

Building a bridge between obesity, inflammation and liver carcinogenesis

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COMMENTARY ON:

Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Eek Joong Park, Jun Hee Lee, Guann-Yi Yu, Guobin He, Syed Raza Ali, Ryan G. Holzer, Christoph H. Österreicher, Hiroyuki Takahashi and Michael Karin. *Cell*, January 2010;140(2):197–208. Copyright 2010. Abstract reprinted with permission from Elsevier Inc. www.ncbi.nlm.nih.gov/pubmed/20141834

Abstract: Epidemiological studies indicate that overweight and obesity are associated with increased cancer risk. To study how obesity augments cancer risk and development, we focused on hepatocellular carcinoma (HCC), the common form of liver cancer whose occurrence and progression are the most strongly affected by obesity among all cancers. We now demonstrate that either dietary or genetic obesity is a potent bona fide liver tumor promoter in mice. Obesity-promoted HCC development was dependent on enhanced production of the tumor-promoting cytokines IL-6 and TNF, which cause hepatic inflammation and activation of the oncogenic transcription factor STAT3. The chronic inflammatory response caused by obesity and enhanced production of IL-6 and TNF may also increase the risk of other cancers.

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In developed countries, obesity and overweight pose major health problems because of chronic diseases and the increased mortality rate related to these conditions. Among the obesity related diseases, cancer has a particular position. In 2003, in a large prospective study, Calle and collaborators found that increased body-mass index (BMI) was significantly associated with increased death rates for all cancers combined. In this study, liver tumors showed the highest increase of risk in men with BMI ≥ 35 (RR = 4.52 CI 95% [2.94–6.94]), whereas in women this excess of risk was lower (RR = 1.68, CI 95% [0.93–3.05]) [1]. Based on clinical and biological associations, several explanations have been proposed to elucidate how obesity could promote the devel-

opment of hepatocellular carcinoma (HCC). First, obesity is known to induce the development of non-alcoholic steatohepatitis (NASH) that is clearly identified as a risk factor for HCC suggesting that insulin resistance and inflammation could promote tumor development. Moreover, as a paradigm, chronic inflammation has been associated with tumor promotion in various diseases and a link between inflammation and tumor development has been clearly demonstrated [2]. In this line, the team of Michael Karin has previously shown that interleukin 6 (IL-6), a pro-inflammatory cytokine produced by Kupffer cells, participates in hepatocarcinogenesis in mouse [3]. They also showed that in females, estrogens inhibit IL-6 production, a possible clue for the enigma of gender difference in HCC occurrence found in epidemiologic data. However, until recently, experimental data analyzing and dissecting the functional consequences of obesity and non-alcoholic fatty liver disease (NAFLD) in inflammation and HCC formation were lacking.

In a study published in January in *Cell*, Michael Karin's team addressed this issue using an elegant strategy [4]. They studied the development of HCC chemically induced by diethylnitrosamine (DEN) in C57/BL6 mice with normal or high fat diet resulting in dietary obesity. HCC was also induced by DEN in a leptin deficient mouse, a classical model for genetic obesity. In this experiment, the authors showed that dietary and genetic obesity strongly enhance the development of HCC with an increased number and size of the tumors when compared to DEN mice on normal chow. Tumors developed in obese mice demonstrated an increased cell proliferation and a decrease in apoptosis, even if HCC were transplanted in lean mice. Obese mice showed an enhanced expression and a high serum level of inflammatory cytokines, especially IL-6 and TNF α (tumor necrosis factor alpha). These two cytokines were responsible, in non-tumor and tumor tissues, of the activation of STAT3 by phosphorylation. STAT3 is an oncogenic transcription factor known to be activated in several tumor types in humans and it is the major transcription factor responsible for the acute inflammatory response in hepatocytes. To demonstrate the key role of IL-6 and TNF α in the increased development of HCC, the authors injected DEN in obese mice genetically inactivated for IL-6 or for the TNF receptor 1 (TNFR1). In KO mice, the promotion of obesity-increased rate of HCC was suppressed. The absence of IL-6 or TNFR1 also prevented the obesity-induced increase in JNK, ERK, and STAT3 phosphorylation. Moreover, obese mice KO for IL-6 and TNF receptor have a lower amount of lipid in the liver and also less inflam-

Received 27 April 2010; received in revised form 19 May 2010; accepted 19 May 2010
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matory infiltrates than obese wild type mice. From these results, we can conclude that IL-6 and TNF α are key factors in activating cell proliferation and in increasing tumorigenesis through STAT3 phosphorylation in obese mice. Moreover, IL-6 and TNF α are also necessary in obese mice for the development of steatosis and steatohepatitis typically found in humans NAFLD (Fig. 1).

One of the important results of this paper is the link demonstrated between the etiology of chronic liver disease (NAFLD) and a particular mechanism of tumor promotion through pro-inflammatory cytokine signaling. It also underscores the role of the IL-6/JAK/STAT signaling pathway that will provide insights into our understanding of hepatocarcinogenesis. STAT3 is consid-

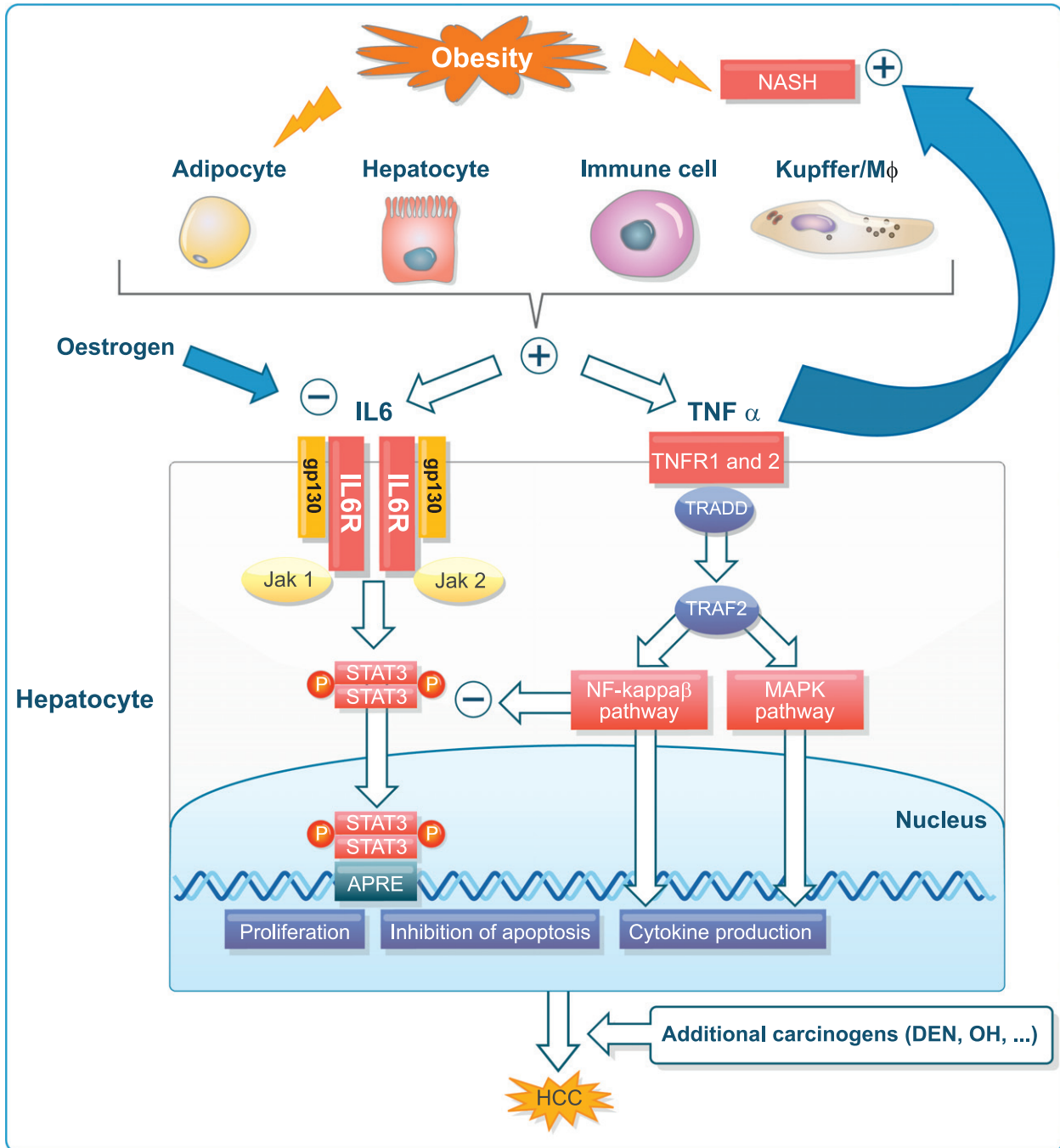


Fig. 1. Implication of IL-6 and TNF α pathway in obesity related hepatocarcinogenesis. NASH, non-alcoholic steatohepatitis; IL-6, interleukin 6; TNF α , tumor necrosis factor α ; IL-6R, IL-6 receptor; JAK 1/2, janus kinase 1 and 2; gp130, glucoprotein 130; STAT3, signal transducer and activator of transcription 3; APRE, acute phase response element; TNFR1/2, TNF receptor 1 and 2; TRADD, tumor necrosis factor receptor type 1-associated DEATH domain protein; TRAF2, TNF receptor-associated factor 2; MAPK, mitogen-activated protein kinase; NF-kappa β , nuclear factor K β ; DEN, diethylnitrosamine; OH, alcohol; HCC, hepatocellular carcinoma; M ϕ , macrophage.

ered as an oncogene in a mouse model of activating mutation [5] but also it has been found activated, through its phosphorylation, in many types of human cancer including HCC [6]. Interestingly, the group of Michael Karin has recently shown in a mouse model that IKK β /NF-kappa β prevents ROS accumulation, STAT3 related activation, and tumor progression [7]. Underlining the importance of the IL-6 pathway in tumorigenesis, we also identified recurrent somatic mutations activating gp130, the transducer of signals for IL-6, in 60% of the benign hepatocellular adenomas with inflammatory phenotype and also in a small subset of HCC [8]. These observations suggest that IL-6 activation could be an early event in hepatocellular tumorigenesis both in mice and humans. This could have a very promising therapeutic implication since the IL-6/JAK/STAT pathway could be specially targeted, for example by a JAK inhibitor developed initially against hematopoietic malignancy. As demonstrated in the present study, treatment with JAK inhibitor (AG490) is followed by a dramatic reduction of tumor growth and STAT3 activation of the DEN-induced HCC in obese mice. On the other hand, the authors showed that obesity activates the mTOR pathway together with AKT inactivation in the non-tumor liver tissues. This result suggests that mTOR inhibitors could be more efficient to prevent the occurrence of HCC related to obesity than targeting AKT itself.

These important findings lead us to ask new questions. In the obese mouse model, induction of liver tumors required DEN; obesity and high levels of cytokine alone are not sufficient. Carcinogen exposure is needed to promote tumorigenesis. In this model, activation of the IL-6 and the TNF α pathways alone is probably not sufficient to induce HCC and the accumulation of other somatic alterations induced by carcinogen exposure are required. In the same way, in humans, gp130 activation is mainly related to benign tumorigenesis and in malignant liver tumors, gp130 is associated with additional β -catenin activating mutations, the oncogene the most frequently mutated in human HCC. Thus, cooperation of IL-6/STAT3 with other carcinogenesis pathways remains to be explored. Finally, in obese mice, adipocytes, Kupffer cells, or hepatocytes can produce IL-6 and TNF α . In the present model, as in human NAFLD, it remains important

to precisely understand the “*primo movens*” of the pro-inflammatory state according to its cellular origin and its role in hepatocarcinogenesis.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Acknowledgment

J.-C.N. is supported by a fellowship from the Association pour la Recherche sur le Cancer (ARC).

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