Connecting the microbiome to obesity-associated cancers

By Kai-Jye Lou, Senior Writer

Multiple epidemiological studies have shown associations between obesity and increased risk for various cancers,[1,2] but the mechanisms underlying the interplay of the two conditions have been poorly understood. New research from Japan suggests obesity-induced changes in the gut microbiome could be one potential culprit,[3] providing new directions to develop microbiome-targeted diagnostics and interventions.

A team led by Eiji Hara, chief of the Division of Cancer Biology at the **Japanese Foundation for Cancer Research**, has traced the association between obesity and increased cancer risk to gut microbiota communities that produce a DNA-damaging bile acid. The work also elucidates the role of cellular senescence in cancer, something Hara has been studying for the past decade.

Senescence typically is viewed as a tumor-suppressive mechanism, but recent studies by Hara and others have found that senescent cells can take on a secretory phenotype and produce and release inflammatory factors as well as growth factors.[4–6]

Some of the factors secreted by these senescent cells have been associated with increased cancer risk in obesity. Hara's group sought to determine whether cells that take on the senescence-associated secretory phenotype could be an underlying contributor to the increased cancer risk in obesity.

To map out a mechanistic pathway linking obesity to cancer, the researchers carried out a series of studies in mice exposed to a carcinogen that rendered them prone to developing hepatocellular carcinoma (HCC) when obese but not when lean. The obese mice showed increased numbers of hepatic stellate cells with the senescence-associated secretory phenotype and had higher levels of deoxycholic acid, a bile acid produced by certain microbial strains in the gut.

Based on their findings, the researchers hypothesized that obesity can increase the production of deoxycholic acid in select populations of gut bacteria, which in turn increases the appearance of senescent hepatic stellate cells that secrete inflammatory factors and drive the development of HCC (*see* **Figure 1, "Model for obesity-associated liver cancer driven by the gut microbiome"**).

Results were published in *Nature*.

Alterations in gut microbiota have been associated with cancer,[7] inflammation[8] and obesity.[9] The bile acid deoxycholic acid is a metabolite produced by some strains of bacteria in the gut. The acid causes DNA damage[10] and enhances liver carcinogenesis.[11]

Last year, researchers at **Columbia University** published data suggesting gut microbiota and signaling through toll-like receptors can drive inflammatory and fibrogenic responses that contribute to carcinogenesis in the liver.[12]

> **"The importance of the current study is that it gives us an understanding of how these three seemingly disparate phenomena are mechanistically linked with one another."**
> *—Judith Campisi, Buck Institute*

"The importance of the current study is that it gives us an understanding of how these three seemingly disparate phenomena are mechanistically linked with one another," said Judith Campisi, a professor at the **Buck Institute** and a senior scientist at the **Lawrence Berkeley National Laboratory**. "My suspicion, though, is that this will be one of multiple mechanisms that can drive obesity-associated cancers."

Campisi noted that there could be other bile acids that drive obesity-associated cancers as well.

"The current study helps set the stage for identifying the types of bugs and metabolites that could be important to obesity-associated HCC," said Peter DiStefano, SVP of R&D at **Second Genome Inc.** "However, the researchers will need to go beyond enumeration and on to characterizing the functional role of these bugs and metabolites in the context of the disease."

Second Genome is developing therapies that can alter the composition and activity of microbial communities in the body. In June, the company partnered with **Johnson & Johnson**'s Janssen Biotech Inc. unit to characterize the role of bacterial populations in the human gut in ulcerative colitis (UC) and identify potential drug targets.

Exploring opportunities

Hara said his group is planning studies to determine whether the results in the mouse model will translate into humans.

Such studies, he said, would include collecting clinical samples and using them to determine whether levels of deoxycholic acid or deoxycholic acid–producing bacteria are higher in obese individuals than in nonobese individuals.

"If our mouse findings translate into humans, one can imagine the possibility of developing methods to predict obesity-associated cancer risk in the general population, for example, by measuring the levels of deoxycholic acid or deoxycholic acid–producing bacteria in fecal samples," Hara told *SciBX*. He expects the group still is three to four years away from developing such a method.

Campisi said the findings provide general ideas on potential therapeutic and interventional strategies but expects the near-term application of Hara's work is likely to be in the diagnostics space.

"The first area of opportunity is that we can now think about ways to identify and treat obese people who are at risk of cancer based

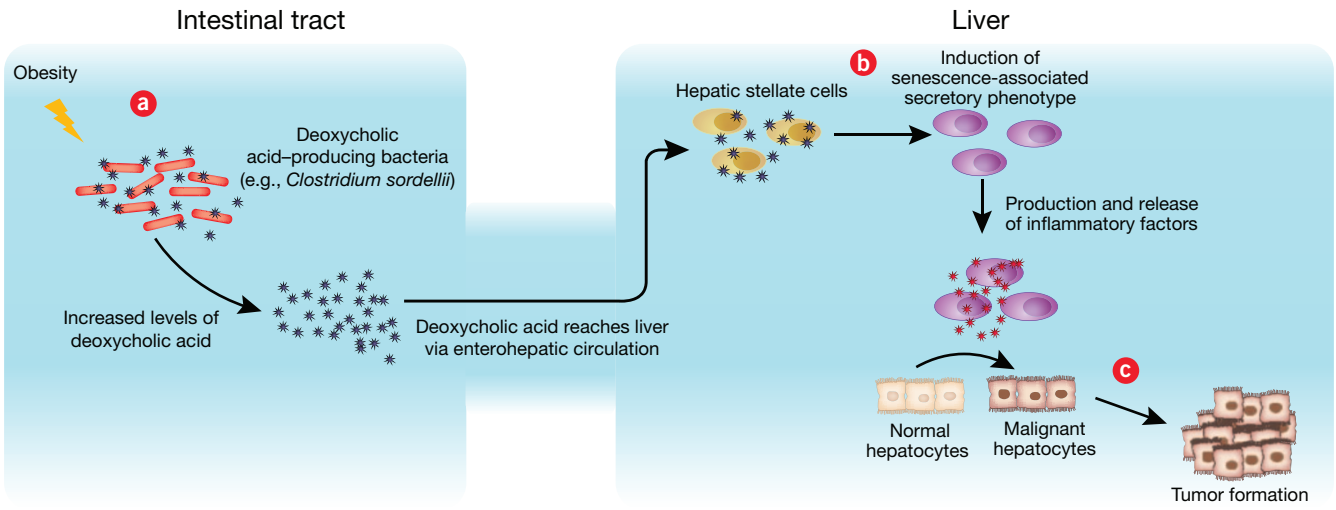

Figure 1. Model for obesity-associated liver cancer driven by the gut microbiome. Obesity is associated with increased risk for various cancers, but the mechanisms underlying the greater risk are unclear. As reported in Yoshimoto *et al.*, obesity appears to drive the development of hepatocellular carcinoma (HCC) through the microbiome.

[**a**] According to the proposed model, obesity results in changes in the gut microbiota that lead to increased levels of deoxycholic acid. [**b**] Molecules of this DNA-damaging bile acid travel via enterohepatic circulation to the liver and induce the senescence-associated secretory phenotype in hepatic stellate cells. [**c**] Inflammatory factors released by the senescent hepatic stellate cells promote malignant transformation in nearby hepatocytes, which leads to tumor formation and HCC.

on targeting the gut microbiota," she told *SciBX*. "A second area one may want to look for therapeutic opportunities is in identifying and interfering with enzymes that mediate the production of deoxycholic acid or other bile acids that could increase cancer risk. A third area of opportunity is in identifying and evaluating compounds that specifically target senescent cells."

"One can imagine the possibility of developing methods to predict obesity-associated cancer risk in the general population, for example, by measuring the levels of deoxycholic acid or deoxycholic acid–producing bacteria in fecal samples."

—Eiji Hara, Japanese Foundation for Cancer Research

Campisi wanted to see studies that identify additional gut microbiome–derived metabolites that are able to induce cellular senescence and what distal tissues they might affect.

DiStefano agreed that it is still too early to pursue specific therapeutic strategies based on the reported findings, but he did note that Hara's work supports the notion that potential targets for diseases in host tissues could reside in microbes.

In addition to determining whether the described mechanism in mice will translate into human systems, DiStefano said it will be important to identify bacterial strains that can alter the amount of deoxycholic acid and to investigate how altering levels of the metabolite will affect the phenotype in HCC and other disease settings.

The Japanese Foundation for Cancer Research has filed a patent covering the reported findings. The work is available for licensing and collaboration. Hara said his group is specifically interested in collaborating with others to develop methods to prevent the growth of bacteria that produce deoxycholic acid and strategies to identify high-risk individuals based on measuring deoxycholic acid levels.

Lou, K.-J. *SciBX* 6(29); doi:10.1038/scibx.2013.743
Published online Aug. 1, 2013

REFERENCES

1. Calle, E.E. & Kaaks, R. *Nat. Rev. Cancer* **4**, 579–591 (2004)
2. Khandekar, M.J. *et al. Nat. Rev. Cancer* **11**, 886–895 (2011)
3. Yoshimoto, S. *et al. Nature*; published online June 26, 2013; doi:10.1038/nature12347
   Contact: Eiji Hara, Japanese Foundation for Cancer Research, Tokyo, Japan
   e-mail: eiji.hara@jfcr.or.jp
4. Kuilman, T. & Peeper, D.S. *Nat. Rev. Cancer* **9**, 81–94 (2009)
5. Rodier, F. & Campisi, J. *J. Cell Biol.* **192**, 547–556 (2011)
6. Takahashi, A. *et al. Mol. Cell* **45**, 123–131 (2012)
7. Arthur, J.C. *et al. Science* **338**, 120–123 (2012)
8. Kamada, N. *et al. Nat. Rev. Immunol.* **13**, 321–335 (2013)
9. Ley, R.E. *et al. Nature* **444**, 1022–1023 (2006)
10. Payne, C.M. *et al. Carcinogenesis* **28**, 215–222 (2007)
11. Kitazawa, S. *et al. Carcinogenesis* **11**, 1323–1328 (1990)
12. Dapito, D.H. *et al. Cancer Cell* **21**, 504–516 (2012)

COMPANIES AND INSTITUTIONS MENTIONED

Buck Institute, Novato, Calif.
Columbia University, New York, N.Y.
Japanese Foundation for Cancer Research, Tokyo, Japan
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Lawrence Berkeley National Laboratory, Berkeley, Calif.
Second Genome Inc., San Francisco, Calif.