Exploiting of the integrin modulating therapy as a therapeutic approach to systemic sclerosis

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

[1]Dept. of Clinical and Experimental Medicine, Section of Pharmacology, Medical School, University of Messina, Messina, Italy
[2]Dept. of Paediatric, Gynaecological, Microbiological and Biomedical Sciences, University of Messina, Messina, Italy

Recently insights in systemic sclerosis (SSc) pathogenesis indicates that mutations in the gene encoding fibrillin-1 (FBN1), affects the FBN-1 RGD motif-containing domain, that mediates cell-matrix interactions by binding to cell-surface integrins. Therefore, aim of this study was to evaluate the effect of cilengitide (a dual αvβ3/αvβ5 inhibitor) in cutaneous fibrosis in a murine model of SSc.

SSc was induced in 20 BALB/c mice by daily s.c. injections of HOCl (100 ml/mouse) for 4 weeks. Mice were then randomized to receive for the following 2 weeks: HOCl alone (n=10) or HOCl + Cilengitide (20 mg/kg/i.p.). Sham animals (n=5) received only HOCl vehicle (saline solution) for 6 weeks. Skin fibrosis was evaluated by Masson's trichrome staining; collagen I deposition and TGF-b were assessed by immunohistochemistry. Skin concentrations of p-FAK, cyclin D, CDK6 and the cyclin inhibitor p16 were evaluated by western blot analysis.

At the end of the 6 weeks of HOCl administration a strong fibrosis was demonstrated by the increase in cutaneous thickness, compared to Sham. The administration of cilengitide reduced fibrosis, collagen I deposition and the other parameters. Cutaneous concentrations of cyclin D were significantly higher in the HOCl group compared to Sham and this increase was significantly reduced in mice treated with cilengitide. Consistently, the concentrations of the cyclin D inhibitor p16 were significantly lower in HOCl compared to controls and increased in the group of mice treated with HOCl + cilengitide.

Considering our results, an integrin modulating therapy could represent a novel therapeutic strategy to treat fibrotic disorders such as systemic sclerosis.