[P-11]

Inhibition by Hyaluronan of Collagen-Induced Activation of Hepatic Stellate Cells

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Synthesis and distribution of extracellular matrix (ECM) components are dynamically altered in response to the pathophysiological processes including infection, inflammation and apoptosis. In particular, the levels of hyaluronan (HA) change with concomitant increases in the levels of collagen (e.g. type I collagen) and fibronectin in chronic liver diseases. Although the pathophysiological role of collagens is extensively studied, little information is available on the role of hyaluronan, an amorphous glycoaminoglycan, in the activation of hepatic stellate cells (HSCs), the collagen-producing cells. The present study was designed to investigate the effects of HA in conjunction with fibrillar (type I) and non-fibrillar (type IV) collagens on the HSC adhesion and activation. The effects of these ECM components on the adhesion and activation of HSCs were determined in the culture dishes coated with HA, fibronectin, collagen type I, type III and type IV using primary cultured quiescent or activated HSCs. Microscopic analysis showed that the extent of HSC adhesion was greatly (2- to 5-fold) increased on the surface of collagen type I or IV. By contrast, HA with or without collagen type I or IV substantially inhibited adhesion of HSCs. Activation of HSCs was monitored by the formation of filopodia and the expression of α-SMA. Collagen type I or IV stimulated activation of HSCs, whereas HA inhibited that of HSCs. Collagen (I)-inducible activation of HSCs was also suppressed by the concomitant presence of HA. Anti-CD44 antibody failed to block the inhibitory effects of HA on the adhesion and the activation of HSCs. These data showed that HA inhibited both the adhesion and the activation of HSCs, whereas collagens stimulated those of HSCs and that the inhibitory effect of HA on HSC activation was not mediated with CD44. Our results imply that disruption of balanced production of HA and fibrillar ECM may play a role in HSC transdifferentiation during the process of chronic liver diseases.

Keyword : Hepatic stellate cells, Hyaluronan, Collagen