Titel des Beitrags: Senescence surveillance of pre-malignant hepatocytes limits liver cancer development.

Abstract: Upon the aberrant activation of oncogenes, normal cells can enter the cellular senescence program, a state of stable cell-cycle arrest, which represents an important barrier against tumour development in vivo. Senescent cells communicate with their environment by secreting various cytokines and growth factors, and it was reported that this 'secretory phenotype' can have pro- as well as anti-tumorigenic effects. Here we show that oncogene-induced senescence occurs in otherwise normal murine hepatocytes in vivo. Pre-malignant senescent hepatocytes secrete chemo- and cytokines and are subject to immune-mediated clearance (designated as 'senescence surveillance'), which depends on an intact CD4(+) T-cell-mediated adaptive immune response. Impaired immune surveillance of pre-malignant senescent hepatocytes results in the development of murine hepatocellular carcinomas (HCCs), thus showing that senescence surveillance is important for tumour suppression in vivo. In accordance with these observations, ras-specific Th1 lymphocytes could be detected in mice, in which oncogene-induced senescence had been triggered by hepatic expression of Nras(G12V). We also found that
CD4(+) T cells require monocytes/macrophages to execute the clearance of senescent hepatocytes. Our study indicates that senescence surveillance represents an important extrinsic component of the senescence anti-tumour barrier, and illustrates how the cellular senescence program is involved in tumour immune surveillance by mounting specific immune responses against antigens expressed in pre-malignant senescent cells.