Summary

Hepatic progenitor cells; also called oval cells, are adult stem cells that reside within or adjacent to canal of Hering. They are believed to arise from hepatoblasts during embryogenesis. Scientists suggest a bone marrow origin as well.

They are quiescent till stimulated by liver injury that is persistent or severe enough to compromise hepatocytes capacity to regenerate the liver. Upon activation, they proliferate as singular cells in addition to atypical ductular reaction. Hepatic progenitors express both hepatocytic and biliary markers and can give rise to both lineages as well.

In addition to their critical role in liver regeneration, hepatic progenitors may play a role in hepatocellular carcinoma development.

This retrospective study included fifty liver biopsies; composed of 6 biopsies of apparently normal liver tissue as a control group , selected 37 biopsies of chronic viral C hepatitis (the study group) ,in addition to 7 biopsies of hepatocellular carcinoma (HCC) on top of cirrhosis as another control group. Ages of the studied 37 cases of chronic hepatitis ranged from 32 to 65.Thirty one cases were males and 6 cases were females.

Histopathological examination was done for confirmation of the grading of hepatitis activity and staging of fibrosis according to both modified Ishak scoring system and Metavir scoring system; in addition to the degree of steatosis according to Andrew et al., (2005).

Avidin_Biotin complex technique using anti-cytokeratin 19(anti-CK19) was applied to detect the presence, number and distribution of singular hepatic progenitor cells (HPCs) as well as atypical reactive ductular structures as a sign for HPCs activation. Correlation between the mean count of singular hepatic progenitor cells as well as atypical reactive ductular/HPF with different clinicopathological variants was done.

Neither form of hepatic progenitors was found in apparently normal liver biopsies. While both forms were found in chronic hepatitis and hepatocellular carcinoma cases.

Singular oval cells were smaller than hepatocytes with oval nuclei and scant cytoplasm together with showing diffuse brownish cytoplasmic staining for anti-CK19. Oval cells was focally arranged as atypical reactive ductules that were characterized by no discernible lumens, flattened to oval epithelial lining and ill-formed ductular profile (irregular anastomosing cords)

In chronic hepatitis, the mean number of each of singular and ductular forms was 2.02 and 3.44/HPF respectively. They were mainly seen within portal areas and expanding fibrous septa with high concentration at their periphery and close association to inflammatory cells. Some HPCS and atypical reactive ductules were seen extending to hepatic parenchyma.

In HCC, the mean number of each of singular and ductular forms was 6.2 and 10/HPF respectively .Singular cells were detected among the malignant parenchymal cells. Both singular hepatic progenitor cells (HPCs) and atypical ductular reaction were seen within the intratumoral fibrous stroma.

There was no statistically significant correlation between the mean number/HPF of each form of hepatic progenitors and the age of patients and there was no significant difference between both sexes.

There was statistically positive significant correlation between the mean count of singular hepatic progenitor cells as well as atypical reactive ductular/HPF and the grade of chronic hepatitis activity, stage of fibrosis and the degree of steatosis.

Close proximity between singular HPCs and atypical ductular reaction and the statistically significant positive correlation between them suggests that such ductules is a byproduct of these singular forms

The mean count of singular hepatic progenitor cells as well as atypical reactive ductules/HPF showed significant increase throughout cirrhosis without yet tumor development, to cirrhosis adjacent to HCC to be the maximum in HCC with high statistically positive significant correlation suggesting a possible role of HPCs in hepatocarcinogenesis.

Conclusion

The present work reported a striking relationship between increasing severity of chronic hepatitis regarding activity and fibrosis, and singular and ductular forms of hepatic progenitor cells. Steatosis is associated with an increase in both numbers of hepatic progenitor cells and atypical ductular reaction. These findings confirm that hepatocytic injury is a potent stimulator for hepatic progenitor cells .Moreover; such progenitors may play an integral role in fighting the sequalae of hepatocytic injury, providing a field of search for their therapeutic applications

Increase the number of singular form of hepatic progenitors was parallel to the number of atypical ductules confirming that such ductules are a product of singular hepatic progenitor cell activation.

The higher number of singular and ductular progenitors in HCC than the adjacent cirrhosis and the cirrhosis without yet tumor development is consistent with the hypothesis that oval cell proliferation may be associated with increased risk of hepatocellular carcinoma in chronic liver disease.

Recommendation

1-Hepatic progenitor cells could have a diagnostic utility in assessment of the severity of chronic hepatitis and/or steatosis.

2- Hepatic progenitor cells could be used as predictor for the risk of hepatocelular carcinoma development in cirrhotic cases.

3-Large scale in vivo and in vitro studies are needed to detect the precise role of hepatic stem cells in chronic hepatitis and cancer to modulate the current therapeutic approaches.