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EDITORIAL

Liver regeneration, stem cells and beyond

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Abstract

Studies of the liver regenerative process have gained prominence in the last few years, especially with the interest in stem cell therapy. The regenerative capacity of the liver, its mechanisms and the role of stem cells will be discussed in this editorial as well as the role of artificial tissues and organs aiming to produce a new liver based on the current literature.

Key words: Liver; Regeneration; Stem cells; Transplant

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INTRODUCTION

Studies of the liver regenerative process have gained prominence in the last few years, especially with the interest in stem cell therapy. The demand for whole liver transplantation in humans far outweighs the organ supply. There is sometimes confusion and often misinterpretation among the liver community regarding the cellular mechanisms responsible for liver regeneration in different types of hepatic growth processes. From the clinical point of view, transplantation of hepatocytes or hepatocyte-like cells could represent an alternative either to orthotopic liver transplant in acute liver failure or for the correction of genetic disorders resulting in metabolically deficient states.

STATE OF THE ART

The source of hepatocytes during regeneration will depend on the nature of the growth process. As pointed out by Fausto[1], in every case it is necessary to ascertain whether it has originated from replication of existing hepatocytes, was generated by differentiation of oval cells or was produced from bone marrow cells. Replication of existing hepatocytes is the quickest and most effective way to generate hepatocytes for liver regeneration and repair.

It is well establish that oval cells will only replicate and differentiate into hepatocytes when the mature hepatocyte replication is delayed or entirely blocked. It is also known that bone marrow cells can generate hepatocytes in transplanted livers but often the frequency of hepatocytes produced by this route is very low. Bone marrow cells play a role as an important source of nonparenchymal cells such as Kupffer cells and endothelial cells.

When considering the origin of intrahepatic bile ducts in liver development and the oval cells in adult liver Endodermal-derived hepatoblasts originate both hepatocytes and intrahepatic bile ducts that express albumin and α-fetoprotein (AFP)[2,3]. At the present, it is established that a bipotential hepatic progenitor cell (HPC) population expands in human liver diseases. Together with indigenous hepatic stem cells, stem cells within the bone marrow are also activated during liver disease and play central roles in inflammation and tissue remodeling. Somatic stem cells are expected to display certain characteristics: (1) self-renewal, (2) multipotentiality, (3) transplantability and (4) functional

long-term tissue reconstitution. Stem cells themselves are required to maintain their undifferentiated state while dividing. Progenitor cells in contrast show a limited ability to self-renew. They comprise distinct subpopulations with variable lineage potential. Moreover unlike stem cells, progenitor cells divide rapidly but cannot be serially transplanted and hence have been named transit amplifying cells. Activation in the context of stem cells refers to an expansion of cell number by proliferation combined with differentiation towards different lineages. HPCs are thought to be bipotential progenitors capable of forming either hepatocytes or cholangiocytes.

The mechanisms controlling the HPC response are under intense investigation. Acute liver injury does not significantly activate the HPC compartment. The most common context in which the HPC reaction is seen is when the cell cycle in hepatocyte regeneration is blocked either by toxins or replicative senescence in rodent models or human diseases. Members of the pro-inflammatory tumour necrosis factor (TNF) superfamily include TNF-α and TWEAK (TNF-like weak induction of apoptosis), both of which appear to play pivotal roles in HPC activation. TNF-α and lymphotoxin (LT), play important roles in both HPC and hepatocyte-mediated regeneration, TWEAK stands out by demonstrating differential effects on the mature hepatocyte and progenitor cells compartments. This therefore positions TWEAK as arguably the most important intercellular signal for inducing the HPC response[4].

Recently a new research field has been developing, the generation of artificial tissues and organs for clinical use. Their main indications in the clinical settings are as sources of material for transplantation, models to study diseases, drug efficacy, and cellular behavior or phenotype. The creation of an artificial tissue requires an extracellular matrix that has architectural, mechanical, and chemical properties similar to the tissue of interest. The ideal matrix should also be perfusable, and withstand physiological culture conditions such as fluid-flow-induced mechanical stress and strain.

Detergent-based perfusion decellularization of whole cadaveric tissues provides a platform for tissue engineering, since after decellularization a matrix with native chemistry, architecture and mechanical properties is left. This decellularized matrix can be reseeded with single or multiple cell types, allowing for the isolation and study of matrix effects on cell phenotype from the confounding complexity of normal tissue. This matrix generation has been successfully applied to the recellularization of liver-decellularized matrix using rat or human cells generating functional tissue. Matrix properties are important, because a cell's niche affects cellular phenotype, including but not limited to migration, axonal guidance, proliferation, and differentiation. This holds true not only for differentiated cells but also for embryonic stem cells and adult tissue-specific stem cells or progenitors. Niche interactions can consist of cell-matrix cues (such as glycosaminoglycans and soluble or matrix-bound proteins) and cell-cell and direct cell-matrix interactions. Examples of niche interactions that influence cell phenotype[5-7] include the observations that hepatocytes exhibit greater phenotypic stability in the presence of extracellular matrix in 2D or 3D cultures, whereas matrix chemistry contributes to hepatic zonation, and that mechanically soft matrix induces quiescence of bone-marrow-derived mesenchymal stem cells.

So, today the development of 3-D functional tissues for drug discovery or therapeutic use, is no longer a dream, several centers have already reached it. The main challenges for the scientist will be the development of a bioartificial liver arising from the matrix associated with the stem cells that can replace the sick liver, is able to maintain its main functions of metabolism, synthesis and even regeneration in order to repair subsequent damage, and that provides good quality of life and also decreases the high rates of mortality that these group of patients unfortunately suffer today all over the world on the liver waiting lists.

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