Editorial

Oval cells in the liver: postulated stem cell derivatives or facultative stem cells?

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Stem cells may be defined as undifferentiated cells capable of the production of a large number of differentiated functional progeny, regenerating the tissue after injury.

In experimental carcinogenesis proliferation of diploid so-called oval cells has been described. Oval cells are small cells with oval nuclei that arise in the periphery of the portal tracts in rat models of hepatocarcinogenesis and injury and can differentiate into either hepatocytes or bile duct cells, i.e., are bipotential. These cells may be equivalent to primitive bile-duct cells of the ductal plate, they can express a-fetoprotein, they can proliferate in other forms of severe liver injury, and they can give rise to hepatocytes in vivo and undergo transformation in culture with the production of a continuous cell line having features of hepatocellular carcinoma.[1] These oval cells have peculiar phenotypic features distinct from both normal and proliferating biliary epithelial cells and from mature hepatocytes. Their precise nature remains controversial, with debate as to whether they are derived from a postulated stem cell or are themselves facultative stem cells.

Whether an equivalent of the oval cells exists in the human is equally controversial. However, immunophenotypic and ultrastructural studies have supported the existence of bipotential progenitor epithelial cells in human liver. These progenitor cells may normally exist in a periportal stem cell compartment in which there is a heterogeneous cell population. There are likely to be interactions between different cells in the periportal region which have an important role in proliferation and differentiation of progenitor cells following liver injury.[2] In fact, ductular oval cells only appear when there is a demand for growth. Under certain circumstances ductular metaplasia does occur, for example in alcoholic liver disease and chronic hepatitis B and C in humans. These ductular cells appearing like hepatocytes with the typical membranous distribution of cytokeratin 8 strongly express cytochrome P450 enzymes normally associated with functional hepatocytes. Albumin and a-fetoprotein expression are also seen in oval cells as well as cytokeratins 7, 8, 18 and 19 in the same manner as authentic bile ducts. Unlike the latter they also express vimentin.[3]

Thus, true oval cells, in addition to their ductular differentiation which has been investigated in the paper of Tsamantas et al, Annals of Gastroenterology, 2000; 13: 24-29, are consistently recognized by their progenitor stem cell-line phenotype with the capacity to differentiate into ductular cells, which are OV-6 positive, as well as lobular hepatocytes.[4,5] Thy-1 antigen is not normally expressed in adult liver, but is expressed in fetal liver, presumably on the hematopoietic cells. Hepatic oval cells express high levels of Thy-1. Immunohistochemistry reveals that the cells expressing Thy-1 are indeed oval cells, because they also express a-fetoprotein, gamma-glutamyl transpeptidase (GGT), cytokeratin 19 and OV-6, all known markers for oval cell identification. Oval cells actually express other heamatopoietic stem cell markers, such as C-kit and CD 34.[6]

In conclusion, Tsamantas et al work is in agreement with studies related to the oval cell proliferation in viral hepatitis.[7,8] Prolonged cell damage by chronic inflammation due to overproduction of nitric oxide and its derivative peroxynitrite and contributing to tumor promotion is being investigated.

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