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A key enzyme upregulating collagen production by scleroderma fibroblasts

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Keywords

dermal fibroblasts, systemic sclerosis, transforming growth factor ?

Context

Systemic sclerosis (SSc) is a fibroproliferative autoimmune disease characterized by the excessive production and deposition of collagen in skin and internal organs. Acting through specific transmembrane receptors, transforming growth factor-? (TGF-?) is known to play a crucial role in the development of tissue fibrosis. The authors had previously identified several signaling molecules other than Smad proteins including protein kinase C-d (PKC-d) as candidates downstream of TGF-? receptors. The aim of the present study was to examine the possible role of PKC-d in the upregulation collagen gene expression in SSc dermal fibroblasts.

Significant findings

Compared to normal fibroblasts, SSc dermal fibroblasts had increased type I and III collagen mRNA and protein as well as upregulation of PKC-d protein. Rottlerin, a specific inhibitor of PKC-d, inhibited collagen gene expression in both normal and SSc fibroblasts. Moreover, this study identified a 129-bp promoter region of the type I collagen gene encompassing nucleotides -804 to -675 which was responsive to the transcriptional inhibition by rottlerin and dominant-negative PKC-d expression.

Comments

These results indicate that PKC-d is a key molecule in the upregulation of type I collagen expression. However, the number of samples obtained from normal and SSc skins was too small to show a significant difference in the amounts of collagen and PKC-d expressed. In addition, most of the results

presented in this paper relied on a single "selective" inhibitor of PKC-d, rottlerin. The following points should be addressed in future studies: 1) identification of transcription factors downstream of PKC-d that interact with a promoter segment encompassing nucleotides -804 -675; 2) comparison of PKC-d activity between SSc and normal fibroblasts; 3) possible differences in collagen and PKC-d expression among subgroups of SSc (e.g., diffuse cutaneous SSc and limited cutaneous SSc).

Methods

ELISA, collagenase digestion assay, northern blotting, *in vitro* nuclear transcription assay, chloramphenicol acetyl transferase gene assay, high-resolution fluorescence immunomicroscopy, western blotting

Additional information

References

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