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INSIGHTS

Gender disparity in HCC: Is it the fat and not the sex?

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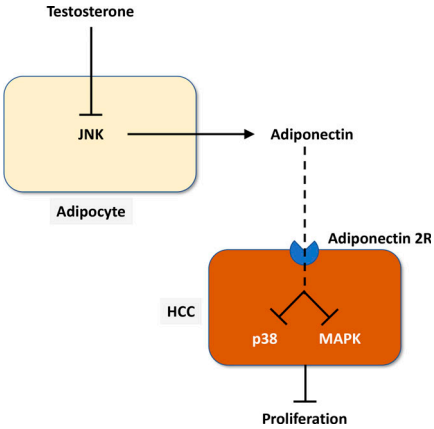
Men are more likely to develop hepatocellular carcinoma (HCC) than women, but it is not clear why. In this issue of *JEM*, Manieri et al. (https://doi.org/10.1084/jem.20181288) identify reduced adiponectin levels as responsible for the increased incidence of HCC in males.

According to the latest estimates of the World Health Organization, 2.35-fold more men were expected to die from primary liver cancer than women. Hepatocellular carcinoma (HCC) was the fourth most common cause of cancer-related death worldwide in 2018, and we know of a number of risk factors such as chronic viral hepatitis, alcohol, liver cirrhosis, and rare genetic conditions (Forner et al., 2018). However, it is not clear why men are more likely to develop HCC than women. Manieri et al., from the Centro Nacional de Investigaciones Cardiovasculares Carlos III, identified a novel mechanism explaining this observation in an accompanying article in this issue of *JEM* (Manieri et al., 2019). The group has studied adiponectin induction and effects on tumor growth in male and female mice as well as adiponectin serum levels in men and women. They come to the conclusion that the lower adiponectin levels found in men account for the increased incidence of HCC in men. Starting out with the observation that both men and male mice have lower adiponectin blood levels, Manieri et al. (2019) observed a faster growth of subcutaneously injected HCC allografts in male mice than in female, which was not seen in castrated or adiponectin knockout mice. Adiponectin overexpression rescued male mice from diethylnitrosamine-induced cancers, which also demonstrated no gender differences. This effect was adiponectin R2 dependent, since female mice demonstrated accelerated tumor growth of adiponectin R2 knockdown tumors, and interestingly, only HCC tumors, but not melanoma or the colon cancer cell line, expressed this receptor, which also explains the specific effect in the context of HCC but not other tumors. Finally, adiponectin overexpression reduced the number of tumors in mice treated with diethylnitrosamine, a carcinogen commonly used in mice for the induction of HCC.



Testosterone supports controls HCC growth by inhibiting adiponectin production.

Next, the authors studied the mechanism of how gender disparity influences adiponectin and the subsequent control on HCC tumor growth. They already knew from earlier studies that JNK in adipose tissue controls adiponectin production (Manieri and Sabio, 2015). Indeed, the authors noticed a sex-dependent difference in JNK activation in adipose tissue and demonstrated that testosterone activates JNK in adipocytes. Adipose tissue–specific deletion of JNK-1 led to higher adiponectin levels in male mice and impaired tumor growth. Next, the authors crossed adiponectin knockout mice with adipose tissue–specific JNK-1–deficient mice and assessed HCC tumor growth. Importantly, there was no difference in tumor growth in JNK-1–deficient and –proficient mice when adiponectin was knocked out. These data, in combination with the results using adiponectin R2 knockdown tumors, led to the question, how does adiponectin impair HCC growth? Adiponectin is known to signal through activation of two pathways: p38 MAPK and AMPK. p38 and AMPK are both known to suppress liver cancer development, and the authors provide data demonstrating that adiponectin activates these pathways in tumor cells in female mice, leading to reduced tumor growth. Thus, testosterone controls HCC tumor growth through a JNK-dependent reduction of adiponectin production in adipocytes preventing AMPK and p38 activation in HCC cells through an adiponectin R2–dependent pathway.

Insights from Tim F. Greten.

This is only the second study in the field addressing the interesting question of why male individuals are at higher risk for HCC. A prior study from Michael Karin's group pointed toward a critical role of IL-6 for the

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observed gender differences in hepatocarcinogenesis. In this case, estrogen inhibited secretion of IL-6 from Kupffer cells exposed to necrotic hepatocytes, leading to reduced IL-6 serum levels and less tumor growth (Naugler et al., 2007). Interestingly, adiponectin has also been shown to block IL-6 production in macrophages (Folco et al., 2009), providing a possible link between these two very interesting studies. These two cytokines, adiponectin and IL-6, also play a very important role in another important medical condition relevant for HCC: nonalcoholic fatty liver diseases. Elevated IL-6 and reduced adiponectin have been reported to correlate with the presence of visceral fat and end-organ inflammation (van der Poorten et al., 2008). Thus, pharmacological intervention of these pathways may be of interest and should be further pursued to identify possible new treatment options for HCC. As a matter of fact, metformin activates AMPK treatment and reduces growth of Hep53.4 tumors in vivo (Manieri et al., 2019); however, it is not clear if similar effects are seen in male and female mice. The data on the use of metformin as a putative chemo-preventive agent are accumulating in HCC (Chen et al., 2013), and clinical trials evaluating its efficacy in advanced disease are ongoing.

From an epidemiological point of view, one interesting question remains. Without any doubt, HCC is more common in men than in women, and this gender difference can be seen worldwide.However, there are a few exceptions to this rule. According to the latest data from the World Health Organization, an equal number of men and women die from HCC in Guatemala. It is not clear if patients in Guatemala are exposed to different risk factors than the rest of the world, but it would be interesting to study adiponectin levels in this patient cohort.

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