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Review

Exploiting the unique regenerative capacity of the liver to underpin cell and gene therapy strategies for genetic and acquired liver disease☆

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ABSTRACT

The number of genetic or acquired diseases of the liver treatable by organ transplantation is ever-increasing as transplantation techniques improve placing additional demands on an already limited organ supply. While cell and gene therapies are distinctly different modalities, they offer a synergistic alternative to organ transplant due to distinct architectural and physiological properties of the liver. The hepatic blood supply and fenestrated endothelial system affords relatively facile accessibility for cell and/or gene delivery. More importantly, however, the remarkable capacity of hepatocytes to proliferate and repopulate the liver creates opportunities for new treatments based on emerging technologies. This review will summarise current understanding of liver regeneration, describe clinical and experimental cell and gene therapeutic modalities and discuss critical challenges to translate these new technologies to wider clinical utility.

This article is part of a Directed Issue entitled: "Regenerative Medicine: the challenge of translation".

Contents

Abbreviations: AAV, adeno-associated virus; AIDS, acquired immunodeficiency syndrome; Apo, B apolipoprotein B; ASS, arginine-succinate synthetase; BM, bone marrow; BMMNCs, bone marrow mononuclear cells; CEHPOB, 4-[(2-carboxyethyl)-hydroxyphosphinyl]-3-oxobutyrate; CoA, coenzyme A; CRISPR, clustered regularly interspaced short palindromic repeats; DDC, 3,5-diethhoxycarbonyl-1,4-dihydrocollidine; DHCA, dihydroxycoprostanoic acid; Dipin, 1,4-bis[N,N′-di(ethylene)-phosphamide]-piperazine; ECM, extracellular matrix; EHS, Engelbreth-Holm-Swarm; ESCs, embryonic stem cells; FAH, fumarylacetoacetate hydrolase; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high density lipoprotein; HGD, homogentisic acid dioxygenase; HGF, hepatocyte growth factor; HIV, human immunodeficiency virus; HPCs, hepatic progenitor cells; HSCs, haematopoietic stem cells; IEM, inborn errors of metabolism; IGF, insulin-like growth factor; IL, interleukin; iPSCs, induced pluripotent stem cells; kb, kilobase; LDL, low-density lipoprotein; LPCs, liver progenitor cells; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MSCs, mesenchymal stem cells; MSH, melanocyte-stimulating hormone; NTBC, 2-(2-nitro-4-trifluoro-methylbenzyol)-1,3-cyclohexanedione; OLT, orthotopic liver transplant; OTC, ornithine transcarbamylsase; PFIC, progressive familial intrahepatic cholestasis; PKU, phenylketonuria; PSCs, pluripotent stem cells; rAAV, recombinant adeno-associated virus; ssDNA, single-stranded DNA; TALENs, transcription activator-like effector nucleases; TGF, transforming growth factor; UC-MSCs, umbilical cord-derived mesenchymal stem cells; uPA, urokinase-type plasminogen activator; ZFNs, zinc-finger nucleases.

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1. The liver in health and disease

The liver is a vital organ for it performs a range of functions essential for the survival of all organisms that have a liver. These include production of most plasma proteins including albumin, which maintains the colloid osmotic pressure and together with other plasma proteins, acts as a carrier of factors required for a range of cell and organ functions. It stores glucose as glycogen, vitamins, iron and copper. It is also the site of detoxification of endogenous and xenobiotics that are harmful by expressing a range of metabolic enzymes. Finally, it is the site of intermediary metabolism that can be viewed as the "currency converter" that facilitates the "commerce" that exists between the metabolic pathways of protein, carbohydrate and lipid respectively. It enables the anabolic and catabolic processes that are essential for life. As a consequence, when the liver malfunctions; often postnatal survival is not possible, and if the organism survives, it cannot grow and develop optimally. For these reasons, the liver grows commensurately with body size and sequentially acquires an increasingly complex repertoire of functions to cope with different demands imposed by the changing environment during development. In the adult, a malfunctioning liver will significantly reduce the quality of life of the individual. To maintain optimal function requires a liver that possesses both a breadth of capability as well as sufficient bulk. It is for this reason that the liver is endowed with rapid and rigidly controlled growth of fully functional hepatocytes in response to damage.

The overall health burden of liver disease worldwide is significant because its impost on both less developed and developed nations is considerable although their respective etiologies are distinct. In the former, viral infection is a primary cause, whereas in the latter it is more related to lifestyle practices such as alcohol consumption and obesity. These "environmental" causes overlie a plethora of genetic conditions which cause a variety of liver pathologies. These include hemochromatosis and inborn errors of metabolism (IEM) such as phenylketonuria, ornithine transcarbamylase deficiency and alpha-1-antitrypsin deficiency. The worldwide burden of liver disease is substantial and increasing. The "Global Burden of Death Study 2010" concluded that liver cancer and cirrhosis account for 1.75 million deaths annually, and deaths from hepatitis B (HBV) and C (HCV) virus infections were estimated to cause 1.3 million deaths, comparable to the respective burdens of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis or malaria (www.healthmetricsandevaluation.org/gbd).

In the United States deaths from liver cancer and cirrhosis number 70,000 annually, an increase of 25,000 over two decades. In the United Kingdom, statistics reveal that deaths from liver disease already outstrip other maladies such as diabetes, cancer, respiratory and circulatory disease by a considerable margin (http://www.britishlivertrust.org.uk/aboutus/media-centre/facts-about-liver-disease/). Alarmingly, it is predicted that while deaths from the other conditions will decline, the contribution from liver disease will not only increase, but accelerate. Increases that are predicted to accelerate are based on the lack of an effective vaccine for HCV and the increasing level of obesity coupled with an ageing population. An Australian study of 440 individuals of a mean age of 78 years revealed 43% had non-alcoholic fatty liver disease that was largely unrecognised (Siow et al., 2014). The current incidence of obesity amongst the young and middle-aged foreshadows a problem of enormous proportions in the next generation of the aged who are expected to live even longer.

Liver pathologies can be viewed as acute and chronic. Acute conditions include physical damage as well as drug induced cell death resulting from toxins knowingly or unknowingly ingested as toxic agents or precursors that are metabolised and converted into toxins by the liver. The loss of hepatocytes rapidly induces a compensatory hyperplasia in remaining healthy cells that will restore the liver mass in a matter of weeks in rodent models and months in humans. Partial hepatectomy is often used in studies to assess the regenerative capacity of liver in rodents. This demonstrates that efficient and effective mechanisms are in place to orchestrate a coordinated and synchronous series of events that restore full functionality to this vital organ (Michalopoulos, 2013).

By contrast, chronic liver disease is more prevalent and manifests initially as fibrosis leading to cirrhosis and almost without exception, reaches an endpoint of liver failure or hepatocellular carcinoma. Presently, the only effective treatment is organ transplant. This is a situation where demand is increasing and availability of organs is decreasing because of poor rates of donation coupled to an increase in the relative numbers of organs that are deemed to be unsuitable for transplant. This predicament is further exacerbated by advances in transplantation medicine, such that an increasing number of genetic disease phenotypes are being deemed amenable to liver transplantation. Alternative strategies besides organ transplantation must therefore be sought in earnest, in anticipation of a substantial increase in demand for this therapeutic modality. One obvious, but challenging approach is cell-based therapy.

2. The liver possesses remarkable regenerative capacity

Since the pioneering experiments of Higgins and Anderson (Higgins and Anderson, 1931), it has been well established that the liver possesses an efficient mechanism to rapidly recover homeostasis following loss of liver mass as a result of chemical or physical insult. Not only does the liver initiate compensatory hyperplasia, but does so in a matter of 2–3 weeks in rodents following partial hepatectomy (Higgins and Anderson, 1931) and 4–6 weeks in humans following liver resection for hepatocellular carcinoma (HCC) when both tumour and adjacent "normal" tissue are removed (Michalopoulos, 2007). The source of new hepatocytes is from remaining mature hepatocytes, rather than from a restricted population of progenitors as demonstrated by widespread incorporation of tritiated thymidine in rats following partial hepatectomy (Stocker and Heine, 1971). This participation of mature hepatocytes in the regenerative process accounts for the rapid kinetics of this resposne. The capacity of this mechanism for cell replacement is underlined by the finding that the same pattern of labeling is observed in 12 sequential rounds of hepatectomy on the same rodent (Stocker et al., 1973). Taking advantage of the mouse model of tyrosinaemia type 1 (fumarylacetoacetate hydrolase deficiency), in which the disease-related hepatotoxicity can be alleviated or induced by provision or deprivation of 2-(2-nitro-4-trifluoro-methylbenzyol)-1,3-cyclohexanedione (NTBC) in the drinking water, Grompe and colleagues estimated from six serial hepatocyte transplantations into recipient mice that there was a 7.3×10^{20}-fold expansion of hepatocytes from an adult donor (Overturf et al., 1997). This equates to at least 69 population