COMMENT

Fas-Mediated Signaling Pathway in Ethanol-Induced Liver Apoptosis: Inhibition by Zinc

JIE LIU[1]

Inorganic Carcinogenesis, Laboratory of Comparative Carcinogenesis, National Cancer Institute at NIEHS, Research Triangle Park, North Carolina 27709

Ethanol-induced hepatic apoptosis has been widely recognized in both experimental and clinical alcoholic diseases. Several molecular pathways have been shown to be involved in alcohol-induced liver apoptosis and necrosis (1). These include ethanol-induced oxidative stress and cytokine production, such as TNF-α (1–2), and the Fas- and cytochrome *c*–mediated caspase-3 activation pathway (3). Clearly, these pathways play integrated roles in alcoholic diseases.

The manuscript by Lambert *et al.* (4) is a logical extension of their recent work showing that the Fas-mediated signaling pathway plays a central role in acute ethanol-induced liver apoptosis (3) and has been selected for a Best Paper Award in the Clinical/Preclinical/Translational Category for 2003. In this paper, the authors demonstrate the protection of zinc against ethanol-induced liver apoptosis, as evidenced by Terminal Deoxynucleotidyl Transferase Nick-End Labeling (TUNEL) assay and electron microscopy. The ethanol-induced increases in caspase-3 and caspase-8 activities are also suppressed by zinc pretreatment. The immunohistochemical staining of Fas ligand (FasL) protein expression provides further evidence that zinc suppressed ethanol-induced expression of FasL. Thus, one important inhibitory mechanism of zinc action in acute ethanol-induced liver apoptosis is the abrogation of Fas/FasL-mediated caspase-8 activation and the subsequent caspase-3 activation, possibly through downregulation of FasL signaling pathways in hepatocytes.

Another important observation of this study is that zinc protection occurs through a mechanism independent of mitochondrial changes. Zinc pretreatment did not prevent alcohol-induced mitochondria swelling but inhibited caspases activation. This is in the line of the fact that neutralization of FasL does not decrease mitochondrial cytochrome-*c* release but inhibits caspase-3 activation (3) and fortifies the notion that the FasL signaling pathway plays an important role in ethanol-induced hepatic apoptosis.

Zinc is an essential trace element that plays important physiological functions as a co-factor of many Zn-requiring enzymes, in the regulation of various signal transduction pathways, and in the induction of a variety of stress proteins against toxic insults. Zinc has been shown to suppress major pathways leading to apoptosis and has direct effects on apoptosis regulators, especially caspases (5). Although this award-winning paper focused only on the role of zinc in ethanol-activated Fas/FasL pathway of apoptosis, this does not exclude the role of zinc in inhibiting other steps involved in alcohol-induced liver apoptosis. For instance, zinc preserves the integrity of the intestinal membrane and prevents alcohol-induced alterations in intestinal permeability and the subsequent release of endototoxin from the intestine into blood, thus reducing alcohol-initiated apoptotic stimuli (6). These effects of zinc on the multiple steps involved in alcohol-adverse effects would certainly make important contributions to the inhibition of alcohol-induced apoptosis.

Taken together, the work of Lambert *et al.* clearly demonstrated the involvement of the Fas-mediated caspase-8 and caspase-3 activation pathway in zinc-mediated protection, downstream of mitochondrial changes. This

[1] To whom correspondence should be addressed at Inorganic Carcinogenesis, Laboratory of Comparative Carcinogenesis, National Cancer Institute at NIEHS, Research Triangle Park, NC 27709. E-mail: Liu6@niehs.nih.gov

1535-3702/04/2295-0000$15.00

effect, together with the effects of zinc on intestinal permeability, induction of metallothionein, and the inhibition of TNF-α–mediated apoptosis pathways, will play an integral role in zinc protection against alcohol-induced liver injury and would have pharmacological and clinical potential for using zinc supplementation as a therapeutic approach for alcoholic diseases.

1. Hoek JB, Pastorino JG. Ethanol, oxidative stress, and cytokine-induced liver cell injury. Alcohol 27:63–68, 2002.
2. Zhou Z, Wang L, Song Z, Lambert JC, McClain CJ, Kang YJ. A critical involvement of oxidative stress in acute alcohol-induced hepatic TNF-alpha production. Am J Pathol 163:1137–1146, 2003.
3. Zhou Z, Sun X, Kang YJ. Ethanol-induced apoptosis in mouse liver: Fas- and cytochrome *c*-mediated caspase-3 activation pathway. Am J Pathol 159:329–338, 2001.
4. Lambert JC, Zhou Z, Kang YJ. Suppression of Fas-mediated signaling pathway is involved in zinc inhibition of ethanol-induced liver apoptosis. Exp Biol Med 228:406–412, 2003.
5. Truong-Tran AQ, Carter J, Ruffin RE, Zalewski PD. The role of zinc in caspase activation and apoptotic cell death. Biometals 14:315–330, 2001.
6. Lambert JC, Zhou Z, Wang L, Song Z, McClain CJ, Kang YJ. Prevention of alterations in intestinal permeability is involved in zinc inhibition of acute ethanol-induced liver damage in mice. J Pharmacol Exp Ther 305:880–886, 2003.