Dysregulation of elastin expression by fibroblasts in pulmonary emphysema: role of cellular retinoic acid binding protein 2

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Résumé en anglais	BACKGROUND: All-trans retinoic acid (ATRA) stimulates elastin synthesis by lung fibroblasts and induces alveolar regeneration in animal models of pulmonary emphysema. However, ATRA treatment has had disappointing results in human emphysema. It was hypothesised that a defect in the ATRA signalling pathway contributes to the defect of alveolar repair in the human emphysematous lung. METHODS: Fibroblasts were cultured from the lung of 10 control subjects and eight patients with emphysema. Elastin and retinoic acid receptor (RAR)-beta mRNAs were measured in those cells in the presence of incremental concentrations of ATRA. RARs, retinoic X receptors (RXRs) and cellular retinoic acid binding protein (CRABP) 1 and 2 mRNAs were measured as well as CRABP2 protein content. The effect of CRABP2 silencing on elastin and RAR-beta expression in response to ATRA was measured in MRC5 lung fibroblasts. RESULTS: ATRA at 10(-9) M and 10(-8) M increased median elastin mRNA expression by 182% and 126% in control but not in emphysema fibroblasts. RAR-beta mRNA expression was induced by ATRA in control as well as emphysema fibroblasts. RARs, RXRs and CRABP1 mRNAs were similarly expressed in control and emphysema fibroblasts while CRABP2 mRNA and protein were lower in emphysema fibroblasts. CRABP2 silencing abrogated the induction of elastin but not RAR-beta expression by ATRA in MRC5 fibroblasts. CONCLUSION: Pulmonary emphysema fibroblasts fail to express elastin under ATRA stimulation. CRABP2, which is necessary for elastin induction by ATRA in MRC-5 cells, is expressed at low levels in emphysema fibroblasts. This alteration in the retinoic acid signalling pathway in lung fibroblasts may contribute to the defect of alveolar repair in human pulmonary emphysema. These results are the first demonstration of the involvement of CRABP2 in elastin expression.
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