# Loss of PTEN expression by mouse fibroblasts results in lung fibrosis through a CCN2-dependent mechanism

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http://dx.doi.org/10.1016/j.matbio.2015.01.017
***Edited by R. Iozzo***

## Abstract

Elevated adhesive signaling promotes fibrosis. Protein phosphatase and tensin homologue (PTEN) dephosphorylates focal adhesion kinase and suppresses the activation of Akt and hence suppresses adhesive signaling. Loss of PTEN expression is associated with lung fibrosis, but whether PTEN expression by type I collagen-expressing cells controls lung fibrosis is unclear. Here, we use mice expressing tamoxifen-dependent cre recombinase expressed under the control of a COL1A2 promoter/enhancer and mice harboring floxed-PTEN and/or floxed-CCN2 alleles to assess whether loss of PTEN expression by type I collagen producing cells results in lung fibrosis in a CCN2-dependent fashion. In vivo, loss of PTEN expression resulted in the overexpression of both collagen type I and the pro-adhesive matricellular protein connective tissue growth factor (CTGF/CCN2). However, α-smooth muscle actin expression was unaffected. Loss of CCN2 expression by lung fibroblasts rescues this phenotype; i.e.., mice deficient in both PTEN and CCN2 in collagen type I-expressing cells do not develop significant collagen deposition in the lung. PTEN expression by collagen type I-expressing cells controls collagen deposition; therapeutic strategies blocking CCN2 may be of benefit in blocking excessive collagen deposition in fibrosis.



## Introduction

Fibrosis is one of the largest groups of diseases for which there is no generally agreed upon therapy. Lung fibrosis [e.g. idiopathic pulmonary fibrosis (IPF) and Fibrosing Alveolitis Complicating Systemic Sclerosis] is associated with severe morbidity [1,2]. Fibrosis is caused by the excessive production of extracellular matrix (ECM) notably collagen type I by fibroblasts present within connective tissue. Understanding the fundamental mechanisms underlying how fibroblasts contribute to lung fibrosis is therefore of high clinical relevance.

Fibroblasts present in fibrotic lesions are characterized by elevated adhesion to ECM and adhesive signaling including focal adhesion kinase (FAK)/PI3K/Akt phosphorylation [3–5]. The phosphatase and tensin homologue (PTEN), a dual protein/lipid phosphatase which dephosphorylates FAK and suppresses the activation of PI3K-Akt signaling, is reduced in fibroblasts in IPF patients [6]. Reduced PTEN expression is seen in SSc skin fibroblasts, and genetic deletion of PTEN in skin fibroblasts results in progressive dermal fibrosis [7]. However, whether loss of PTEN expression by lung fibroblasts is sufficient to result in lung fibrosis is unclear.

It has been hypothesized that the matricellular protein CTGF (connective tissue growth factor/CCN2) is a central mediator of fibrosis and may be a novel antifibrotic therapeutic approach [8]. Conditional CCN2 knockout mice were recently used to show that CCN2 was required for skin fibrosis in the

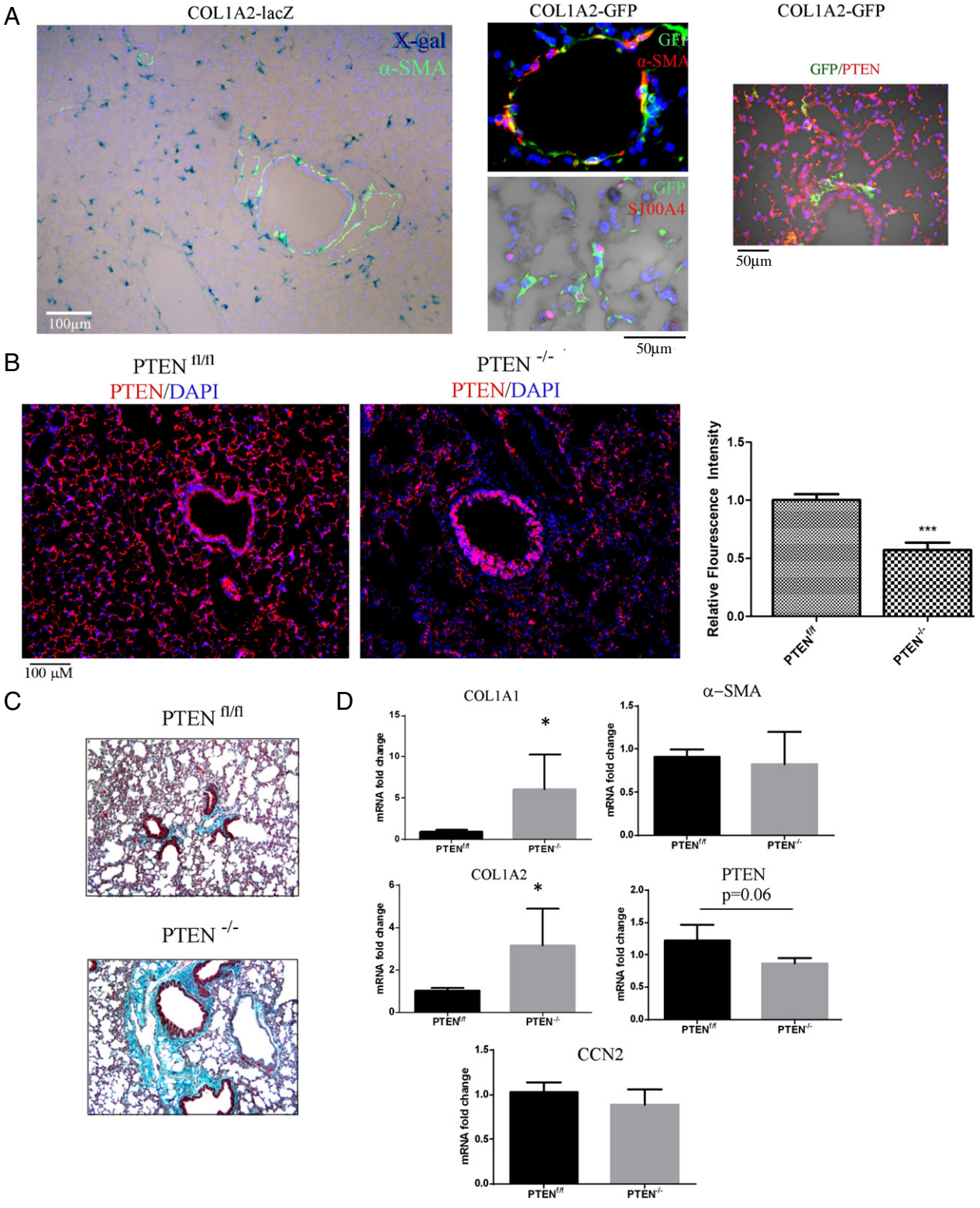


**Fig. 1** (*legend on next page*).