Glutathione S-transferase expression in primary biliary cirrhosis supports concept of "ductular metaplasia" of hepatocytes

Bile duct proliferation is a feature of many cholestatic diseases. The mechanism of this phenomenon is unknown but there is some support for the concept of "ductular metaplasia." For example, Van Eyken et al used an immunocytochemical approach to show, in a variety of cholestatic diseases, that hepatocytes can express cytokeratins which in the normal liver are restricted to the bile duct cells.

The glutathione-S-transferases (GST; EC 2.5.1.18) are a large gene enzyme family that catalyse the conjugation of reduced glutathione with a variety of electrophiles. By immunological and catalytic criteria, the major cytosolic isoenzymes can be categorised into four classes, α, μ, θ and π. Time and tissue specific changes in the expression of these GST classes has been described in developing human tissues and these data suggest that changes in GST expression are related to changes in cell phenotype.++

We now describe observations of glutathione-S-transferase expression in primary biliary cirrhosis that provide further evidence for the concept of "ductular metaplasia".

Samples of liver were obtained from 10 patients who had undergone liver transplantation at the Liver and Hepatobiliary Unit, Queen Elizabeth Hospital, Birmingham, England. A diagnosis of end stage cirrhosis as result of primary biliary cirrhosis was confirmed biochemically, serologically, and histologically. Paraffin wax sections (4 μm) were cut, dewaxed, and the expression of α, μ, and π classes of GST demonstrated by immunocytochemical localisation as described before.++

In all cases the biliary nodules of hepatocytes were positive for α GST. At the periphery of these nodules, cells that might represent an intermediate phenotype undergoing transformation to bile duct type cells were negative for α GST as were bile duct epithelial cells.

The polymorphic GSTM1 gene encodes the predominant μ class isoenzyme in human liver. In those who expressed this gene, GSTM1 isoforms demonstrated strong positivity in hepatocytes but were not expressed in bile duct epithelium or those cells putatively undergoing metaplasia.

In general, μ class expression was restricted to the bile ducts and "ductal metaplastic" cells, these both strongly positive. In some cases a weak diffuse positivity was also observed in occasional regenerating nodules of hepatocytes.

As shown in the table cells with an intermediate phenotype undergoing "ductular metaplasia" from hepatocyte to bile duct type cells expressed μ class GST but not the α or μ class isoforms. Although such cells were seen only on the periphery of the cirrhotic nodules, in many instances they were clearly continuous with surrounding hepatocytes. These "metaplastic" cells, therefore, did not show the typical hepatocyte pattern of strong positivity for α and μ class isoforms but, rather, similar GST expression to bile duct epithelial cells. This observation is consistent with the concept of "ductular metaplasia" and corroborates data in patients with extrahepatic biliary atresia showing altered expression of π GST in hepatocytes.++

It was interesting to note diffuse positivity for π class GST in some regenerating nodules, though it was not usually expressed by adult hepatocytes. Expression of π class GST by hepatocytes is normally seen only in fetal liver and may therefore be an indication of increased cell proliferation.+++
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