MAYO CLINIC

Cellular Therapy for Liver Disease

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CME Activity

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Abstract

Regenerative medicine is energizing and empowering basic science and has the potential to dramatically transform health care in the future. Given the remarkable intrinsic regenerative properties of the liver, as well as widespread adoption of regenerative strategies for liver disease (eg, liver transplant, partial hepatectomy, living donor transplant), hepatology has always been at the forefront of clinical regenerative medicine. However, an expanding pool of patients awaiting liver transplant, a limited pool of donor organs, and finite applicability of the current surgical approaches have created a need for more refined and widely available regenerative medicine strategies. Although cell-based therapies have been used extensively for hematologic malignant diseases and other conditions, the potential application of cellular therapy for acute and chronic liver diseases has only more recently been explored. New understanding of the mechanisms of liver regeneration and repair, including activation of local stem/progenitor cells and contributions from circulating bone marrow–derived stem cells, provide the theoretical underpinnings for the rational use of cell-based therapies in clinical trials. In this review, we dissect the scientific rationale for various modalities of cell therapy for liver diseases being explored in animal models and review those tested in human clinical trials. We also attempt to clarify some of the important ongoing questions that need to be addressed in order to bring these powerful therapies to clinical translation. Discussions will cover transplant of hepatocytes and liver stem/progenitor cells as well as infusion or stimulation of bone marrow–derived stem cells. We also highlight tremendous scientific advances on the horizon, including the potential use of induced pluripotent stem cells and their derivatives as individualized regenerative therapy for liver disease.

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We are now living in a golden age of regenerative and individualized medicine in which sweeping scientific advances are poised to fundamentally alter the way we approach health and disease, as well as the delivery of medical therapies. In this new era, there is a growing armamentarium of therapeutic options that may benefit patients with acute or chronic liver disease. For the past 30 years, many patients with end-stage liver

disease (ESLD) have benefitted from liver transplant as a treatment option. As a regenerative medicine option designed to "replace" a failing liver, liver transplant has transformed the care of patients with liver disease and the practice of hepatology. However, due in part to epidemic levels of chronic hepatitis C virus infection and nonalcoholic fatty liver disease, the applicability of this lifesaving procedure has now become more limited because of a mismatch between the number of patients awaiting liver transplant and the availability of suitable donor organs. Thus, the fatality rate of patients on the waiting list for liver transplant can be as high as 20%, depending on the severity of the underlying hepatic disease and the availability of organ donors in a specific United Network for Organ Sharing region.[1]

The remarkable innate ability of the liver to regenerate and the advent of living donor liver transplant have partially addressed the shortage of organs for transplant. In this way, transplant hepatology has always been at the forefront of clinical regenerative medicine. However, the limited applicability of current surgical paradigms has continued to stimulate extensive research into other approaches in the realm of liver regenerative medicine,[2,3] including the enticing and seemingly limitless potential of cell-based therapies.

In this review, we focus on the potential role of various modalities of cellular therapy as a means to "repair" or "regenerate" a failing liver or to augment native liver regeneration after hepatectomy or living donor liver transplant. We begin with discussions of hepatocyte and liver stem/progenitor cell (LSPC) transplant. Thereafter, we review the use of circulating or bone marrow–derived stem cell therapies for chronic liver disease, including a review of the clinical trials to date. We conclude with a discussion of the future of cell-based therapy in hepatology, including the astonishing diagnostic and therapeutic potential of induced pluripotent stem cells (iPSCs) and their derivatives in liver disease. We will not address artificial and bioartificial liver support devices, which are outside the scope of the current review and have been reviewed in detail elsewhere.[4]

HEPATOCYTE TRANSPLANT

Initial attempts at cellular therapy for liver disease consisted of using primary hepatocytes infused via the portal vein to patients with ESLD or certain genetic and metabolic liver disorders.[5-12] Various reports have indicated a beneficial effect. However, the observed improvements in liver function are rather modest and of uncertain duration. The hepatocytes are typically harvested from livers that are not deemed to be suitable for liver transplant, but these cells are limited in number, variable in quality, and not able to be expanded in vitro. The ability of hepatocytes to effectively repopulate a diseased liver appears to be limited to a select group of disorders that allow a growth advantage to the transplanted cells (such as hereditary tyrosinemia, Wilson disease, or progressive familial intrahepatic cholestasis).[13] Furthermore, these procedures continue to require immunosuppression, and there has been insufficient experience to define the amount and duration of immunosuppression needed in this setting. Lastly, how long these hepatocytes will be viable and the nature of their interaction with native hepatocytes remain unclear. All these factors have conspired against making primary hepatocyte transplant a current option for patients with ESLD or metabolic/genetic disorders. There is a growing body of literature seeking alternative sources of abundant, high-quality hepatocytes for transplant in patients with acute liver failure, chronic liver disease, and during regeneration after large hepatic resections.[14,15] Several approaches are in development, including hepatocytes derived from cell lines, xenotransplant of animal-derived hepatocytes, and even in vivo expansion of human hepatocytes in fumarylacetoacetate hydrolase-deficient animal incubators.[16-18] Although these approaches are promising, further basic science advances will be needed before these methods can be translated to human studies.

LIVER STEM/PROGENITOR CELLS

Liver stem/progenitor cells (also known as oval cells in rodents) are thought to represent tissue-specific, bipotential precursors to liver parenchymal cells. When hepatocyte replication is impaired or overwhelmed, the LSPCs residing in the terminal bile ductules (canals of Hering) are activated to proliferate and differentiate. Numerous studies have investigated the activation of the liver stem cell compartment in various forms of chronic liver disease,[19] including chronic viral hepatitis,[20-23] alcoholic liver disease,[23,24] and fatty liver disease.[25,26] Although