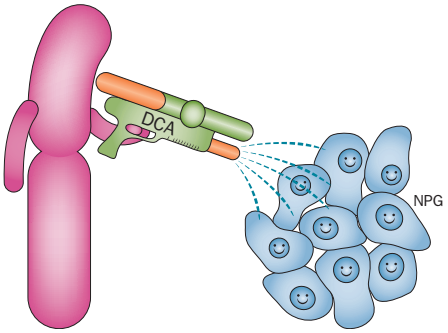
Nature Reviews Clinical Oncology **10**, 428 (2013); published online 9 July 2013; doi:10.1038/nrclinonc.2013.121

LIVER CANCER

Gut microbiota feeds obesity-induced liver cancer



The worldwide increase in obesity means that it has reached epidemic proportions, and obesity is associated with an increased risk of multiple types of cancer. The mechanisms that underlie obesity-associated cancer, however, are poorly understood. Previous studies have shown that senescent cells release inflammatory cytokines and proteases as part of the senescence-associated secretory phenotype (SASP) in response to oncogenic activation. Some SASP factors, such as IL-6 and PAI-1, are known to increase the risk of cancer in obese individuals. Thus, Eiji Hara and coauthors wanted to explore whether SASP contributes to obesity-associated cancer.

In a previous study, Hara and his team had already established a system to visualize the dynamics of the cellular senescence response in living animals. The researchers used a mouse strain in which expression of a gene that induces the SASP could be monitored noninvasively using a bioluminescence imaging technique. Tumour initiation with DMBA (a chemical carcinogen that causes *Ras* mutations at high frequency) caused luminescence in the abdomens of obese mice that were fed a high-fat diet. The researchers demonstrated that these mice developed liver cancer, whereas lean mice fed a standard diet did not. The researchers observed a similar response in mice deficient in leptin, indicating that obesity and diet together can promote liver cancer development.

Crucially, Hara's team showed that changes in the gut microbiota, which can lead to increased levels of deoxycholic acid (DCA)—a gut bacterial metabolite—was responsible for the DNA damage that led to tumour development. High serum levels of DCA were noted in mice fed a high-fat diet, but treatment with the antibiotic vancomycin, to target bacteria found in high abundance in obese mice, reduced both the levels of DCA and the development of liver cancer.

"The most significant finding of our study is that there is a link between obesity and SASP through DCA, a microbial metabolite," explains Hara, who goes on to highlight the clinical implications of these results. "Notably, similar phenotypes were observed in human hepatic stellate cells in patients with nonalcoholic steatohepatitis, suggesting that the mouse model to some extent recapitulates the human situation."

Hara and his team describe their future research plans: "we intend to examine whether our findings can be applied to human obesity-associated cancer by measuring the levels of blood DCA and DCA-producing bacteria in obese people. We also want to know how the population of DCA-producing gut bacteria is increased by obesity. We hope that our future studies will lead to the development of new strategies for cancer prevention."

Lisa Hutchinson

Original article Yoshimoto, S. *et al*. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. *Nature* doi:10.1038/nature12347