Introduction:

Nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) are among the commonest causes of cirrhosis and liver failure in the developed world.[1,2,3,4,5] Excessive consumption of alcohol in humans results in a spectrum of liver abnormalities, ranging from simple fatty liver to steatohepatitis and cirrhosis, which may be present independently or in combination. Infiltration of the liver by lymphocytes and neutrophils is an important feature of alcoholic hepatitis; it initiates a cascade of effector mechanisms that ultimately lead to hepatocyte death, fibrosis, and cirrhosis. Only a minority of consistently heavy drinkers with steatosis ever develop clinically important liver disease,[5,6] implying that host or environmental factors determine the evolution of alcohol-related liver damage. Ingestion of alcohol leads to increased production of reactive oxygen species (ROS), which are generated during metabolism of alcohol by cytochrome P450 2E1 enzyme, and excessive alcohol consumption is associated with increases in lipid, protein, and DNA peroxidation. Consistent with this disease model, the risk factors for the development of progressive liver damage in alcohol drinkers include both polymorphisms in alcohol-metabolizing enzymes and polymorphisms in genes associated with a more vigorous inflammatory response in addition to exogenous factors including obesity, exposure to other hepatotoxins, and infection with hepatitis C virus.[7,8,9]

Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as a leading cause of liver dysfunction and cirrhosis in the developed world and is part of a spectrum of metabolic diseases associated with obesity, dyslipidemia, insulin resistance, and type 2 diabetes mellitus.[3,10] Over 90% of patients with NAFLD have at least one of the features of the metabolic syndrome (central obesity, increased fasting glucose, hypertriglyceridemia, low high-density lipoprotein, increased cholesterol, or hypertension), and one third have at least three. Furthermore, the presence of the metabolic syndrome is associated with a threefold increased risk of developing steatohepatitis and progressive fibrosis.[11] The exact mechanisms leading to steatosis are not fully understood. The role of defective lipid metabolism and fatty acid oxidation in both AFLD and NAFLD has been reviewed in detail,[12] and in both diseases excessive triglyceride accumulation in hepatocytes triggers subsequent liver damage. The similarities to ALD extend to the fact that less than 20% of patients with nonalcoholic steatosis develop clinically significant liver injury, and this observation led Day and James to propose a two-hit hypothesis for the pathogenesis of nonalcoholic steatohepatitis (NASH) in which the first hit, "steatosis", sensitizes the liver to

induction of inflammation by a second or multiple subsequent pathogenic insults that promote oxidative stress and steatohepatitis.[4] Excessive lipolysis in NAFLD results in increased delivery of free fatty acids (FFAs) to the liver; this enhances peroxisome proliferator–activated receptor α activity and oxidation of FFAs, resulting in the generation of hydrogen peroxide, superoxide, and peroxides that generate oxidative stress resulting in lipid peroxidation, cytokine induction, and mitochondrial dysfunction.[13,14] Steatosis and FFAs can also activate hepatocyte apoptosis through several death receptors including tumor necrosis factor (TNF)–related apoptosis-inducing ligand (TRAIL) and fas.[15,16,17] Abnormal oxidative stress is exacerbated if the hepatocyte free radical–scavenging systems are overwhelmed and a lack of antioxidants such as vitamin C and α-tocopherol increases susceptibility to lipid peroxidation.[18] Hence, the imbalance between oxidants and antioxidants predisposes fatty livers to greater injury when exposed to ROS.[12] The alcohol metabolizing enzyme CYP2E1 is elevated in murine models of NASH,[19] and production of oxidants generated by CYP2E1 and CYP4A has been linked to the pathogenesis.[20]

Fatty liver disease represents a histological spectrum of disease encompassing steatosis, steatohepatitis, and cirrhosis.[21] The histological lesions induced by NAFLD are indistinguishable from those seen in ALD.[22] The initial lesion is steatosis, which is typically present in a macrovesicular form and mainly involves perivenular regions of the liver parenchyma. Two main patterns of inflammation and fibrosis are seen in cases that progress to steatohepatitis. The most characteristic lesion in adults with steatohepatitis (alcoholic and nonalcoholic) also involves perivenular regions of the liver parenchyma. The essential features are liver cell injury with ballooning and apoptosis of hepatocytes and Mallory bodies associated with an inflammatory cell infiltrate that typically includes neutrophils as well as lymphocytes. The lesion is associated with perisinusoidal and pericellular fibrosis,[21] and the severity of the inflammatory damage correlates with outcome.[23,24] The second pathway of inflammation involves portal and periportal regions, consists mainly of lymphocytes, and may be associated with interface hepatitis and progressive periportal fibrosis.[21] This pattern of liver injury is particularly seen in pediatric NAFLD but may also occur in adults with NAFLD and, to a lesser extent, in ALD. Although the initiating insults in each disease are different, the outcome in terms of inflammatory cell recruitment is similar. Thus, the present review defines the molecular events that promote lymphocyte recruitment to and retention in the liver during steatohepatitis.