Increased interleukin-1 levels are an early hallmark of pulmonary remodelling in Fra-2 mouse model of scleroderma

Gungl A[1], Crnkovic S[1,2], Biasin V[2], Marsh LM[2], Sahu-Osen A[2], Ghanim B[2,3], Klepetko W[3], Odler B[2], Kovacs G[2,4], Eferl R[5], Olschewski H[4], Olschewski A[1,2], Kwapiszewska G[1,2].

[1]Department of Physiology, Medical University of Graz, Graz, Austria. [2]Ludwig Boltzmann Institute for Lung Vascular Research, Graz, Austria. [3]Department of Surgery, Division of Thoracic Surgery, Medical University of Vienna, Vienna, Austria. [4]Division of Pulmonology, Medical University of Graz, Graz, Austria. [5]Institute of Cancer Research of the Medical University of Vienna, Austria.

Rationale: Pulmonary hypertension (PH) and pulmonary fibrosis (PF) worsen the clinical outcome of scleroderma patients. However, the factors responsible for vascular and parenchymal remodelling are still unclear. Here, we have investigated the sequence of events leading to pulmonary remodelling in SSc.

Methods: The longitudinal development and progression of SSc was studied in the Fra-2 TG mouse model. Signalling pathways and extracellular matrix protein expression were investigated in primary human pulmonary arterial smooth muscle cells (PASMCs) and parenchymal fibroblasts (PFs) after IL-1α or IL-1β stimulation. Human lung tissue and plasma samples were applied to translate our findings to SSc patients.

Results: In Fra-2 TG mice, vascular remodelling was evident already at 8 weeks, prior to the development of pulmonary fibrosis, and accompanied by elevated IL-1α levels. IL-1 activated the JNK and p38 kinases in PASMCs and PFs, whereas NF-κB and ERK were activated in PFs and PASMCs, respectively. IL-1 stimulation downregulated collagen 1 and α-Sma, but increased the expression of IL-6 and tenascin C (TNC) in both cell types, without affecting their proliferation. Similarly, *in vivo* elevated IL-1α in Fra-2 TG mice was followed by increased IL-6 and TNC at 16 and 24 weeks on mRNA and protein levels concomitant with enhanced phosphorylation of STAT3. Circulating TNC levels were increased in patients with manifested lung fibrosis (mean ± SD: 61.3 ± 38.8 ng/ml) compared to healthy controls (19.2 ± 6.9 ng/ml), patients with PH (27.6 ± 8.2 ng/ml) and SSc without pulmonary fibrosis (29.5 ± 17.9 ng/ml).

Conclusions: Increased Fra-2/IL-1 levels exert indirect pro-fibrotic effects on resident pulmonary cells through IL-6 and TNC. Furthermore, TNC serves as a potential marker to discriminate patients with and without pulmonary fibrosis.