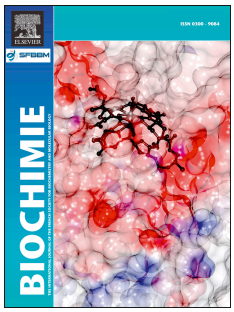
Accepted Manuscript



Type I collagen induces mesenchymal cell differentiation into myofibroblasts through YAP-induced TGF-β1 activation

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PII: S0300-9084(18)30128-7

DOI: 10.1016/j.biochi.2018.05.005

Reference: BIOCHI 5417

To appear in: *Biochimie*

Received Date: 21 January 2018

Accepted Date: 14 May 2018

Please cite this article as: X. Liu, X. Long, W. Liu, Y. Zhao, T. Hayashi, M. Yamato, K. Mizuno, H. Fujisaki, S. Hattori, S.-i. Tashiro, T. Ogura, Y. Atsuzawa, T. Ikejima, Type I collagen induces mesenchymal cell differentiation into myofibroblasts through YAP-induced TGF-β1 activation, *Biochimie* (2018), doi: 10.1016/j.biochi.2018.05.005.

Abstract

In organ fibrosis, mechanical stress and transforming growth factor beta-1 (TGF-β1) promote differentiation into myofibroblast from mesenchymal cells, leading to extracellular matrix (ECM) remodeling or active synthesis, deposition or degradation of ECM components. A major component of ECM, type I collagen (col I) triple helical molecules assemble into fibrils or are denatured to gelatin without triple-helicity in remodeling. However, whether changes of ECM components in remodeling have influence on mesenchymal cell differentiation remains elusive. This study adopted three states of collagen I existing in ECM remodeling: molecular collagen, fibrillar collagen and gelatin to see what are characteristics in the effects on two cell lines of mesenchymal origin, murine 3T3-L1 embryonic fibroblast and murine C2C12 myoblasts. The results showed that all three forms of collagen I were capable of inducing these two cells to differentiate into myofibroblasts characterized by increased expression of alpha-smooth muscle actin (α-SMA) mRNA. The expression of α-SMA is positively regulated by TGF-β1. Nuclear translocation of Yes-associated protein (YAP) is involved in this process. Focal adhesion kinase (FAK) is activated in the cells cultured on molecular collagen-coated plates, contributing to YAP activation. On the other hand, in the cells cultured on fibrillar collagen gel or gelatin-coated plates, oxidative stress but not FAK induce YAP activation. In conclusion, the three physicochemically distinct forms of col I induce the differentiation of mesenchymal cells into myofibroblasts through different pathways.