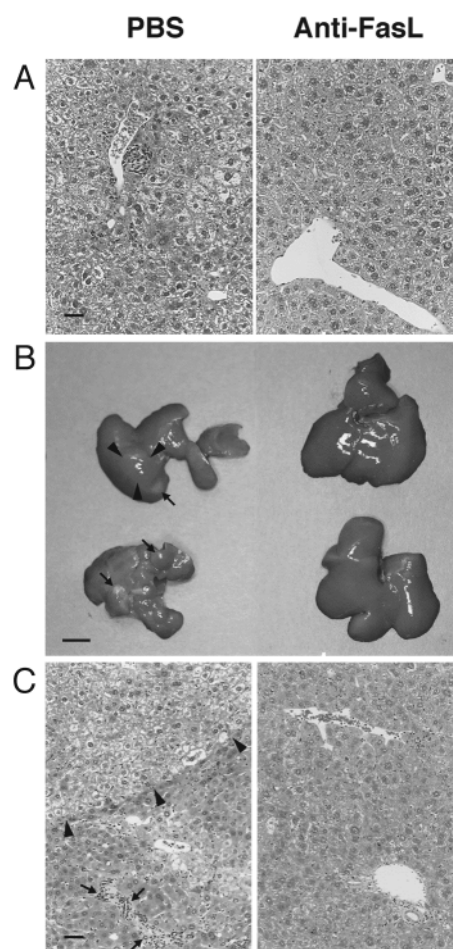


Prevention of Hepatocellular Carcinoma Development Associated with Chronic Hepatitis by Anti-Fas Ligand Antibody Therapy

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Hepatitis B virus (HBV) and Hepatitis C virus are widespread pathogens, and cause chronic liver inflammation, leading to hepatocellular carcinoma (HCC). Both clinical and experimental research has suggested that cytotoxic T lymphocytes (CTLs) and its major cytotoxic molecule, Fas ligand play a pivotal role in the pathogenesis of viral hepatitis. However, it has not been directly investigated whether FasL is involved in the development of HCC. In this study, using the unique animal model of chronic hepatitis leading to HCC, we have successfully demonstrated that anti-FasL antibody treatment prevented hepatocyte apoptosis, proliferation, liver inflammation, and the eventual development of hepatocellular carcinoma. The results indicate that FasL is involved not only in direct hepatocyte killing but also in the process of inflammation and hepatocellular carcinogenesis in chronic hepatitis. This is also the first demonstration that amelioration of chronic inflammation by some treatment actually caused reduction of cancer development.

Figure. Prevention of progressive liver dysplasia and HCC development by anti-FasL mAb treatment. The transgenic mice described in the legend to Figure 1 were sacrificed 9 (A) and 15 (B and C) months after the splenocyte transfer. (A) A 9-month liver specimen with PBS (left) or anti-FasL mAb treatment (right). (B and C) Fifteen months after the splenocyte transfer, livers from PBS-injected animals displayed marked atrophy and multiple liver tumors (arrows) up to 11 mm in diameter (arrowheads) (B, left). A representative specimen illustrates the classical histological features of HCC (arrowheads), and the surrounding hepatic parenchyma displays focal lobular inflammatory infiltrates associated with degenerating hepatocytes (arrows) (C, left). Most of livers from anti-FasL mAb-injected animals did not show apparent atrophy or liver tumors (B, right). A representative specimen demonstrates minimal portal infiltrates and very mild lobular disarray (C, right). Liver sections were stained with hematoxylin and eosin. The bars represent 40 μ m in (A and C), and 10 mm in (B).



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