Editorial

NCOA5, a molecular link between type 2 diabetes and liver cancer

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Abstract: It is reported that nuclear receptor co-activator 5 (*NCOA5*) is a possible susceptibility gene to both type 2 diabetes (T2D) and hepatocellular carcinoma (HCC). The link between these two diseases is an important area of study with the growing prevalence of T2D. Thus, discovery of a genetic link may have great impact on the field. The group used *NCOA5*$^{+/-}$ mice to observe the effects of the gene's haploinsufficiency on the symptoms of T2D and HCC and claimed *NCOA5*'s regulation of *IL-6* in the pathogenesis of the diseases.

Keywords: Nuclear receptor co-activator 5 (*NCOA5*); hepatocarcinoma; type 2 dibetes (T2D)

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According to a February 2014 report from the World Health Organization (WHO), liver cancer is escalated to be the 2nd leading cause of cancer-related death worldwide (after lung cancer). Hepatocellular carcinoma (HCC) is a major form of liver cancer with more than 700,000 diagnosed cases yearly (1). Many risk factors including gender, hepatitis B and C, cirrhosis, and obesity have been known to be associated with the cancer development (2). Recent epidemiological studies indicate that type 2 diabetes (T2D) results in a three-fold increased risk of HCC and is associated with a more grim prognosis and clinical course for HCC patients, independent of the underlying cirrhosis (3). Although the correlation of T2D with HCC development has been widely recognized, the molecular mechanisms connecting these two diseases are poorly understood. T2D is becoming increasingly prevalent in both the developed and the developing world while other risk factors such as hepatitis B and C are declining (4). As a result of this increasing prevalence, the need to investigate the linkage between T2D and HCC grows more important. Previous work has implicated inflammation in the pathogenesis of T2D and HCC (5), pointing specifically to proinflammatory cytokines such as *IL-6* and TNF-α (6), but a genetic link between these molecules and the diseases remains unclear.

In a most recent report (7), Gao and his colleagues described a link between these two diseases by investigating the role of nuclear receptor co-activator 5 (*NCOA5*). The interest in *NCOA5* sprouted from linkage analysis showing that the *NCOA5* gene lies in the 20q13.1 region that was shown to be associated with T2D (8). This suggests a possibility of *NCOA5* to be an important gene in the development of the two diseases. *NCOA5* encodes for a co-regulator for the estrogen receptors (ER) α and β, and the orphan nuclear receptor Rev-ErbAβ and is known to modulate ERα-mediated transcription (9). The group investigated the role of *NCOA5* in the pathogenesis of T2D and HCC, in the context of inflammation, particularly *IL-6* involvement.

In this study, *NCOA5* knockout mice were generated in two genetic backgrounds and male mice that were *NCOA5*$^{+/-}$ (homozygotes were infertile) developed apparent late-onset HCC by 18 months. Female mice with the same genotype, however, did not develop these tumors. It was also shown that mutant male mice became insulin resistant at a relatively young age. Consistent with this observation, insulin stimulated phosphorylation of IR-β, IRS-1 and AKT was reduced in livers of *NCOA5*$^{+/-}$ mice. Moreover, *NCOA5* haploinsufficiency resulted in insufficient β-cell compensation and decreased size and number of islets as

compared to wild-type mice. Mice with insulin resistance, but without HCC (6-10 months), developed hepatic inflammation, steatosis, and dysplasia. In addition, the liver of *NCOA5*$^{+/-}$ mice had increased serum levels of alanine aminotransferase and α-fetoprotein. These results indicate that *NCOA5*$^{+/-}$ mouse livers have a micro-environmental niche primed for HCC development.

The authors also showed that *NCOA5* deficiency resulted in elevated *IL-6* expression in Kupffer cells in male mice. This increased *IL-6* expression led to increased activation of Stat3 and Socs3, which are known to be negative regulators of insulin signaling. The group then sought to investigate how *NCOA5* may regulate *IL-6* expression. *NCOA5* is a known regulator of ERα and ERα, which negatively regulates NF-κB-induced *IL-6* expression (9). Indeed, quantitative chromatin immunoprecipitation (qChIP) in mouse macrophage cells demonstrated increased *NCOA5* and ERα recruitment to the *IL-6* promoter with estrogen stimulation. In addition, a reporter gene assay showed that *NCOA5* decreased LPS-induced NF-κB-mediated *IL-6* promoter activity. Increased RNA Pol II recruitment to the *IL-6* promoter was also detected in *NCOA5*$^{+/-}$ livers. Therefore, these results indicate that *NCOA5* haploinsufficiency increases *IL-6* gene transcription by disrupting ERα-mediated repression of *IL-6* transcription. To test the role of *IL-6* on glucose intolerance and HCC development in *NCOA5*$^{+/-}$ male mice, the group generated *NCOA5*$^{+/-}$*IL-6*$^{+/-}$ mice, which express marked decrease in *IL-6* expression in the liver. Decreased *IL-6* expression significantly improved fasting blood glucose, insulin resistance and tumor nodule size but was unable to stop the initiation of HCC in male mice.

While *IL-6* is important in the development of glucose intolerance and HCC, Gao *et al.* (7) attempted to identify other possible genes that could be involved. By using mouse signal transduction pathway PCR array, they identified multiple HCC-related genes in the NF-κB, androgen and insulin pathways such as androgen receptor (AR), fatty acid synthase (FAS), and TGF-β that are negatively regulated by *NCOA5*. The precise roles of these genes in HCC development induced by *NCOA5* deficiency remain to be defined in the future. Finally, the group analyzed human HCC tissue samples and found *NCOA5* expression was significantly reduced in 40% of tumors compared to the adjacent non-tumor tissues. Sequencing results revealed an alternatively spliced isoform of *NCOA5* mRNA, which codes for s-*NCOA5*, a truncated protein that lacks the transcriptional activation domain. The expression of this truncated form was elevated in 43% of HCC samples compared to the adjacent non-tumor tissues.

While the report clearly states a link between T2D and HCC, the mouse phenotype showed only insulin resistance and glucose intolerance and thus cannot definitively be characterized as T2D. However, it is prefaced that *NCOA5* is merely a susceptibility gene and not a causative gene. In addition, the data showed smaller pancreatic islet sizes in the heterozygous animals, with no functional assay of β cell functions. Experiments to measure pancreatic β cell function, and assays to examine hepatic glucose production and peripheral insulin sensitivity in adipocytes and muscles in *NCOA5*$^{+/-}$ and wild-type mice will be necessary. Since T2D is implicated in many cancers and is becoming increasingly prevalent in developed countries, identification of *NCOA5* haploinsufficiency as a possible link between T2D and HCC may have profound impact on the field. In addition, the mouse model created from the study can be used as a means to probe the therapeutic effect of pharmaceuticals on HCC patients with T2D. Future studies should be aimed at identifying factors that modulate *NCOA5* expression as well as a more detailed explanation of *NCOA5*'s effect on insulin production and β-cell function. This study provides new insights into the molecular mechanism underlying T2D and HCC, and suggests that inhibition of *IL-6* may be a therapeutic window for modulating this effect.

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