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Link Between Obesity and Enhanced Cancer Risk Elucidated

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Debra Kain

Epidemiological studies indicate that being overweight or obese is associated with increased cancer risk. The most dramatic effect of obesity on cancer risk has been noted for a common form of liver cancer called hepatocellular carcinoma or HCC. Modeling the effect of obesity in mice, researchers at the University of California, San Diego School of Medicine have conclusively demonstrated that obesity is tumor-promoting and have obtained evidence that this effect depends on induction of low-grade, chronic inflammation.

Their results, published January 22 by the journal *Cell*, may suggest novel therapy to prevent HCC development in obese men who suffer from chronic liver disease.

Michael Karin, PhD, Distinguished Professor of Pharmacology in UCSD's Laboratory of Gene Regulation and Signal Transduction, who led the study, found that obesity enhanced the development of HCC by stimulating the production of tumor-promoting cytokines - interleukin-6 (Il-6) and tumor necrosis factor (TNF) - that also cause chronic inflammation. Production of these signaling molecules, which are elevated in obese mice and in humans, causes inflammation of the liver and activation of a tumor-promoting transcription factor, a protein called STAT3. This protein in turn activates the formation and growth of liver cancer.

The primary role of TNF is in the regulation of immune cells, but its deregulated production can cause diseases such as rheumatoid arthritis or Crohn's disease. Ironically, while TNF was also tested for its ability to kill cancer, its chronic production was found to actually enhance tumor development.

IL-6 is known to be involved in the pathogenesis of rheumatoid arthritis, but previous work in the Karin lab has shown that IL-6 also contributes to the chronic inflammation that leads to liver cancer. HCC - a devastating complication of chronic liver disease and inflammation caused by risk factors such as hepatitis B and C viruses, or alcoholic liver disease - makes up the majority of liver cancers in humans and is the third-leading cause of death worldwide. Recent epidemiological studies have confirmed the critical role of IL-6 in the progression of viral hepatitis to HCC in humans. However, the mechanisms by which obesity strongly increased the risk of HCC had remained a mystery.

"The chronic inflammatory response caused by obesity and enhanced production of circulating IL-6 and TNF may also increase the risk of other cancers," Karin added.

The actual increase in cancer risk is dependent on the type of cancer and the body-mass-index (BMI). The largest effect of BMI higher than 25 (the recommended BMI level) is seen on HCC; the risk of this type of liver cancer is increased by up to 4.5-fold in men with a BMI of between 35 and 40. But the effect of excess body weight increases the risk of all cancers - 1.5-fold in men and 1.6-fold in women, according to Karin.

"In addition to HCC, obesity markedly increases the risk of pancreatic, gastrointestinal tract and kidney cancers," he said. "Given the prevalence of obesity in the Western and developing worlds, even a modest increase in cancer risk represents a major public health problem."

The new UCSD research suggests that anti-TNF drugs, currently used in the treatment of chronic inflammatory diseases, may be used to prevent HCC development in obese men who suffer from chronic liver disease. According to the studies in mice, inhibition of TNF signaling may even prevent hepatosteatosis, or accumulation of fat in the liver.

Additional contributors to the paper include Eek Joong Park, Jun Hee Lee, Guann-Yi Yu,Guobin He, Syed Raza Ali, Ryan G Holzer, and Hiroyuki Takahashi, UCSD Laboratory of Gene Regulation and Signal Transduction, Departments of Pharmacology and Pathology; and Christoph H. Österreicher, UCSD Department of Medicine.

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Media Contact: Debra Kain, 619-543-6163, ddkain@ucsd.edu