

Pharmacological blockage of CYP2E1 and alcohol-mediated liver cancer: is the time ready?

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Chronic alcohol consumption is a major risk factor worldwide affecting significantly both mortality and years of life lost (YLL) (1). *Ca.* 5% of the western world show risky alcohol consumption and in some countries such as China a regional yearly increase of alcohol consumption of over 400% has been observed recently (2,3). The liver is the major target organ of alcohol. According to the recently published 'Global Burden of Disease Study 2010', liver cirrhosis and liver cancer are ranked at position 12 and 16 in the global deaths statistics (1). Thus, in 2010, *ca.* 1 million people died from liver cirrhosis with one third directly attributable to alcohol. This is a considerable number when comparing with coronary heart disease with 7 million deaths and the leading cause of mortality. In central Europe, liver cirrhosis even ranks at the fourth position in YLL. Hepatocellular cancer (HCC) is now the most common fatal complication of patients with alcoholic cirrhosis. Moreover, it shows the second fastest increase of all tumors worldwide after kidney tumors and alcohol-associated HCC ranks on third position after HCCs caused by viral hepatitis B and C.

These epidemiological data explain the high interest and rationale in better understanding the molecular mechanisms of alcohol-driven hepatocarcinogenesis to identify novel targeted approaches for the future. Indeed, alcohol itself has only recently been recognized as carcinogen. Carcinogenesis by alcohol is complex and still poorly understood which has many reasons (4). First, it is rather the metabolites and side products such as acetaldehyde or reactive oxygen species (ROS) via enzymatic reactions that render alcohol highly toxic. These metabolites are largely dependent on the genetic background, induction kinetics

and other detoxifying capacities (5). Second, side products such as ROS are still difficult to measure and to model so that we still lack enough information which species are generated in which compartments and to which extent (6). Finally, animal models drastically differ from humans with regards to alcohol sensitivity, metabolism and consequences namely with regard to the liver.

In this context, the work by Ye *et al.* deserves great attention and puts our understanding of alcohol-mediated carcinogenesis an important step further (7). In his pioneering work, Charles Lieber could establish the cytochrome P4502E1 (CYP2E1)-dependent microsomal ethanol oxidizing system (MEOS) as an important pathway of ethanol metabolism (8). The induction of CYP2E1 by chronic alcohol intake results in an enhanced activation of procarcinogens to carcinogens, induction of oxidative stress, and release of inflammatory mediators (9). Deletion of CYP2E1 in mice has been shown to decrease ROS and DNA adduct formation (10) and less diethylnitrosamine (DEN)-induced hepatic tumors (11). Notably, the CYP2E1 inhibitor chlormethiazole (CMZ) has been shown to protect from ethanol-induced liver injury in rodents and DNA adduct formation in human hepatoma cells over-expressing CYP2E1 (12). However, a direct evidence of CMZ-protection in ethanol-promoted hepatocarcinogenesis *in vivo* was still missing.

In the present study, using CMZ as an inhibitor of CYP2E1, Ye *et al.* demonstrated for the first time a clear role of CYP2E1 in a DEN-initiated but ethanol-promoted hepatocarcinogenesis rat model. CMZ significantly reduced hepatic expression of CYP2E1. They observed significantly more pre-neoplastic lesions (p-GST positive

foci) in ethanol-fed rats without CMZ after one month and independent of DEN. Although the model did not allow to observe carcinoma but adenoma and the group size was limited to six animals, the data are striking and show for the first time a clear protection from ethanol-driven hepatocarcinogenesis using a pharmacological approach. The authors also present first mechanistic insights: In line with previous report (13), ethanol-feeding resulted in significantly decreased levels of cleaved caspase-3, increased nuclear protein expression of NF- κ B p65 subunit, cyclin D1 protein and TNF- α mRNA. Thus, increased proliferation and reduced apoptosis seem to be important conditions for carcinogenesis in this model. Notably, CMZ treatment not only prevented alcohol-promoted tumor formation but also restored reduced hepatic retinoic acid which is known to play an important role in tissue differentiation and carcinogenesis. Whether plasma insulin-like growth factor 1 and hepatocyte proliferation also contribute to the CMZ-mediated effects as reported recently remains unclear (14). It would be also very interesting to see whether CMZ could prevent formation of liver cancers in models solely relying on ethanol. Such an ethanol-fed mice model without the use of DEN has been very recently presented by Tsuchishima *et al.* (15). These authors observed HCC in 50 % of mice after 70 weeks almost only in the ethanol group with marked upregulation of CYP2E1 and 4-HNE.

The work of Ye *et al.* opens the fascinating strategy that pharmacological inhibition of CYP2E1 *per se* could prevent the development of alcohol-mediated liver cancers in the future. This is still a long way to go and several questions remain that should be answered in further studies: can these findings be recapitulated in other liver cancer model without cancer-initiating DEN treatment such as described by Tsuchishima *et al.* (14)? Is the tumor-inhibiting effect of CMZ restricted to CYP2E1 inhibition or are other mechanisms involved? Can they be observed in humans where CMZ is regularly used for alcohol detoxification? Although CMZ itself has addictive potentials and should not be taken continuously, it could lead to novel alcohol withdrawal regimens or trigger the development of novel CMZ-like drugs with a safer drug profile. So far, data on the hepatoprotective effects of CMZ are not yet available in humans but the time has come to prove these concepts.

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