The synthetic peptide, containing the syndecan-binding sequence within laminin a3 LG4 module, accelerates wound closure in animal model

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The extracellular matrix (ECM) glycoprotein thrombospondin-1 (TSP-1) has been reported to activate the latent complex of TGF-β, the major effects of which in mesenchymal cells is stimulation of the synthesis of ECM. Previous reports suggested the involvement of an autocrine TGF-β loop in the pathogenesis of scleroderma. In this study, we examined whether TSP-1 plays a role in maintaining the autocrine TGF-β loop in scleroderma. TSP-1 expression was increased in scleroderma patients compared with in healthy controls in vivo and in vitro. TGF-β blocking antibody or TGF-β1 antisense oligonucleotide markedly reduced the up-regulated TSP-1 expression in scleroderma fibroblasts but had little effect on normal fibroblasts. The expression of TSP-1 is up-regulated in scleroderma fibroblasts possibly at the posttranscriptional level just like in normal fibroblasts stimulated with exogenous TGF-β1. TSP-1 blocking peptide or antisense oligonucleotide had an inhibitory effect on the up-regulated α2(I) collagen and phospho-Smad3 levels in scleroderma fibroblasts but had little effects on normal fibroblasts. The transient overexpression of TSP-1 up-regulated α2(I) collagen and phospho-Smad3 levels in normal fibroblasts but had no major effect on scleroderma fibroblasts. Furthermore, these effects of transiently overexpressed TSP-1, which possibly occurred via the activation of latent TGF-β1, were abolished by the TGF-β1 antisense oligonucleotide. These results indicate that the constitutive overexpression of TSP-1 may play an important role in autocrine TGF-β signaling and accumulation of ECM in scleroderma fibroblasts.