become irreversible, leading to progressive fibrosis and cirrhosis. The irreversible activation may be driven by the changes the cells make in the extracellular matrix, such as deposition of type I collagen, production of TGF-β by the HSC themselves (resulting in a positive feedback loop) and depletion of retinyl ester stores in the HSC. In addition, the HSC also make ICAM-1, MIP-2, PAF, SCF-1, and MCP-2, chemokines and adhesion molecules that may be important in the migration of leukocytes into the liver.[28] All of these factors may lead to progressive liver damage even if the patient stops drinking.

Increased Risk of Alcoholic Liver Disease in Women

Given the recent new knowledge about the pathogenesis of alcoholic liver disease, it is worth revisiting the differences in responses to alcohol between men and women.[29] Recent studies have shown that men and women have similar sized livers. This results in a larger liver mass/body mass ratio for women. When the rate of alcohol metabolism is normalized to liver mass, men and women have similar metabolic rates.[30] However, blood alcohol levels after comparable doses of alcohol will usually be higher in women than in men because of the women's lower body mass and lean body mass, resulting in a lower volume of distribution in the women. It has also been found that female rats are more susceptible to alcohol-induced liver injury in the Tsukamoto-French model.[31] This may relate to more pronounced accumulation of fat in their livers, lower levels of fatty acid binding protein (and thus higher concentrations of unbound free fatty acids), increased plasma endotoxin, increased expression of the endotoxin receptor (CD14) in Kupffer cells and lipopolysaccharide binding protein, more pronounced central hypoxia, and more marked activation of NF-κB in the HSC. Thus, many mechanisms may conspire to make female alcoholics more prone to the development of alcoholic hepatitis and cirrhosis.

New Therapies for Alcoholic Liver Disease

Recent abstracts have indicated that S-adenosylmethionine may reduce mortality in cirrhosis due to its ability to protect against oxidative stress. Pentoxiphylline was also reported to improve outcomes in alcoholic hepatitis. This may be due to inhibition of activation of the HSC and reduction in production of inhibitors of metalloproteases. The full publication of these studies is eagerly awaited. Large, multi-center studies on the effectiveness of dilinoleoyl-phosphatidyl choline in hepatic fibrosis will be concluded soon. Propylthiouracil, which was reported in the 1980's to improve alcoholic hepatitis, was recently reported to have additional effects. It can inhibit neutrophil myeloperoxidase, and may thereby reduce oxidative stress caused by hypochlorous acid made in the neutrophils. This discovery may lead to the development of other inhibitors that do not interfere with thyroxine production.

Future therapies may be suggested based on the mechanisms of injury discussed above. These include better antioxidants, inhibitors of CYP2E1, inhibitors of NF-κB activation or of eicosanoid production by Kupffer cells, and antagonists or antibodies against PDGF, TNF-α, and TGF-β. Of course, the best long term therapy will be the development of drugs or psychological therapies effective in reducing craving for alcohol and effective in treating alcoholism.

References

1. Thomasson HR, Edenberg HJ, Crabb DW, Mai XL, Jerome RE, Li TK, Wang SP, Lin YT, Lu RB, Yin SJ: Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. Am J Hum Genet 1991; 48: 677–681
2. Tanaka F, Shiratori Y, Yokosuka O, Imazeki F, Tsukada Y, Omata M: Polymorphism of alcohol-metabolizing genes affects drinking behavior and alcoholic liver disease in Japanese men. Alcohol Clin Exp Res 1997; 21: 596–601
3. Harada S, Agarwal DP, Goedde HW, Tagaki S, Ishikawa B: Possible protective role against alcoholism for aldehyde dehydrogenase isozyme deficiency in Japan. Lancet 1982; 2: 827
4. Neumark YD, Friedlander Y, Thomasson HR, Li TK: Association of the ADH2*2 allele with reduced ethanol consumption in Jewish men in Israel: a pilot study. J Stud Alcohol 1998; 59: 133–139
5. Edenberg HJ, Jerome RE, Li M: Polymorphism of the human alcohol dehydrogenase 4 (ADH4) promoter affects gene expression. Pharmacogenetics 1999; 9: 25–30
6. Harada S, Okubo T, Nakamura T, Fujii C, Nomura F, Higuchi S, Tsutsumi M: A novel polymorphism (−357G/A) of the ALDH2 gene: linkage disequilibrium and an association with alcoholism. Alcohol Clin Exp Res 1999; 23: 958–962
7. Chou WY, Stewart MJ, Carr LG, Zheng D, Stewart TR, Williams A, Pinaire J, Crabb DW: An A/G polymorphism in the promoter of mitochondrial aldehyde dehydrogenase (ALDH2): effects of the sequence variant on transcription factor binding and promoter strength. Alcohol Clin Exp Res 1999; 23: 963–968
8. Goate AM, Edenberg HJ: The genetics of alcoholism. Curr Opin Genet Dev 1998; 8: 282–286
9. Hrubec Z, Omenn GS: Evidence of genetic predisposition to alcoholic cirrhosis and psychosis: twin concordances for alcoholism and its biological end points by zygosity among male veterans. Alcohol Clin Exp Res 1981; 5: 207–215
10. Reed T, Page WF, Viken RJ, Christian JC: Genetic predisposition to organ-specific endpoints of alcoholism. Alcohol Clin Exp Res 1996; 20: 1528–1533
11. Galli A, Price D, Crabb D: High-level expression of rat class I alcohol dehydrogenase is sufficient for ethanol-induced fat accumulation in transduced HeLa cells. Hepatology 1999; 29: 1164–1170
12. Kliewer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, Koble CS, Devchand P, Wahli W, Willson TM, Lenhard JM, Lehmann JM: Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors α and γ. Proc Natl Acad Sci USA 1997; 94: