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The role of bile duct reactive change in the pathogenesis of liver fibrosis due to hepatitis C

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Abstract

The question addressed here is: does the bile duct reactive component of hepatitis C disease progress during the progression of the disease to cirrhosis? The question is important because if the answer to the question is yes, then an important correllary question is: does the bile duct reactive component contribute to the fibrotic change which leads to cirrhosis? The first question is addressed in the present study of a series of liver biopsies taken at the four stages of liver fibrosis in patients with hepatitis C. Sixty-four patients with hepatitis who had been biopsied for staging purposes were reviewed retrospectively. The liver biopsies were routinely stained with antibodies for liver cells, bile duct cells, activated stellate cells and cells in S phase of the cell cycle and histochemical stains for collagen and basement membrane. Selective biopsies were stained for stem cells and oval cells. There was a progressive increase in metaplastic bile ductules but the increase did not reach a significant level until stages III and IV of fibrosis. There was a positive correlation between the number of ductules formed and the stage of liver fibrosis. The incidence of proliferating metaplastic ductules was low and did not change significantly during the progression of the stage of the fibrosis. Stains for oval cells and stem cells were negative. It is concluded that the answer to the question posed is: bile ductule reaction does increase during the development of cirrhosis caused by hepatitis C but the increase is due to bile ductular metaplasia, not due to proliferation.

Keywords: Bile ductule; Metaplasia; Liver fibrosis; Oval cells; Stem cells

Introduction

Liver cirrhosis is the result of progressive liver damage due to chronic insults such as alcohol abuse and hepatitis C virus infection. It is characterized by hepatic fibrosis, liver cell nodule formation and increased bile ductule formation in the periportal region and in the fibrous septa (French, 1994, 2000). This increase in bile ductules has been termed "bile ductular reaction" (Roskams et al., 2004) rather than ductular proliferation. The origin of these bile ductules is still controversial as to whether they are the result of proliferation of pre-existing bile ductular cells or the differentiation of progenitor cells or the transformation from hepatocytes (bile ductular metaplasia).

In the present study, the ductules will be referred to as metaplastic ductules. There are several hypotheses proposed regarding the increasing bile ductules in chronic hepatitis. These neoductular structures were first thought to result from liver cells which had undergone metaplasia in the same way that liver transforms to bile ducts in the fetal liver (reviewed by Cocjin et al., 1996). This ductule-liver cell transformation occurs during fetal development as the result of cell–matrix and cell–cell interactions which regulate biliary epithelial cell differentiation (Lemaigre, 2003). Recently, it has been postulated that they are derived from oval-like progenitor cells with intermediate (hepatocytic/biliary) morphological feature and combined immunophenotype (Tan et al., 2002). The role of oval cells which are derived from hematopoietic stem cells in generating biliary epithelial cells was postulated (Crosby et al., 2001). The stem cells were identified using the markers c-kit and CD34. In another study, it was shown that typical ductules proliferate but metaplastic ductules (atypical ductules) are transformed from hepatocytes (Harada et al., 1998).

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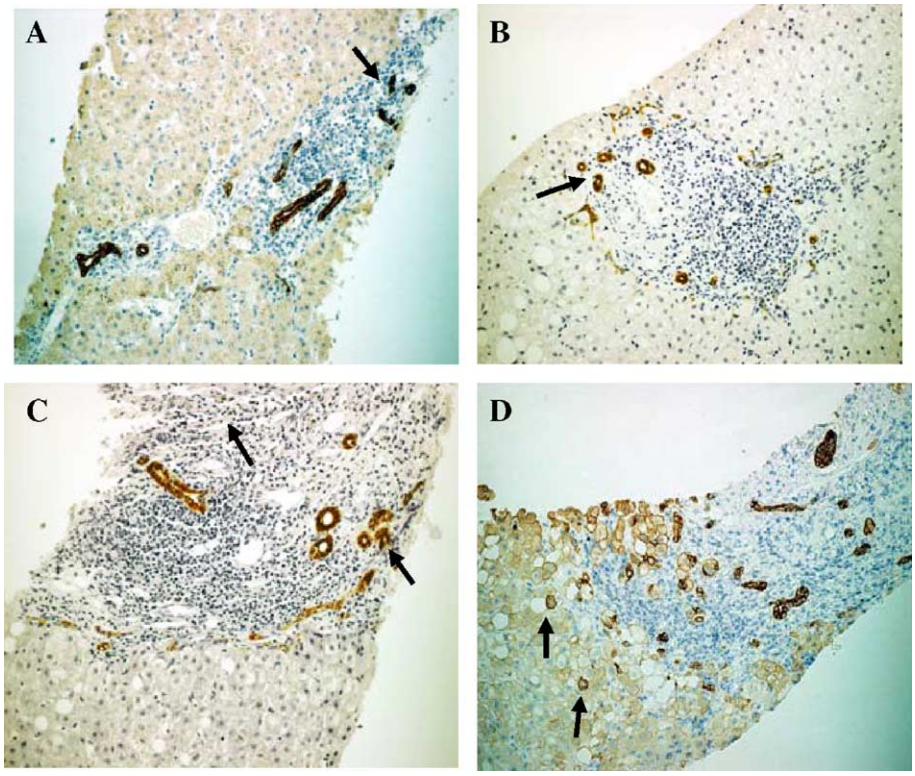

Fig. 1. (A) Metaplastic ductular cells (arrows) stain dark brown with AE1 and 3 antibody in stage 1, fibrosis. (B) Stage 2. (C) Stage 3. (D) Stage 4. Note the dark brown stained hepatocytes (arrows) which are beginning to transform into metaplastic ductules, ×420.

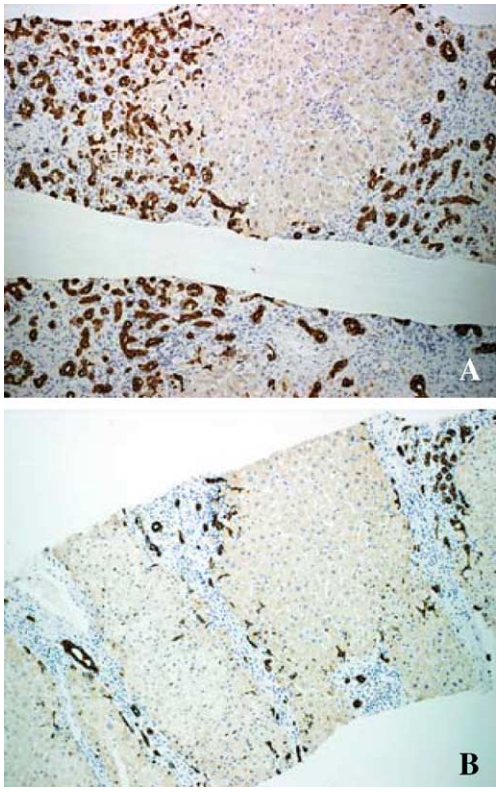

Fig. 2. (A, B) Ductular cells stain dark brown with AE1 and 3 and are densely concentrated in the periportal areas at stage 4 fibrosis. (A) ×210, (B) ×210.

The hypothesis that bile ductular metaplasia is the cause of fibrosis and cirrhosis in focal nodular hyperplasia and chronic hepatitis was proposed (Butron Vila et al., 1984; Yoshioka et al., 2004). In one study, where liver cells were transplanted to the spleen, bile duct transformation from the transplanted hepatocytes was observed (Fukada et al., 2004). This would negate the oval cell progenitor hypothesis because there are no oval cell progenitor cells residing in the spleen. It was shown in

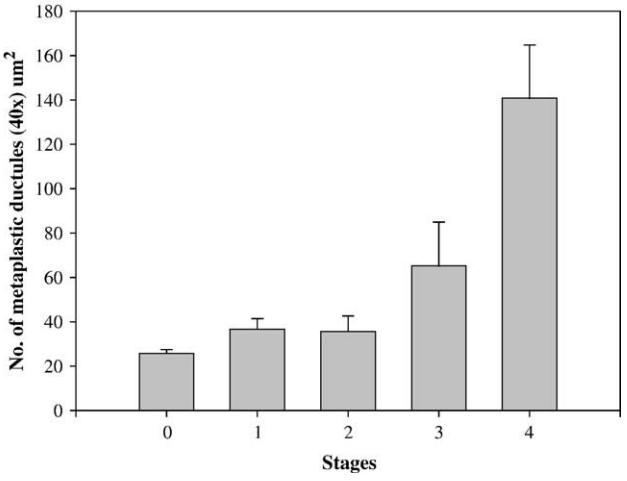

Fig. 3. Numbers of metaplastic ductular cells at the all stages of fibrosis.