Propylthiouracil prevents cutaneous and pulmonary fibrosis in the reactive oxygen species murine model of systemic sclerosis

A. Bitto[1], G. Pizzino[1], N. Irrera[1], G. Bagnato[1], D. Altavilla[2], F. Squadrito[1]

[1]Dept. of Clinical and Experimental Medicine, University of Messina
[2]Dept. of Paediatric, Gynaecological, Microbiological and Biomedical Sciences, University of Messina

Recent advances suggest that the cellular redox state may play a significant role in the progression of fibrosis in systemic sclerosis (SSc). Another, and as yet poorly accounted for, feature of systemic sclerosis is its overlap with thyroid abnormalities. Previous reports demonstrate that hypothyroidism reduces oxidant stress (Gabrielli et al., 2008; Dooley et al., 2012; Tsou et al., 2012). Aim of the study is therefore to evaluate the effect of propylthiouracil (PTU), and of the hypothyroidism induced by it, upon the development of cutaneous and pulmonary fibrosis in the oxidant stress murine model of systemic sclerosis. Chronic oxidant stress systemic sclerosis was induced in BALB/c mice by daily subcutaneous injections of HOCl for 6 weeks. Mice (n=25) were randomized in three arms: HOCl (n=10), HOCl plus PTU (n=10) or vehicle alone (n=5). PTU administration was initiated 30 minutes after HOCl subcutaneous injection and continued daily for 6 weeks. Skin and lung fibrosis were evaluated by histological methods. Immunohistochemical staining for alpha-smooth muscle actin (α-SMA) in cutaneous and pulmonary tissues was performed to evaluate myofibroblast differentation. Lung and skin concentrations of vascular endothelial growth factor (VEGF), extracellular signal-related kinase (ERK), rat sarcoma protein (Ras), Ras homolog gene family (Rho), and transforming growth factor (TGF) β were analyzed by western blot. Injections of HOCl induced cutaneous and lung fibrosis in BALB/c mice. PTU treatment prevented both dermal and pulmonary fibrosis. Myofibroblast differentiation was also inhibited by PTU in the skin and lung. The increase in cutaneous and pulmonary expression of VEGF, ERK, Ras and Rho in mice treated with HOCl was significantly prevented in mice co-administered with PTU. PTU, probably through its direct effect on reactive oxygen species or indirectly through thyroid function inhibition, prevents the development of cutaneous and pulmonary fibrosis by blocking the activation of the Ras-ERK pathway in the oxidant stress animal model of systemic sclerosis.

References

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