MINI REVIEW

Human cirrhosis: Monoclonal regenerative nodules derived from hepatic progenitor cells abutting ductular reaction

Cirrhose chez l’homme : nodules de régénération monoclonaux dérivés de cellules souches hépatiques en connexion avec la réaction ductulaire

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Summary

Cirrhosis is a premalignant condition leading to hepatocellular carcinoma. Cirrhotic nodules are surrounded by a rim of CK 7/CK19-positive biliary cells termed ductular reaction. Half of all regenerative cirrhotic nodules are thought to be monoclonal by studying the pattern of inactivation of the X-linked human androgen receptor gene (HUMARA). Using a new technique for lineage tracing in human liver based on the identification in the mitochondrial DNA of mutations in the cytochrome c oxidase (CCO) gene, the authors discovered that 20% of regenerative nodules were monoclonal; in addition they showed that hepatic progenitor cells within abutting CCO-deficient cells of the ductular reaction had the same mutations as the adjacent regenerative nodule, indicating a common cell origin. It is the first direct evidence that regenerative nodules in cirrhosis can be derived from hepatic progenitor cells.

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Cirrhosis is defined histologically as a diffuse process in which the normal anatomical lobules are replaced by architecturally abnormal nodules separated by fibrous tissue. Knowing that cirrhosis is a premalignant condition leading to hepatocellular carcinoma, a number of attempts have been made to establish the clonality of regenerative nodules (RNs), often by examination of X chromosome-linked markers in females. In liver cirrhosis, approximately half of all RNs have been found monoclonal by studying the pattern of inactivation of the X-linked human androgen receptor gene (HUMARA) [1]. However, in this type of approach the distribution of X-inactivated cells in the liver is not taken into account (the progeny of a single X-inactivated embryonic cell may be clustered together giving a false information concerning clonality).
Cirrhotic nodules are surrounded by a rim of CK 7/CK19-positive biliary cells termed ductular reaction (DR). Examination of cirrhotic explants of diverse diseases reveals that most intras portals hepatocytes (ISH), whether as nodules or as loose clusters, are associated with DR [2]. Three-dimensional reconstruction of ISH in hepatitis C-related cirrhosis demonstrates that in that setting virtually all ISH are associated with DRs, which form a structural and probably physiological link to the biliary tree. Therefore, if proliferation of hepatocytes in the early stages of chronic hepatitis C accounts for much of hepatocyte regeneration, in cirrhosis, the biliary tree becomes more proliferative as hepatocyte replication diminishes.

A reaction of ductular phenotype, possibly but not necessarily of ductular origin, in chronic liver disease may arise from:

- proliferation of preexisting cholangiocytes;
- progenitor cells (local so-called hepatic progenitor cells [HPCs]) and/or circulating cells probably bone marrow-derived;
- rarely, biliary metaplasia of hepatocytes.

The progenitor functioning of the DR attracts much attention [3]. In particular, cells of intermediate morphology and intermediate immunophenotyping are of interest. These cells are referred to as intermediate hepatobiliary cells, defined as larger than 6 microns in diameter (the approximate size of the normal canal of Hering cell, i.e., the smallest cholangiocytes), but less than 40 microns (the typical size of a hepatocyte), with other features suggesting dual characteristics of both hepatocytes and cholangiocytes. These include, but are not limited to: simultaneous expression of biliary antigens (e.g., keratins 19, 7, OV-6) and hepatocyte antigens (e.g., HepPar1, albumin, alpha-1-antitrypsin, biliary glycoprotein-1 detected by canalicular staining with polyclonal anti-CEA, and, occasionally, alphafetoprotein), other markers such as NCAM-1/CD56, and structural features such as basement membrane formation typical of cholangiocytes and canalicular membranes typical of hepatocytes.

Staining with NCAM, CK19, and HepPar1 has revealed a distinctly biphasic structure to DRs that are embedded in cirrhotic tissue. Spatial analysis of cells that are singly HepPar1-positive, or CK19-positive, has revealed hepatocytic and biliary poles, respectively, in the DRs. The location of singly NCAM-positive cells in DRs suggests that they may be bipotent liver stem/progenitor cells. The locations of other intermediate hepatobiliary cells, which have combinations of markers, suggest that CK19+/NCAM+ cells are transitional cells in the biliary lineage and that rare cells that are negative for all three markers are transitional cells in the hepatocytic lineage.

The working cell lineage model for DRs is presented below [4]:

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Hepatocyte    ← Stem cell    → Bile duct
NCAM−/CK19−/HepPar−   NCAM+ /CK19−/HepPar−   NCAM−/CK19+/HepPar−
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Transitional cells in the hepatic lineage are negative for the three markers.
for the process of activation and differentiation of HPCs. Differentiation of HPCs to hepatocytes occurs at this fibrotic interface, leading to buds of intraseptal hepatocytes, and the RNs we see may represent further evolution of this process.

This study opens new questions especially in the field of carcinogenesis. Are those monoclonal nodules the one who will transform into high grade dysplastic nodule? We should not wait very long before knowing the answer.

Conflict of interest statement

The authors have not declared any conflict of interest.

References


