Document details

Back to results | 1 of 1

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A central bioactive region of LTBP-2 stimulates the expression of TGF-β1 in fibroblasts via akt and p38 signalling pathways (Article)

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Abstract

View references (63)

Latent transforming growth factor-β-1 binding protein-2 (LTBP-2) belongs to the LTBP-fibrillin superfamily of extracellular proteins. Unlike other LTBPs, LTBP-2 does not covalently bind transforming growth factor-β1 (TGF-β1) but appears to be implicated in the regulation of TGF-β1 bioactivity, although the mechanisms are largely unknown. In experiments originally designed to study the displacement of latent TGF-β1 complexes from matrix storage, we found that the addition of exogenous LTBP-2 to cultured human MSU-1.1 fibroblasts caused an increase in TGF-β1 levels in the medium. However, the TGF-β1 increase was due to an upregulation of TGF-β1 expression and secretion rather than a displacement of matrix-stored TGF-β1. The secreted TGF-β1 was mainly in an inactive form, and its concentration peaked around 15 h after addition of LTBP-2. Using a series of recombinant LTBP-2 fragments, the bioactivity was identified to a small region of LTBP-2 consisting of an 8-Cys motif flanked by four epidermal growth factor (EGF)-like repeats. The LTBP-2 stimulation of TGF-β expression involved the phosphorylation of both Akt and p38 mitogen-activated protein kinase (MAPK) signalling proteins, and specific inactivation of each protein individually blocked TGF-β1 increase. The search for the cell surface receptor mediating this LTBP-2 activity proved inconclusive. Inhibitory antibodies to integrins β1 and αVβ5 showed no reduction of LTBP-2 stimulation of TGF-β1. However, TGF-β1 upregulation was partially inhibited by anti-αVβ3 integrin antibodies, suggestive of a direct or indirect role for this integrin. Overall, the study indicates that LTBP-2 can directly upregulate cellular TGF-β1 expression and secretion by interaction with cells via a short central bioactive region. This may be significant in connective tissue disorders involving aberrant TGF-β1 signalling. © 2017 by the authors. Licensee MDPI, Basel, Switzerland.

Reaxys Database Information

View Compounds

Author keywords

Akt Fibroblast Fibrosis LTBP-2 p38 MAPK TGF-β

Indexed keywords

EMTREE drug terms: beta1 integrin, beta3 integrin, beta5 integrin, fibrillin 1, fibroblast growth factor 2, latent transforming growth factor beta binding protein, mitogen activated protein kinase, mitogen activated protein kinase p38, protein c fos, protein c jun, protein kinase B beta, synaptophysin, transforming growth factor beta1

EMTREE medical terms: Akt signaling, Article, cell count, controlled study, enzyme linked immunosorbent assay, fibroblast, genetic transcription, human, human cell, immunoblotting, protein expression, protein phosphorylation, real time polymerase chain reaction, signal transduction, upregulation, Western blotting

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