LECTURE

Pathogenesis of Alcoholic Liver Disease: Newer Mechanisms of Injury

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Abstract. The understanding of how alcohol damages the liver has expanded substantially over the last decade. In particular, the genetics of alcoholism, the genesis of fatty liver, the role of oxidant stress, interactions between endotoxin and the Kupffer cell, and the factors that control activation of the hepatic stellate cell (HSC) have been the focus of a great deal of research. Genetic mechanisms for increasing the risk of alcoholism include alterations in alcohol metabolizing enzymes as well as neurobiological differences between individuals. The development of fatty liver may involve both redox forces, oxidative stress, and alterations in peroxisome proliferator activated receptor function. Oxidative stress is now known to involve both microsomal and mitochondrial systems. Recent studies implicate stimulation of Kupffer cells by portal vein endotoxin as a cause of release of cytokines and chemokines, hepatocyte hyper-metabolism, and activation of HSC. These actions appear to be in part gender-dependent and may explain the susceptibility of women to alcoholic liver disease. Activation of HSC underlies liver fibrosis and cirrhosis of all types; control of this activation might permit control of the progression of fibrosis. These advances suggest a number of new approaches as therapy for alcoholic liver injury. (Keio J Med 48 (4): 184–188, December 1999)

Key words: alcoholic liver disease, alcohol metabolism, Kupffer cells, hepatic stellate cells, oxidative stress

Introduction

Alcoholic liver disease (ALD) continues to be a major cause of cirrhosis and death around the world. While the ultimate control of alcoholic liver disease will require the prevention of alcohol abuse, better understanding of the hepatotoxicity of alcohol may lead to treatments of fatty liver and alcoholic hepatitis, prevention or delay of occurrence of cirrhosis, or modulation of the interactions between alcohol consumption and HCV infection. Furthermore, insights gained from studying alcoholic liver injury may extrapolate to non-alcoholic fatty liver and steatohepatitis.

Advances in understanding alcohol toxicity that have occurred in the last decade can be grouped under the topics of genetics of alcoholism, causes of fatty liver, the roles of oxidant stress and protein adducts, the importance of endotoxin, control of hepatic stellate cell (HSC) activation, and the risks of alcoholic liver disease in women. These will be discussed in turn.

Genetic Predisposition to Alcoholism

The genetic predisposition to alcoholism has been proven by a number of classical genetic studies, including twin, adoption, and high-risk familial clustering studies. The strongest genetic associations identified to date are those between risk of alcoholism and genes encoding alcohol metabolizing enzymes. In particular, individuals having the genes encoding high activity alcohol dehydrogenase (ADH) (β2 ADH encoded by *ADH2*2*) or the dominant negative allele for aldehyde dehydrogenase ALDH2 (*ALDH2*2*) are at reduced risk of alcoholism.[1–3] It is noteworthy that in addition to the well-known prevalence of *ADH2*2* in Asians, it has recently been identified in about 20% of Israelis. This gene locus also appears to reduce the risk of alcohol abuse in that population.[4] The effect of these vari-

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