Senescence-associated inflammatory secretome and cancer development

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ABSTRACT

Cellular senescence, a state of irreversible cell proliferation arrest provoked by a variety of potentially oncogenic signals, initially functions as a tumor suppression mechanism. Recent studies, however, reveal that cellular senescence could eventually exhibit tumor-promoting effects such as senescence-associated secretory phenotypes (SASPs), a phenomenon that senescent cells secrete a series of proinflammatory cytokines or matrix-remodeling factors that could contribute to chronic inflammation and/or tumorigenesis. However, since most studies on SASPs were carried out using tissue culture cells, it remains unclear how SASP factors influence chronic inflammation and/or carcinogenesis *in vivo*. Because obesity is known to be associated with chronic inflammation and cancer, we hypothesized that SASPs might affect obesity-associated cancer development. Neonatal mice were therefore treated with a single dose of DMBA, a chemical carcinogen that cause oncogenic mutation in H-Ras gene, followed by high fat diet (HFD) feeding for 30 weeks. Interestingly, a significant number of hepatocellular carcinomas (HCCs) were observed in HFD-, but not normal diet (ND)-fed mice. Note that genetically obese mice fed with normal diet also developed HCCs, indicating that "obesity", but not HFD itself, accelerated development of HCCs. Intriguingly moreover, histological analyses revealed that the hepatic stellate cells in the liver stromal tissue around the hepatocellular carcinoma cells exhibited several features of cellular senescence such as p16 expression, p21 expression, DNA damage and cell cycle arrest. Furthermore, senescent hepatic stellate cells also express multiple inflammatory cytokines including IL6, implying that the secretion of SASP factors from senescent hepatic stellate cells might promote the development of HCCs. Indeed, depletion of senescent hepatic stellate cells by injecting siRNA oligo against HSP47 significantly suppressed HFD-induced HCC development. These results, together with the observation that mice lacking IL6 are somewhat resistant to obesity-induced HCC development, suggest that SASP factors in hepatic stellate cells are likely to promote HCC development. Senescent hepatic stellate cells were also observed in human non-alcoholic steatohepatisis (NASH)-based liver cancers, implying that senescent hepatic stellate cells could be a therapeutic target for NASH-based hepatocellular carcinomas.