Dokumenttyp: journal article

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Titel des Beitrags: The impact of MFG-E8 in chronic pancreatitis: potential for future immunotherapy?

Abstract: The glycoprotein MFG-E8 mediates phagocytic clearance of apoptotic cells and influences the pathogenesis and progression of inflammatory diseases. MFG-E8 was shown to attenuate the progression of inflammation and to improve survival in septic rats. Accumulating evidence suggests an immunomodulatory link between MFG-E8 and the pro-inflammatory chemokine fractalkine, which may determine the severity of pain, fibrosis, and inflammation in chronic pancreatitis (CP). The expression and localization of MFG-E8 was investigated in CP (n=62), and normal pancreas (NP; n=34) by QRT-PCR, Western-blot and immunohistochemistry analyses. Results were correlated with mRNA expression of fractalkine, CX3CR1, and with the presence and degree of pain and fibrosis. Human pancreatic stellate cells (hPSCs) were isolated from CP tissues and evaluated for MFG-E8 mRNA expression after fractalkine stimulation. MFG-E8 mRNA was significantly overexpressed in CP and isolated hPSCs when compared to NP. Western-blot and immunohistochemistry analysis confirmed accumulation of MFG-E8 in CP, with noticeably increased MFG-E8 immunoreactivity in tubular complexes. MFG-E8 expression correlated significantly with fractalkine expression, severe fibrosis, and the
presence of pain in CP patients. Stimulation of hPSCs with fractalkine led to a significant increase in MFG-E8 expression. In the present study, we demonstrated for the first time that MFG-E8 is significantly up-regulated in CP patients and together with fractalkine correlated noticeably with severe fibrosis and the presence of pain. hPSCs overexpress MFG-E8 upon fractalkine stimulation in vitro, which underlines the suggested immunmodulatory link in CP and may be a key mechanism in CP fibrogenesis and pain generation. Taken together, these novel findings suggest that MFG-E8 blockade may be a promising tool for future immunotherapy in CP to attenuate both fibrosis and pain sensation.