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Transforming growth factor-β-induced CUX1 isoforms are potentially associated with fibrosis in systemic sclerosis lung fibroblasts

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Scleroderma, or systemic sclerosis (SSc), is a connective tissue disease characterized by excessive type I collagen (COL1) deposition in many organs including the lungs, kidneys and skin. Approximately 40% patients with diffuse SSc experience pulmonary fibrosis, a major cause of mortality. Although the aetiology of this disease is poorly understood, tissue scarring occurs after injury following the release of several mediators including TGF-β, PDGF, CTGF, Wnt1 and ET-1. These factors stimulate fibroblasts to differentiate into myofibroblasts, which are characterized by the expression of α-SMA and excessive production of extracellular matrix molecules such as COL1. In the enhancer region of the human type I collagen alpha 2 (*COL1A2*) gene, we identified cis-elements for the transcription factor CUX1. However, the role of CUX1 in fibrosis remains unclear. Here we investigated the role of CUX1 in the regulation of COL1 expression and delineated the mechanisms underlying the regulation of COL1A2 expression by CUX1 in SSc lung fibroblasts. The binding of CUX1 to the COL1A2 enhancer region was assessed using electrophoretic mobility shift assays after treatment with transforming growth factor (TGF)-β. Subsequently, the protein expression levels of CUX1 isoforms were determined using western blotting. Finally, the expression levels of COL1 and fibrosis-related cytokines were determined. The binding of CUX1 isoforms to the COL1A2 enhancer region increased after TGF-β treatment. TGF-β also increased the protein levels of the CUX1 isoforms p200, p150, p110, p75, p30 and p28. Moreover, SSc lung fibroblasts showed higher levels of CUX1 isoforms than normal lung fibroblasts, and treatment of SSc lung fibroblasts with a cathepsin L inhibitor (IW-CHO) decreased COL1 protein expression and reduced cell size. In SSc and diffuse alveolar damage lung tissue sections, CUX1 localised within α-smooth muscle actin-positive cells. Our results suggested that CUX1 isoforms play vital roles in connective tissue deposition during wound repair and fibrosis.

Biography

Tetsurou Ikeda has completed his PhD from Hiroshima University (2001). He studies the mechanism of regulation of COL1A2 gene, which is over-expressed in the case of fibrosis. Recent his study indicates that accumulation of CUX1 isoforms induced by TGF-β might occur in the enhancer region of COL1A2 gene.

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