



Opinion

Hepatic Regenerative Medicine: Molecular Background and Potential Therapeutic Tools



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The liver is known for its potential regenerative power upon injury. Recent insights from regenerative medicine have paid great attention to understanding the molecular basis of liver tissue regeneration, opening the gate for several trials of developing new therapeutic technologies alternative to transplantation. Our opinion letter focused on liver-related regenerative medicine debates and its potential role as an alternative liver replacement therapy in hepatocellular damage.

The hepatic lobule represents the functional/anatomical unit of the liver and is composed of parenchymal cells (hepatocytes and cholangiocytes) and nonparenchymal cells (Kupffer cells, liver sinusoidal endothelial cells, and hepatic stellate cells).¹ It is responsible for developing a complex intrahepatic network that is linked throughout the body to extrahepatic organs through the activation of over 100 genes encoding cytokines, hormones, growth and transcriptional factors, and cellular constituents to replenish the old/lost hepatocytes during homeostasis and injury.² The hepatic homeostatic renewal mechanism restores the exact number of needed liver cells to maintain the vital physiologically related metabolic, biosynthetic, and detoxification functions; however, the concept of liver stem cell coexistence has been debated. In regard to hepatic regeneration in response to acute/chronic injury of different etiologies and curative hepatic surgeries performed for several indications, various hypotheses have been endorsed for a decade in several animal model studies.^{3,4}

First, in the presence of zonal restricted liver damage, other regions with different groups of hepatocytes can expand, thus restoring the injured zone to maintain hepatic functions. While after a partial hepatectomy/living donor liver transplantation, new generations of different hepatocyte subpopulations arise from the porto-central zones of hepatic lobules (the priming phase, metabolic and growth factor phase, and termination phase) with different rates based on various factors such as spatially known morphogens or the ploidy status. Owing to lineage tracing techniques, distinct pools of hepatocytes and cholangiocytes (epithelial cell adhesion

molecule progenitor cells) have been identified upon liver regeneration and/or homeostasis; therefore, interpretation of the results should be made with caution and supported by immunostaining of liver cell markers.^{5,6} At first, researchers suggested that their replication was mainly confined to the periportal region owing to the identification of the hybrid hepatocyte population that rapidly proliferates in response to chronic injuries as they co-express cholangiocyte-specific genes in parallel with hepatocyte nuclear factor 4 α , a key hepatocyte marker, and major facilitator superfamily domain containing 2a periportal hepatocytes that can make up to 3–4 layers.^{7,8} However, additional studies have detected pericentral activity during the regeneration process such as high glutamine synthetase expression and activation of Wnt pathway genes that are released from neighboring hepatic endothelial cells. Moreover, the axin 2-positive hepatocytes that maintain an actively proliferating state around the central vein by expressing upregulated T-box transcription factor 3 aid in embryogenesis. Furthermore, current studies support the identification of regeneration mechanisms throughout the whole hepatic lobular regions via the detection of leucine-rich repeat-containing G-protein coupled receptors 4 and 5 as well as R-spondin ligand activity that potentiates the Wnt/ β -catenin signaling pathway. Additionally, the detection of leucine-rich repeat-containing G-protein coupled receptor 4-positive hepatocytes and high expression of telomerase reverse transcriptase in hepatocytes shows self-renewal upon injury and homeostasis; nevertheless, extensive research is needed for further characterization of the cellular and molecular mechanisms underlying hepatic regeneration.^{9–11} Hence, the recent emerging advances in the field of hepatic regenerative medicine will push researchers to develop therapeutic tools for diseased liver replacement.

Currently, liver transplantation represents the chief effective regenerative therapy for advanced liver disease; however, the availability of compatible liver donors remains an obstacle.¹² Other ongoing experimental treatment options include microfluidic chip-based technology (liver-on-a-chip), bioengineered scaffolds (liver tissue engineering) with different biomaterials, and bioartificial livers. Their concept relies on mimicking the main physiological function of liver cells *in vitro* and represents an advancing field of technology that may hold promising results within the tissue engineering sector. However, their efficacy is still debatable due to a lack of clinical evidence.^{13–15} Finally, stem cell therapy, including hematopoietic stem cells, mesenchymal stem cells, embryonic stem cells, induced pluripotent stem cells, and endothelial progenitor cells has been carried out. In particular, liver-derived induced

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pluripotent stem cells show distinct clinical results for autologous use as a liver stem cell-based therapy as they can arise from autologous stem cells, thereby avoiding the immunological incompatibility-related side effects. Moreover, the induced pluripotent stem cells extracted from liver donor grafts may be an acceptable ethical issue. Nevertheless, the long-term efficacy of such therapy is still unproven, and further extensive experimental comparative trial studies on a larger scale using animal models are needed.^{16–18}

In conclusion, significant emerging progress has been made in the field of hepatic regenerative medicine as researchers have paid great attention to inventing therapeutic solutions for diseased liver replacement rather than performing the known curative hepatic surgeries in order to minimize or avoid their related side effects for a better outcome. However, further extensive studies with a comparative analysis on a larger scale are needed to prove their efficacy.

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