Structural architecture of collagen and collagen-fibronectin networks is associated with the invasive behavior of liver cancer cells

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Abstract

Purpose

The remodeling of the extracellular matrix (ECM) is a key feature of tumor development in the liver, particularly in hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). Fibrosis and cirrhosis are risk factors for tumorigenesis and define serious structural changes in the ECM. Fibrotic-induced collagen and fibronectin alter the stiffness and heterogeneity of the ECM. A stiffened and heterogeneous ECM promotes the proliferation, migration, and invasion of tumor cells. Direct effects of structural changes in the ECM on HCC/iCCA cancer cells are insufficiently studied.

Methods

HCC and iCCA cells were examined in contact with differently structured collagen and collagen-fibronectin networks. The structural architecture of the networks was defined by combining the normalized stiffness, pore size, and network distribution values as the ECM Architectural Index (EAI). The effects of cell-matrix interactions on cell stiffness, invasiveness, and the ability to interact with network structures through fiber displacement in relation to network architecture were determined.

Results

Increased EAI caused a decrease in cell stiffness, an increase in cell invasiveness, and altered fiber displacements. Different effects on HCC and iCCA cells depending on the EAI were identified. High EAI resulted in low cell stiffness and high cell invasion across cancer cell types.

Conclusions

We present a model system that is applicable to identify structurally induced influences of the extracellular matrix on cancer cells and to investigate the risk factor of structural changes in the tumor environment.