are not induced.[14] PPAR or fatty acyl-CoA oxidase knockout mice develop steatohepatitis similar to that seen with alcoholics.[15,16] PPAR-α mRNA was also reported to be decreased in the liver of rats fed ethanol chronically.[17] Finally, the author's laboratory has observed that alcohol metabolism by hepatoma cells impairs the function of transfected PPAR-α (unpublished observations, Galli and Crabb). Further work will be required to understand the role of this interesting receptor in the development of fatty liver.

Roles of Oxidant Stress and Adduct Formation

One problematic finding is that with prolonged alcohol feeding of baboons, the redox shift in the liver becomes less severe, but the fat accumulation persists. This suggests that after several weeks of alcohol use, the redox state is no longer the primary cause of fatty liver.[18] The best candidate for the perpetuation of fatty liver at this stage is oxidative stress. There are two primary ways by which chronic alcohol use can induce oxidative stress: induction of CYP2E1 and reductive pressure on the mitochondrial electron transfer system. Induction of CYP2E1 is well-established to occur with chronic alcohol use; in fact, cells expressing CYP2E1 are known to undergo oxidative damage and apoptosis that can be prevented with free radical scavengers.[19] CYP2E1 is leaky in that electrons transferred to it from CYP450 reductase can be transferred to molecular oxygen in the absence of substrate. The preferential expression of CYP2E1 in the central zone of the liver is consistent with the prominence of alcohol-induced injury to this part of the liver. More recently, several groups have shown that ethanol metabolism is capable of causing acute oxidative stress (as demonstrated by dichlorofluorescein fluorescence) in perfused liver and isolated hepatocytes.[20,21] This oxidative stress apparently can be handled in most individuals by antioxidant defense mechanisms. The most prominent defense in the mitochondrion is the presence of glutathione and glutathione peroxidase. It is noteworthy that mitochondrial glutathione is preferentially depleted in the alcohol-fed baboon or rat. The existence of oxidative stress has been demonstrated in humans by the finding that ethanol use increases the urinary excretion of 8-epiprostaglandin-F2α and the breath excretion of ethane (both products of lipid peroxidation and decomposition).

Protein adducts continue to be recognized as a potential mechanism for ethanol toxicity. Adducts are formed between a number of liver proteins and acetaldehyde, hydroxyethyl radical, and peroxidative aldehydes like 4-hydroxynonenal. The proteins identified to date include tubulin, Δ^4-3-ketosteroid 5β-reductase (37 kD protein), CYP2E1, and various membrane proteins in hepatocytes and Jun N-terminal kinase in stellate cells. Among the most provocative studies are those that showed increased sensitivity of the liver to ethanol in animals immunized with protein-acetaldehyde adducts, then fed ethanol. The immunized, alcohol-fed animals developed hepatic inflammation and fibrosis, while animals that were only immunized or only alcohol-fed did not.[22]

The Role of Endotoxin and the Kupffer Cell

There is a growing appreciation that portal vein endotoxin and activation of the Kupffer cells are important in alcoholic liver injury. Recent studies show that alcohol feeding increases endotoxin levels in the portal vein, that chronic ethanol feeding induces the expression of the endotoxin binding protein and its receptor present on the Kupffer cell (CD14), and that inactivation of Kupffer cells by gadolinium chloride ameliorates the injury seen with chronic ethanol administration in the Tsukamoto-French model.[23] The consequences of Kupffer cell activation are wide spread, as the cells release: TNF-α, which is a cause of hepatocyte apoptosis; IL-1 and IL-6 which elicit an acute phase response; eicosanoids, which are implicated in the increased rate of hepatocyte oxygen consumption during ethanol metabolism; reactive oxygen species; chemokines that stimulate migration of leukocytes into the liver; and platelet-derived growth factor (PDGF), a major stimulator of HSC proliferation (see below). It is also interesting to note that the mere presence of fatty liver (even without ethanol consumption) increases the sensitivity of the liver to the effects of endotoxin.[24]

Pathways of HSC Activation

The final element in alcoholic liver injury is activation of the HSC and production of collagen in the hepatic interstitium. This fibrogenic process seems to require the activity of Kupffer cells and interaction of Kupffer cell-derived cytokines with the HSC. Currently, an area of great interest is the control of the earliest stage of HSC activation. One of the very earliest events is the activation of NF-κB in the HSC, but the signal responsible for this is as yet unknown.[25] This might relate to changes in the matrix which they contact in the liver (for example, by modification by acetaldehdye), formation of protein adducts in the HSC (with acetaldehyde, 4-hydroxynonenal, malondialdehyde) or by oxidative stress originating in the hepatocytes or within the stellate cells themselves (HSC are known to express ADH and ALDH, but not CYP2E1).[26,27] However, once NF-κB is activated, the cells can be stimulated to divide by PDGF, and stimulated to produce collagen by TGF-β and possibly IL-1. With time, this activation may