WITH OVER 60% OF THE POPULATION consuming alcohol during the past year, and 32% admitting to engaging in alcohol binging episodes, alcohol abuse continues to be a comorbid condition for several diseases, but in particular for liver disease. Liver disease is one of the most salient pathophysiological conditions resulting from alcohol abuse and a major cause of alcohol-related morbidity and mortality; progressing from fatty liver to alcoholic hepatitis and, in approximately 10–15% of these individuals, progressing to liver cirrhosis (3). Because not all individuals who consume alcohol develop alcoholic liver disease in any of its forms, this variability has been attributed not only to the pattern and duration of alcohol abuse, but to gene environment interactions that appear to be essential in the development and progression of the disease (4). Extensive studies using animal models of both acute and chronic alcohol abuse have provided insight into the possible mechanisms contributing to development of alcohol-induced liver disease. Overall, nutritional composition of the diet and duration of the alcohol exposure have been shown to be key factors in the development of liver pathology (8). Moreover, central to the pathophysiology are the metabolic perturbations resulting from alcohol metabolism, which in turn modulate cellular responses including those involved in the inflammatory response and protection from oxidative injury. Intercellular signals involving not only hepatic parenchymal, Kupffer, and stellate cells but also those of adipose tissue have been recently identified as key factors in mediating alcohol-induced alterations in liver function (6, 7). Still, the initial mechanisms that are deranged preceding the development of full-blown liver disease remain to be elucidated. This issue of the journal features two review articles that provide insights into two specific metabolic pathways, protein and fat, affected by alcohol, allowing the reader to draw parallels between the two.

Karinch et al. (2) review the responses of hepatic protein synthesis to acute and chronic alcohol consumption. Animal studies described in this review have demonstrated that alcohol abuse, modeled by the acute administration of intoxicating doses of alcohol, as well as the chronic feeding of an alcohol diet result in suppression in the rate of hepatic protein synthesis without affecting the availability of amino acids, high-energy phosphates, or hepatic RNA content, indicating that alcohol impacts on translational efficiency. The studies described have identified a block in the initiation of the protein synthetic pathway caused by the excessive and sustained phosphorylation of eIF2α, a key eukaryotic initiation factor. This sustained phosphorylation of eIF2α locks the eIF2α-eIF2B complex into an inactive form and prevents eIF2B from functioning as an exchange factor for GDP to GTP, a step necessary for ternary complex formation (eIF2-GTP-met-tRNA\textsubscript{met}) and central in peptide translation (see Fig. 1). These effects of alcohol appear to be the result of an imbalance of the activity of the kinase and phosphatases regulating eIF2α phosphorylation. The alcohol-induced suppression in hepatic protein synthesis occurs following acute alcohol intoxication, is not further accentuated in response to chronic alcohol feeding, is more accentuated in females, and is not immediately restored following cessation of alcohol consumption. Interestingly, although acute alcohol intoxication does not appear to affect peptide elongation, this may be responsive to chronic alcohol feeding, a mechanism that is still not fully understood. Moreover, significant alterations in hepatic protein processing and degradation contribute to the overall dysregulation of hepatic protein metabolism in response to alcohol abuse (1).

The review on alcohol and lipid metabolism presented by Sozio and Crabb (5) presents an updated discussion on mechanisms involved in alcoholic steatosis. Overall, their review presents supporting evidence for a role for abnormal methionine metabolism. This impairment is characterized by a defect in homocysteine conversion to methionine as well as a decrease in methionine adenosyltransferase activity, leading to a decrease in S-adenosylmethionine (SAMe) and excess homocysteine levels. Together, the excess homocysteine levels, increased acetaldehyde, and reactive oxygen species generation through alcohol metabolic pathways, lead to an unfolded protein response in the endoplasmic reticulum, called ER stress. This, in turn, activates sterol regulatory element-binding proteins (SREBP-1c/2c), resulting in increased lipogenesis and expression of proapoptotic proteins. Additional signaling mechanisms involved in lipid metabolism have also been identified to be altered by alcohol feeding. The activity of peroxisome proliferator-activated receptor-α (PPARα), which activates fatty acid oxidation and export, necessary in the prevention of triglyceride accumulation and involved in antioxidative and antiapoptotic mechanisms, is suppressed by alcohol feeding. Moreover, the activity of AMP-activated protein kinase (AMPK) is also suppressed in ethanol-fed rodents. Because AMPK activation increases fatty acid oxidation and decreases lipogenesis, the alcohol-induced inhibition of its activity further contributes to alcohol-induced steatosis.

Although the cellular protein synthetic pathway constituents affected by alcohol have been characterized, little is known about the mechanisms through which alcohol produces these effects. Alcohol metabolism can be partially ascribed a role in the inhibition of hepatic protein synthesis, as demonstrated by the ameliorating effects of 4-methylpyrazole administration. Furthermore, the review on alcohol and lipid metabolism extends the discussion beyond the enzymatic pathways affected by alcohol, providing clues as to potential pathways that may contribute to steatosis. It is noteworthy that these path-
ways are affected not only by alcohol metabolism and the generation of reactive oxygen species and acetaldehyde but also by inflammatory mediators such as tumor necrosis factor and adipose-derived hormones like adiponectin, whose production and release are, in turn, also affected by alcohol. None of the identified pathways appear to be fully accountable for alcohol-induced alterations in fat metabolism, and all of them are in turn modulated by comorbid, behavioral, and environmental factors, including dietary composition, drugs, and infections. One could probably extend that assumption to the alcohol-induced alterations in protein synthesis.

All together these reviews should provide the reader with current concepts on the mechanisms of alcohol-induced alterations in protein and lipid metabolism that have been identified through rigorous and controlled experimental approaches in animal models. These concepts further our contextual understanding of the specific metabolic alterations induced following acute and chronic alcohol exposure, and on current testable hypothesis of alcoholic-induced liver injury.

**REFERENCES**


*Fig. 1. Alcohol oxidation to acetaldehyde may occur through cytosolic alcohol dehydrogenase (ADH), cytochrome P-450 2E1, or peroxisomal catalase (in that order of importance). Acetaldehyde is oxidized to acetate by mitochondrial aldehyde dehydrogenase (ALDH2). Products of this metabolic pathway result in cellular depletion of S-adenosylmethionine (SAMe) and increased levels of homocysteine, acetaldehyde, and reactive oxygen species (ROS). Together, these factors cause an unfolded-protein response in the endoplasmic reticulum (ER) called ER stress. This activates sterol regulatory element-binding pathways (SREBP-1c and -2c), resulting in triglyceride accumulation. AMP kinase (AMPK), a key regulator of metabolism, drives fatty acid (FA) oxidation and export through activation of peroxisome proliferator-activated receptor-α (PPARα); suppresses SREBP-1c, decreasing lipogenesis; and inhibits acetyl-CoA carboxylase (ACC), which through decreased malonyl-CoA levels and carnitine palmitoyltransferase I (CPT I) activity decreases synthesis and increases oxidation of fatty acids. Activity of AMPK is inhibited by alcohol, ER stress, tumor necrosis factor (TNF), and ROS. Adiponectin released from adipose tissue, which activates AMPK, is in turn suppressed by chronic alcohol consumption. All together, these alcohol-induced effects lead to deranged lipid metabolism and development of fatty liver. Hepatic protein synthesis is suppressed through what appears to be a roadblock in peptide chain initiation. The key step affected by alcohol involves the inability of cycling between the active and inactive forms of the elf2-elf2B complex, preventing the formation of the 43S preinitiation complex. Moreover, with chronic alcohol exposure, the defect extends to the ability of the elf4 complex to effectively regulate the association between the 43S complex and the 5′ cap of mRNA to form the 48S preinitiation complex (pre-IC). Defects in the protein synthetic pathway appear to be the result of a possible dysregulation between the kinase and phosphatase involved in phosphorylation of selected initiation factors. The upstream signals involved are yet to be fully elucidated. Red dotted lines, inhibition of pathway or activation; green solid lines, stimulation or activation of pathway.*