SELECTIVE UPREGULATION OF PDGF-α RECEPTORS BY TGF-β IN SCLERODERMA FIBROBLASTS

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TGF-β, a multifunctional cytokine, is an indirect mitogen for human fibroblasts through PDGF, particularly the A ligand-α receptor arm of that system¹. TGF-β effects on PDGF α receptor expression were studied in scleroderma fibroblasts.

MATERIALS AND METHODS

Each 3 confluent, quiescent fibroblasts of newborn foreskin, adult skin and scleroderma were preincubated with the indicated concentrations of TGF-β, followed by binding with several (0.125-8ng/ml) concentrations of ¹²⁵I PDGF-AA. Receptor expression is presented as the ratio of the number of receptors per cell after TGF-β treatment to the numbers of receptors per cell before TGF-β treatment. The cells were stimulated with the indicated concentrations of TGF-β alone, PDGF-AA (10ng/ml) alone or preincubated with the indicated concentrations of TGF-β, then stimulated with PDGF-AA. Values are depicted as the ratio of mitogenic responses (DNA synthesis) to PDGF-AA after TGF-β pretreatment compared to responses to PDGF-AA without TGF-β pretreatment³. TGF-β effects were also studied in vitro by radioimmunoprecipitation analysis, northern blot and immunohistochemistry³.

RESULTS AND DISCUSSION

Increases in the number of PDGF α receptors due to TGF-β occurred consistently with scleroderma fibroblasts (Fig.1) and correlated with mitogenic responses (Fig.2). Radioimmunoprecipitation analysis of metabolically labeled cells demonstrated increases in new PDGF α receptor synthesis. Steady-state levels of corresponding mRNAs increased. Immunohistochemical examination of scleroderma and control skin biopsies revealed the presence PDGF-AA in scleroderma (data not shown). The data obtained are consistent with the hypothesis that activation of the PDGF-AA ligand/α receptor pathway is a characteristic of the scleroderma fibroblast and may contribute to the expansion of fibroblasts in scleroderma.
Fig. 1 Concentration-dependent modulation of PDGF α receptors in response to TGF-β in newborn foreskin, adult skin and scleroderma skin fibroblasts.

Fig. 2 Concentration-dependent effects of TGF-β preincubation on mitogenic responses to PDGF-AA in fibroblasts.

REFERENCES