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Why Liver Cancer Is More Prevalent in Males than in Females

Production of a protein that promotes inflammation appears to be linked to the higher incidence of liver cancer in men than in women, researchers at the University of California, San Diego (UCSD) School of Medicine have determined in mouse studies. Their discovery that female mice produce far less of the protein called interleukin-6 (IL-6) in response to liver injury than males do, and that production of this protein is suppressed by estrogen, may point the way to therapies to reduce the incidence of liver cancer in males. IL-6 contributes to the chronic liver inflammation that leads to cancer.

The research team was led by Michael Karin, Ph.D., professor of pharmacology in UCSD's Laboratory of Gene Regulation and Signal Transduction. The findings will be published in the July 6 issue of the journal *Science*.

"Males show a higher rate of inflammation than females in the same diseases, including cancer," said Willscott Naugler, M.D., clinical instructor in UCSD's Department of Medicine and first author of the paper. "We wondered if increased inflammation was behind the higher incidence of liver cancer in males and, if so, how and why?"

Heptocellular carcinoma (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. Overall, men are three to five times more likely to develop HCC than women; however, in individuals who are under 50, HCC is seen seven to 10 times more frequently in men. A similar or even more pronounced gender disparity is seen in mice.

In order to understand the mechanisms underlying gender disparity in HCC, the UCSD researchers used a chemical carcinogen, DEN, to induce cancer in mice. This resulted in HCC in 100 percent of male mice, but only in 10 to 20 percent of their female littermates.

The researchers discovered that normal female mice given DEN produced far less IL-6 than the males. Comparing the normal mice to knockout mice missing the IL-6 cytokine, the scientists found that when knockout mice were given DEN, both males and females developed liver cancer at the same, lower, rates.

"By eliminating IL-6, we reduced the incidence of liver cancer in the males by close to 90%," Karin said. "However, the missing IL-6 made no further difference in female mice."

The researchers then treated normal male mice with estrogen, and exposed them to DEN. The IL-6 level in those males was reduced to the same level as in female mice, as was the degree of liver injury. Experiments on specialized cells in the liver that produce IL-6 showed that estrogen acts on these cells to suppress IL-6 production.

A similar mechanism may account for the gender bias in liver cancer in humans, according to the researchers. Their discovery could lead to development of therapies to reduce development of liver cancer in males by either decreasing the levels IL-6 in males, interfering with IL-6 action or by administering estrogen-like compounds to males in order to inhibit production of IL-6.

"While some organs, such as breasts, are clearly influenced by gender, others – like the liver – are not," said Naugler. "So it's quite interesting that liver inflammation is so markedly suppressed by estrogens. It raises the possibility that organs not usually associated with gender differences may be governed by the same principle. Bladder cancer, for example, occurs more frequently in males than females, and the differences may be a result of higher IL-6 levels and inflammation in male bladders."

Additional contributors to the paper include Toshiharu Sakurai, Sunhwa Kim, KyoungHyun Kim and Ahmed M. Elsharkawy of UCSD's Laboratory of Gene Regulation and Signal Transduction, Department of Pharmacology and Cancer Center; and Shin Maeda, Division of Gastroenterology, Asahi Life Foundation, Toyko. The study was funded in part by the National Institute of Diabetes and Digestive and Kidney Diseases, the Japan Society for the Promotion of Science, the Human Frontier Science Program, and the National Institute of Health and National Cancer Institute. Michael Karin is an American Cancer Society Research Professor.