Hepatocellular Carcinoma Column: Editorial

Glucose intolerance and hepatocellular carcinoma: recent findings for old diseases

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Abstract: In the last years, an increasing number of evidences on the influence of metabolic syndrome on the occurrence of hepatocellular carcinoma (HCC) have been developed. Type 2 mellitus diabetes (T2MD) has been found to increase the occurrence of primary liver tumors and to define a more aggressive carcinogenetic process. Furthermore, several preclinical and observational studies and a recent meta-analysis have shown that anti-diabetic drugs can modify the risk of HCC development in patients with T2DM. However, despite these evidences, underlying molecular mechanisms linking both pathological conditions have to be completely cleared yet. The study published by Gao *et al*. has found a possible molecular link between the two conditions, describing the predisposition to T2DM and HCC given by the haploinsufficiency of nuclear receptor coactivator 5 (NCOA5) in murine models. The authors have generated Ncoa5+/– (haploinsufficient) male mice and shown that 94% of male mutant mice developed HCC within 18 months of age, this in contrast with Ncoa5+/+ and Ncoa5+/– female mice. These results suggest that NCOA5 haploinsufficiency is linked to HCC development in male mice. Moreover, mutant male mice showed significantly elevated levels of fasting blood glucose and markedly decreased glucose tolerance and insulin sensitivity compared to Ncoa5+/+ littermates. This well-constructed work sheds light on the molecular link between T2DM and HCC and opens the way to further biological and clinical studies in the field of liver tumor prevention and treatment.

Keywords: Nuclear receptor coactivator 5 (NCOA5); interleukine-6 (IL-6); hepatocellular carcinoma (HCC); diabetes mellitus

Submitted Feb 18, 2014. Accepted for publication Feb 24, 2014.
doi: 10.3978/j.issn.2304-3881.2014.02.15
View this article at: http://www.thehbsn.org/article/view/3497/4543

In the last years, an increasing amount of researches on the influence of glucose intolerance and, in general, of the main features of metabolic syndrome on the occurrence of hepatocellular carcinoma (HCC) have been developed.

Type 2 mellitus diabetes (T2MD) has been found to increase the occurrence of primary liver tumors and to define a more aggressive carcinogenetic process, thus hallmarking a subset of tumors at poorer prognosis, even after curative treatments (1,2).

Furthermore, several preclinical and observational studies have shown that anti-diabetic drugs can modify the risk of HCC development in patients with T2DM (1). This finding has been confirmed in a recent meta-analysis (3).

Despite these evidences, underlying molecular mechanisms linking both pathological conditions have to be completely cleared yet.

Although the role of inflammation in the pathogenesis of metabolic syndrome and HCC is well-known (4,5), definitive data on inflammatory cytokines involved in both pathways (i.e., glucose intolerance and liver carcinogenesis) are lacking. Among such molecules, an increasing interest has been focused on interleukine 6 (IL-6). A recent work by He *et al*. has cleared the tumor promoting role of IL-6 in HCC (6) and its involvement in inducing hepatic insulin resistance is renown (7). Gao *et al*. have found a possible molecular link between the two conditions, describing the predisposition to T2DM and HCC given by the haploinsufficiency of nuclear receptor coactivator 5 (NCOA5) in murine models (8). NCOA5 is known to modulate estrogen-mediated signaling pathways and to suppress IL-6 expression (9,10).

Gao *et al*. have generated Ncoa5+/– (haploinsufficient) male mice and shown that 94% of male mutant mice developed HCC within 18 months of age. This in contrast with Ncoa5+/+ and Ncoa5+/– female mice. These results suggest that NCOA5 haploinsufficiency is linked to HCC development in male mice. In order to demonstrate a correlation between NCOA5 gene and T2DM, mice underwent glucose tolerance tests and Ncoa5+/– male mice showed significantly elevated levels of fasting blood glucose and markedly decreased glucose tolerance and insulin sensitivity compared to Ncoa5+/+ littermates. The proposed mechanism is inhibition of both hepatic insulin signaling and pancreatic beta cell compensation.

At the age of 6-10 months, Ncoa5+/– males showed all the degrees of liver inflammation, from the steatosis up to fibrosis and subsequent dysplasia. As a consequence, serum alanine aminotransferase, alpha-fetoprotein, and hepatic triglycerides were elevated with respect to wild-type mice. Moreover, the Ncoa5+/– liver exhibited more cell death and compensatory proliferation, a key driver of carcinogenesis. Additionally, authors demonstrated the effect of NCOA5 haploinsufficiency on *IL-6* gene expression (namely, in increasing its expression). Increased IL-6 expression reduced insulin sensitivity, via STAT3 and SOCS3 activation, and HCC burden, as already found by He *et al*. (6).

Moreover, other molecules other than IL-6 have been found by Gao *et al*. to play a pivotal role in the different pathologies exhibited by Ncoa5+/– mice. Among them, androgen receptor (AR) and TGF-b which are both negatively regulated by NCOA5.

Finally, Gao *et al*. found that NCOA5 expression is significantly reduced in 40% of HCC tissues as compared to the adjacent non-tumoral area.

Despite the big amount of data provided by Gao *et al*., some aspects remain controversial.

First of all, environmental and dietary factors somehow influence the development and the pathological course of T2DM and HCC. Further studies, conducted in human subjects, are warranted in order to better specify the role of nutrients and environment in NCOA5 modulation and in which degree such a regulatory effect induces HCC and diabetes occurrence. Second, the influence of male gender on the results shown in this study needs to be further defined, particularly hormonal factors (for instance the aforementioned link between estrogen signaling and NCOA5) have to be investigated. Lastly, further details on the pathogenetic role of NCOA5 in diabetes occurrence need to be cleared.

However, this well-constructed work sheds light on the molecular link between T2DM and HCC and opens the way to further biological and clinical studies in the field of liver tumor prevention and treatment. Furthermore, it reinforces the role of inflammatory mediators and estrogen signaling in liver carcinogenesis, framing these concepts in the more general topic of the correlation between metabolic syndrome and HCC.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Facciorusso A, Barone M. Glucose intolerance and hepatocellular carcinoma: recent findings for old diseases. Hepatobiliary Surg Nutr 2014;3(2):91-92. doi: 10.3978/j.issn.2304-3881.2014.02.15