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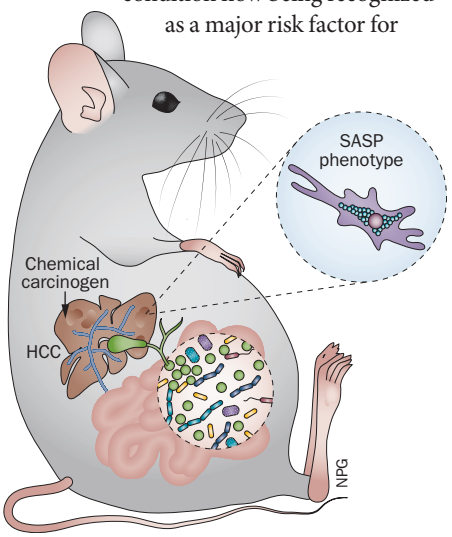
GUT MICROBIOTA

Obesity-induced microbial metabolite promotes HCC

New findings published in *Nature* demonstrate the complex links between obesity, the gut microbiota and the development of cancer. Obesity induces changes to the gut microbiota and its metabolites to promote a senescence-associated secretory phenotype (SASP) in hepatic stellate cells that in turn facilitates the development of hepatocellular carcinoma (HCC) in mice, the authors report.

The prevalence of obesity has continued to increase rapidly worldwide, with the condition now being recognized as a major risk factor for several types of cancer (including HCC and oesophageal cancer). As such, Yoshimoto and colleagues wanted to understand the underlying mechanisms that contribute to the development of obesity-associated cancer, in particular cellular senescence and the role of SASP (that is, secretion of a signature profile of inflammatory cytokines, chemokines and proteases in senescent cells).



The researchers induced tumour development in mice by treatment with a chemical carcinogen at the neonatal stage. These mice were then fed either a high-fat or normal diet as a control for 30 weeks. Strikingly, all mice fed a high-fat diet developed HCC, but not the control mice; genetically obese mice treated with the chemical carcinogen also developed HCC.

Investigating the underlying mechanisms, Yoshimoto *et al.* found that the high-fat diet fed to the mice altered the composition of the gut microbiota, resulting in increased production of deoxycholic acid (a secondary bile acid and metabolic by-product of the gut microbiota known to cause DNA damage). Enterohepatic circulation of deoxycholic acid provoked SASP in hepatic stellate cells, which in turn led to the production of proinflammatory cytokines and tumour-promoting factors in the liver that promote HCC upon exposure to a chemical carcinogen.

Importantly, blocking the production of deoxycholic acid or depleting the gut microbiota (via treatment with oral antibiotics) reduced the development of HCC, alongside a notable decrease in senescent hepatic stellate cells in the mouse model. A similar reduction in HCC tumours was observed in mice lacking a SASP inducer or in those in which senescent hepatic stellate cells were depleted. Interestingly, signs of cellular senescence and SASP (in the hepatic stellate cells located in the area of HCC) were observed in histological samples from 8 of 26 patients with NASH who developed HCC.

"These findings provide valuable new insights into the development of obesity-asssociated cancer and open up new possibilities of control," write the authors.

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Original article Yoshimoto, S. *et al.* Obesity-induced gut microbial metabolite promotes liver cancer via senescence secretome. *Nature* doi:10.1038/12347