Hepatocyte senescence activates hepatic stellate cells to drive liver fibrosis

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Introduction

Cellular senescence is a complex, orchestrated stress response culminating in cell cycle arrest. Senescent cells are resistant to apoptosis and so accumulate within organs, resulting in an age and duration related decline in organ function. The senescent associated secretory phenotype (SASP) generated by senescent cells has both autocrine and paracrine effects. Hepatic stellate cells (HSCs) are responsible for collagen production and extracellular matrix deposition and are the major source of liver fibrosis. Activation of quiescent HSCs is a key event in fibrogenesis. In patients with liver disease across all the common aetiologies, there is a strong association between the number of senescent hepatocytes and fibrosis stage as well as close apposition between senescent (p21+) hepatocytes and tracts of fibrosis.

Aim

We hypothesise that senescent hepatocytes contribute to HSC activation via the SASP in a paracrine manner.

Method

Human HSCs and HSC cell lines were cultured with supernatants generated from untreated (control) or hepatocyte cell lines rendered senescent in vitro. Activation of HSCs was determined by qRT-PCR for pro-inflammatory and pro-fibrotic genes. Western blot analysis was used to confirm activation of related pathways. Collagen and α-smooth muscle actin (αSMA) production were assessed by Western blotting and immunofluorescence.

Results

Supernatants from senescent but not control hepatocyte supernatants activated HSC cell lines and human HSCs to a pro-fibrogenic phenotype in vitro. Pro-inflammatory (IL1β, IL6 and TNFα) and pro-fibrogenic (pro-collagen, αSMA, TIMP1, and TGFβ) gene expression was up-regulated in resting HSCs following 24 hour incubation with supernatants from senescent hepatocytes. In similar fashion MAPK signaling pathways were activated within 30 minutes of exposure to supernatants from senescent hepatocytes. HSCs produced both collagen and αSMA within 48 hours of activation by the senescent hepatocyte secretome.

Conclusion

Senescent hepatocytes activate hepatic stellate cells and drive liver fibrosis in a paracrine manner via the SASP. Inhibition of the SASP in man could reduce hepatic fibrosis.