemodynamic pattern at PAH diagnosis. However, at study enrolment, they were more likely to present a pericardial effusion, they had worse performance at the six-minute walking test, higher BNP levels and poorer functional lung performances than patients with IPAH. CTD- PAH patients showed a worse survival rate at 1 year (86% *vs*. 93%) and a higher rate of hospitalisation. Among CTD patients, apart from epidemiological and obvious disease- related differences, the haemodynamic pattern resulted similar. However, SSc patients had the highest BNP levels, the poorest pulmonary function test results and the poorest survival rate at 1 year (82% *vs*. 94%).
This is a comprehensive clinical, echographic and haemodynamic characterisation of a very large cohort of patients with CTD associated PAH. The authors highlighted the unique feature of SSc-associated PAH respect to other CTDs and suggested intriguing pathogenetic explanations.

Treatment

Title: Bosentan treatment of digital ulcers related to systemic sclerosis: result from the RAPIDS-2 randomised, double-blind, placebo-controlled trial.
Authors: Matucci-Cerinic M, Denton CP, Furst ED, Mayes MD, Hsu VM, Carpentier P, Wigley FM, Black CM, Fessler BJ, Merkel PA, Pope JE, Sweiss NJ, Doyle MK, Hellmich B, Medsger TA, Morganti A, Kramer F, Korn JH, Seibold JR.
Ann Rheum Dis 2010 Sep 28 [Epub ahead of print]
Summary: This is a multicentre randomised, double- blind, placebo-controlled trial evaluating the effect of bosentan treatment on ischemic digital ulcers (DUs) healing and prevention in patients with Systemic Sclerosis (Ssc). One hundred and eighty-eight SSc patients with at least one active DUs at study entry were enrolled and randomised to receive bosentan 62.5 mg twice daily for 4 weeks and then 125 mg twice daily or placebo for a treatment period of 24 weeks. At the end of the treatment, the bosentan arm resulted in a 30% reduction in the occurrence of new Dus with respect to the placebo arm, while no differences were observed in the time of healing of the cardinal ulcer. No differences were recorded between the two groups in pain experience and disability. A post hoc analysis showed that the greatest treatment effect was observed in the subgroup of patients with at least four DUs at baseline (-2.1; p=0.02). As far as safety and tolerability are concerned, the overall incidence of adverse events was similar in the bosentan and placebo group, and serious adverse events occurred respectively in 9.4% and 16.7% of patients. Peripheral oedema and aminotranferases elevation were the most frequent adverse events in the bosentan group (18.8% and 12.5% respectively) causing early discontinuation respectively in 2.1% and 5.2% of patients.
These results confirm previous findings showing a benefit of bosentan in preventing digital ulcers but not in healing the existing ones in patients with SSc. In addition, the greater therapeutic effect was demonstrated in the presence of more than four ulcers at baseline thus identifying a subgroup of patients who could take more advantage from the treatment. Liver function abnormalities and peripheral oedema resulted in significant possible side effects thus needing a tight follow-up.