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Induction of hepatic regeneration in an experimental model using hepatocyte differentiated MSCs

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Abstract

Background and Objectives: Scaffolds are threedimensional (3D) matrices that provide support for cells to attach, proliferate, and differentiate, facilitating extracellular matrix formation. The study aimed to examine the differentiation potential of Mesenchymal stem cells (MSCs) into hepatocytes in 2D and 3D culture systems to improve their in vitro differentiation, and test their functionality in vivo.

Methods: MSCs were generated from umbilical cord blood. Hepatogenic differentiation was induced on 2D and 3D cultures and characterized by morphology, scanning electron microscopy, immunocytochemistry and Gene expression. Albumin and α-1 antitrypsin (AAT) in culture supernatants were measured. Differentiated Cells were administered IV into a murine model of carbon tetra (CCL4) induced liver cirrhosis which were divided into 3 groups, a) Pathological control group, b) and c) Groups treated with hepatogenic differentiated MSCs cultured on 2D and 3D culture system respectively. After 12 weeks of injection, liver pathology was examined.

Results: The hepatogenic differentiated MSCs stained positively for albumin, alpha fetoprotein (AFP), Heppar1, cytokeratin7, 18, and OV6 with more mature cells, hexagonal in shape with central nuclei forming large sheets in groups in 3D culture system. AAT secretion and Indocyanine green uptake were significantly increased. in 3D system. In experimental model, MSC-3D treated group exhibited maximal restoration of liver architecture with absent septal fibrosis and marked improvement of ALT, AST.

Conclusions: Both 3D and 2D culture system are effective in functional hepatogenic differentiation from MSCs. In vivo hepatogenic differentiation is more effective on 3D scaffold, with better functional recovery.

Introduction

The liver has two functional characteristics that are fundamental to the maintenance of the organism's homeostasis. First, it centralizes the systemic metabolism and thus controls and modulates the functions of the central and peripheral nervous systems, the immune system, and the endocrine system. Hence, liver failure can cause encephalopathy, immunosuppression, and diabetes, respectively. Second, it intervenes between the splanchnic and systemic venous circulation, determining an abdominal portal circulatory system. For this reason, hepatic pathology can be the cause of portal vein flow obstruction with hypertension in the splanchnic venous circulation and development of portosystemic collateral circulation.

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When the liver suffers an injury, either by viruses (hepatitis A, B, or C), toxic substances (alcohol), or immune (primary biliary cholangitis), metabolic (nonalcoholic fatty liver disease (NAFLD)), or tumoral (hepatocarcinoma) diseases, it displays a great capacity for regeneration.

Liver Failure and Regeneration from Intrinsic cells

Liver Failure Types

Liver failure is the consequence of a pathological progression that begins with hepatic parenchymal dysfunction and continues with progressive degrees of insufficiency until organ failure. At present, three types of liver failure are fully characterized:

(a) Chronic Liver Failure. This condition is hepatic cirrhosis in its final stages of evolution. The evolution of cirrhosis depends mainly on its etiology. There are numerous classification systems to characterize the degree of liver failure and to predict the prognosis of cirrhotic patients. The most commonly used classification both for its simplicity and because it achieves an adequate evolutionary prediction is the so-called Child-Pugh-Turcotte score, which classifies three stages of cirrhosis, A, B, and C, the latter having the poorest prognosis. This score is based on severity of 3 impartial parameters (serum albumin level, serum bilirubin level, and prothrombin time) and 2 subjective parameters (ascites and encephalopathy)

(b) Also, to evaluate short-term mortality, a Model for End-Stage Liver Disease (MELD) has been instituted, based on the determination of creatinine and bilirubin, and it is an international normalized ratio. MELD is mainly used to prioritize treatment by liver transplant to patients with poorer prognoses

(c)Acute Liver Failure. It is the sudden decompensation of hepatic function without previous hepatic pathology or with discrete hepatic insufficiency. Patients show encephalopathy and coagulation alterations, although to classify the various types of acute liver failure, the timing of the appearance of the symptoms is used. Depending on whether the signs and symptoms appear at one week, between one and three weeks, or between three and twenty-six weeks is called hyperacute, acute, or subacute, respectively

(d)Acute-on-Chronic Liver Failure. This condition is the functional liver failure characteristic of patients with cirrhosis who suffer from acute decompensation. It is a multifactorial hepatic pathology with ascites, hepatic encephalopathy, gastrointestinal hemorrhage, and/or bacterial infection. These patients evolve rapidly in terms of multiorgan failure and high mortality rates. At present, it is considered that this syndrome is different from decompensated cirrhosis, given it has distinguishing characteristics, such as the fact that the systemic inflammatory response is more severe, although it is not caused by sepsis or by alcoholism

All of the abovementioned types of hepatic insufficiency would benefit from treatment by mesenchymal stem cell transplantation or by stimulating the intrinsic regenerative capacity of the hepatic parenchyma. In this sense, in chronic liver failure it appears more appropriate to test "in situ" regenerative therapies as there is a hepatic functional reserve susceptible to be activated.