Minireview

Therapeutic strategies to improve liver regeneration after hepatectomy

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Impact Statement

We explain the process of liver regeneration after hepatectomy and the therapeutic strategies that could improve liver regeneration. Accumulated studies have reported that liver regeneration could be induced by promoting proliferation of and metabolism in hepatocytes and transplantation of mesenchymal stem cells. This review may provide clues to discover and develop successful treatments for patients who undergo liver resection or transplantation.

Abstract

Chronic liver disease is one of the most common diseases worldwide, and its prevalence is particularly high among adults aged 40–60 years; it takes a toll on productivity and causes significant economic burden. However, there are still no effective treatments that can fundamentally treat chronic liver disease. Although liver transplantation is considered the only effective treatment for chronic liver disease, it has limitations in that the pool of available donors is vastly insufficient for the number of potential recipients. Even if a patient undergoes liver transplantation, side effects such as immune rejection or bile duct complications could occur. In addition, impaired liver regeneration due to various causes, such as aging and metabolic disorders, may cause liver failure after liver resection, even leading to death. Therefore, further research on the liver regeneration process and therapeutic strategies to improve liver regeneration are needed. In this review, we describe the process of liver regeneration after hepatectomy, focusing on various cytokines and signaling pathways. In addition, we review treatment strategies that have been studied to date to improve liver regeneration, such as promotion of hepatocyte proliferation and metabolism and transplantation of mesenchymal stem cells. This review helps to understand the physiological processes involved in liver regeneration and provides basic knowledge for developing treatments for successful liver regeneration.

Keywords: Liver, regeneration, hepatocyte, hepatectomy, mesenchymal stem cells, therapy

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Introduction

Chronic liver disease (CLD) is a progressive destruction of liver tissue and functions over time, and a leading cause of mortality worldwide as end-stage liver disease.[1] In addition, its high prevalence and mortality in the economically active adult population aged 40–60 years contribute to its significant economic burden.[2] However, there are no drugs for treating CLD. Liver transplantation is currently considered the only fundamental treatment for CLD, but it is not widely available because of the limited number of donor livers compared with the large pool of potential recipients.[3] In addition, impaired liver recovery after liver resection may occur in both the live liver donors and the transplant recipients.[4] Side effects including immune rejection response and biliary complications may also occur in recipients.[5,6] Hence, strategies for successful liver regeneration after liver resection are needed to maintain the metabolic functions of the liver for the survival of both donor and recipient. But a lack of understanding about liver regeneration has limited progress in the development of treatment strategies. In this review, we provide insights for the development of liver regeneration strategies by explaining the process of liver regeneration after partial hepatectomy (PHx) and reviewing currently suggested possible treatments for liver regeneration.

Regenerative response of the liver to PHx

Over the past several decades, most of our understanding about liver regeneration has been acquired from studies

using the PHx model, in which two-thirds of the liver is surgically removed.[7] After PHx, the remaining liver enlarges to compensate for the loss of liver mass by facilitating hepatocyte proliferation.[8] Immediately following PHx, remaining hepatocytes recognize various pathogen-associated molecular patterns and damage-associated molecular patterns secreted by damaged cells or necrotic cells and begin to prepare for cell proliferation.[9,10] The liver plays a pivotal role in systemic glucose homeostasis, and within 4 h after PHx, the loss of liver tissue limits the glucose supply throughout the body, and the blood glucose level decreases markedly.[11,12] To support the enormous energy demand required by hepatic cell proliferation, hepatic and systemic glucose alteration occurs.[13] Then, hepatocyte proliferation occurs from 12 h and reaches a peak at 24 h after PHx.[14] Liver mass increases significantly in the period from 24 to 72 h post-PHx.[14,15] During the same time frame, systemic glucose depletion stimulates lipolysis in adipose tissue and enhances transfer of fatty acids into the liver as an alternative energy source.[16] Fatty acid intake in the liver leads to rapid accumulation of hepatic triglycerides (TG), in turn leading to transient regeneration-associated steatosis.[17] Following sufficient hepatic cell proliferation, the remnant liver decreases excess cell proliferation through apoptosis between 60 and 96 h after PHx.[18] Finally, the liver returns to its original size within five to seven days after PHx.[19]

During liver regeneration, mature hepatocytes in the remaining liver replicate to replenish the lost hepatocytes in response to various cytokines and growth factors, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and hepatocyte growth factor (HGF).[20,21] TNF-α secreted from Kupffer cells stimulates them to release IL-6, which binds to glycoprotein 130 expressed by hepatocytes.[22,23] IL-6 interacting with glycoprotein 130 activates STAT3 in hepatocytes, and the activated STAT3 induces expression of genes related to proliferation, such *as c-Jun, c-Fos, and c-Myc*, and leads hepatocytes to enter cell cycle.[23–25] Once hepatocytes undergo the cell cycle, various mitogens promote transition to the G1/M phase. The HGF, produced by non-parenchymal cells, stimulates the PI3K/AKT signaling pathway that triggers the cell cycle transition to the S phase and promotes DNA synthesis in hepatocytes by inducing expression of cyclin D.[26–28] In addition, Wnt proteins released from non-parenchymal cells induce nuclear translocation of β-catenin in hepatocytes.[29] Then, activated β-catenin upregulates the expression of mitogenic proteins, including c-myc and cyclin D1, in hepatocytes.[30] In the presence of mitogens, hepatocytes continue the cell cycle and are capable of achieving the required liver mass. When sufficient liver mass is present, hepatocyte proliferation is suppressed by antiproliferative cytokines, including IL-1 and transforming growth factor (TGF)-β.[31,32] TGF-β, the most well-known antiproliferative cytokine, stimulates translocation of R-Smad into the nucleus, and there, activated R-Smad reduces expression of cyclin D, E and cyclin-dependent kinase (CDK) 2, 4 to inhibit DNA synthesis in the hepatocytes.[14,33] Downregulated DNA synthesis inhibits hepatocyte proliferation, leading to termination of liver regeneration.

Therapeutic strategies for liver regeneration after partial hepatectomy

As described above, liver regeneration is a complex and well-orchestrated process in which various cytokines and cellular signals are intertwined. This being so, surgical intervention, including liver transplantation or liver resection, is considered an effective treatment for CLD. However, despite the strong regenerative capacity of the liver, unsuccessful liver restoration could result in post-hepatectomy liver failure, which is life-threatening.[34–36] Therefore, promising therapeutic strategies that facilitate the liver regeneration process are necessary. Until now, various attempts have been explored to promote liver regeneration by promoting hepatocyte proliferation and glucose/lipid metabolism and transplanting mesenchymal stem cells (MSCs) into the resected liver (Figure 1). In this section, we review these therapeutic strategies that have the potential to enhance liver regeneration.

Stimulating proliferation during liver regeneration

Hepatocyte proliferation in the remnant liver could be promoted by proliferative cytokines or activating directly signaling pathways.[37] In the PHx liver, administration of anakinra, an IL-1 receptor antagonist, upregulated proliferating cell nuclear antigen (PCNA) compared with the vehicle-giving group.[38] Kalinin *et al*.[39] demonstrated that treatment with the protein internalin B generated from *Listeria monocytogenes*, which mimics HGF, activated extracellular signal-regulated kinase and upregulated expression of cyclin D1 and CDK 2, 4 in rats with PHx. Wnt/β-catenin signaling is also shown to contribute to liver mass recovery. In rats that underwent transplantation with a liver 30% of normal size after removal of the entire liver, treatment of Wnt agonist upregulated the expression of cyclin D1 and replenished ATP content, which serves as the energy supply for regeneration.[40] The Wnt/β-catenin pathway activated by a thyroid hormone receptor-β agonist also increased cyclin D1 expression in PHx mice.[41] Long non-coding RNA small nucleolar RNA host gene 12 (SNHG12) is known to be involved in cellular proliferation and metastasis in various cancer cells by activating Wnt/β-catenin signaling.[42,43] In mice receiving PHx, SNHG12 overexpression significantly increased PCNA-positive hepatocytes by stimulating Wnt/β-catenin signaling, whereas the liver regeneration promoted by SNHG overexpression was alleviated by Wnt inhibitor IWR-1.[44] Inhibition of factors that interfere with the cell cycle can also boost liver regeneration. As a cell cycle halter, p21 suppressed cell cycle progression in hepatocytes and impeded liver regeneration.[45,46] Ritschka *et al*.[47] demonstrated that senolytic compound ABT-737, which is a class of drugs that causes selective elimination of senescent cells, increased regenerative capacity in the livers of mice after PHx by inhibiting expression of p21. Counteracting the role of TGF-β is also a possible solution for helping hepatocyte proliferation in resected liver. Treatment with galunisertib, a small molecular inhibitor of TGF-β1 receptor type 1, upregulated the levels of cyclin E1 and CDK2 and the number of hepatocytes expressing Ki-67 in the PHx liver, thereby promoting liver regeneration.[48]

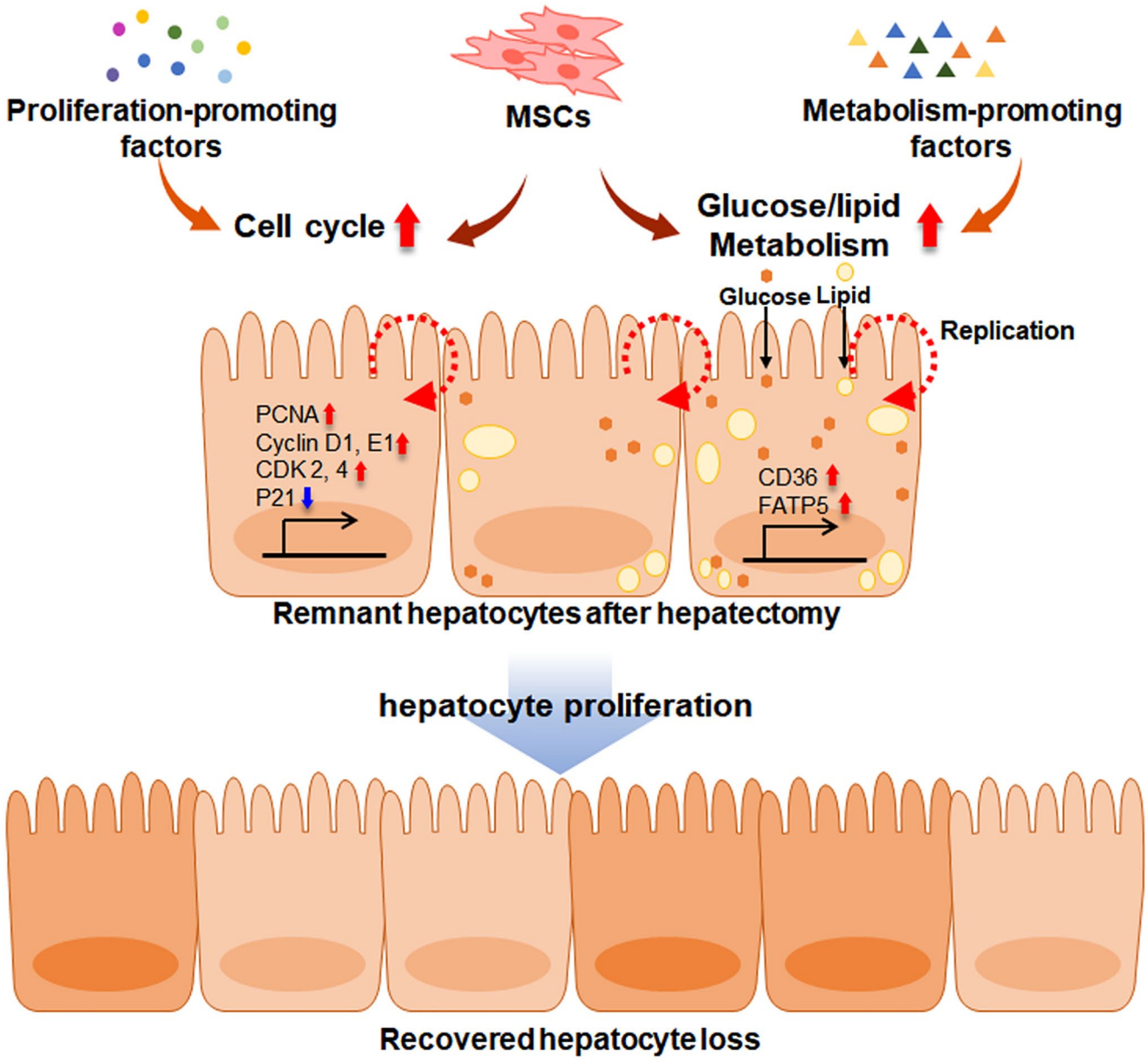

Figure 1. A schematic description of therapeutic strategies to promote liver regeneration. Therapeutic factors and mesenchymal stem cells (MSCs) can facilitate liver regeneration by improving hepatocyte proliferation and metabolism. Proliferation-promoting factors, such as anakinra, internalin B, Wnt agonist, thyroid hormone receptor-β agonist, long non-coding RNA small nucleolar RNA host gene 12, ABT-737, and galunisertib, impact the cell cycle progression in hepatocytes. They upregulate the levels of proliferating cell nuclear antigen (PCNA), cyclin D1, E1, and cyclin-dependent kinase (CDK) 2,4, and downregulate expression of p21, promoting hepatocyte proliferation. Metabolism-promoting factors, such as G49, replication initiator 1, and adipocyte differentiation–related protein, enhance the expression of cluster of differentiation 36 (CD36) and fatty acid transport protein 5 (FATP5), which elevate uptake of glucose and lipid into hepatocytes and contribute to the increase of the metabolism supplying energy required for hepatocyte proliferation. Transplantation of MSCs also helps in liver regeneration through influencing hepatocyte proliferation and metabolism.

Several studies have reported that advancing the induction of metabolic reprogramming promotes liver regeneration. Pyruvate dehydrogenase kinase 4 (PDK4) is a crucial mediator for gluconeogenesis. PDK4 deletion enhanced hepatic insulin signaling and fatty acid uptake and accelerated recovery of liver mass and hepatocyte proliferation in animal models of PHx.[49] G49 is a dual agonist of glucagon-like peptide-1/glucagon receptor and modulates glucose uptake and glycogen synthesis. G49 treatment increased the survival rate of mice with nonalcoholic steatohepatitis after PHx and elevated hepatocyte proliferation by enhancing glucose oxidative metabolism.[50] In addition, it has been shown that disruption of hepatic lipid metabolism results in impaired liver regeneration, suggesting that promoting transient hepatic lipid accumulation is an important strategy to enhance liver regeneration. Reduced lipid transport to and storage in the liver could interrupt liver restoration. Replication initiator 1 (REPIN1) is a transcriptional factor upregulating cluster of differentiation 36 (CD36), which is a well-known marker of lipid transport into hepatocytes.[51] Abshagen *et al.*[52] showed that REPIN1 deletion lowered the expression of CD36 and fatty acid transport protein 5 and

suppressed transient hepatic steatosis. Adipocyte differentiation-related protein (ADRP) inhibits very low-density lipoprotein secretion and increases hepatic TG storage.[53] ADRP-deficient mice had delayed liver regeneration because of decreased accumulation of hepatic TG after PHx.[54] Based on these findings, promoting the proliferation-related signaling pathway and the metabolism supplying the energy required for hepatocyte proliferation are promising strategies for liver regeneration. Therefore, further studies on these mechanisms are needed to develop therapeutic agents for treating the resected liver.

Potential of MSCs and MSC-derived scretome for improving liver regeneration

Along with controlling various events that enhance regenerative capacity in liver tissue, stem cell transplantation is an additional therapeutic approach to promote better liver regeneration.[55] Stem cells are widely studied and employed based on their regenerative ability. Among the various types of stem cells, MSCs are considered one of the most effective multipotent cells and are widely applied in various disease treatments as a regenerative therapy.[56–58] Also, MSCs are known to promote hepatocyte proliferation, modulate immune and inflammatory responses, and regulate neovascularization in the liver.[20,59,60] MSCs isolated from rat bone marrow (BM-MSCs) transplanted into rats with PHx migrated to the liver, where they promoted hepatocyte proliferation and improved the serum albumin level.[61,62] Ding *et al*.[63] reported that BM-MSCs activated the AKT/GSK-3β/β-catenin pathway, which upregulated liver glycogen synthesis and hepatocyte proliferation. Transplantation of rat BM-MSCs was also shown to activate mTOR signaling, which improved mitochondrial function and promoted fatty acid oxidation, supplying energy required for liver regeneration in rats with PHx.[64] Furthermore, injecting normal BM-MSCs into albumin-deficient rats with PHx increased albumin-producing hepatocytes derived from the donor BM-MSCs.[65] In addition to BM-MSCs, MSCs isolated from adipose tissue (AD-MSCs) were reported to promote liver regeneration in rodent models which had undergone hepatectomy.[66] Transplantation of AD-MSCs upregulated the hepatic regeneration-associated factors such as Erk1/2, JNK, p38 MAPK, c-Fos, and c-Jun and contributed to liver regeneration in rats after PHx.[67] Transplantation of AD-MSCs decreased the apoptosis of hepatocytes, increased the proliferation of hepatocytes, and facilitated the recovery of liver mass and function.[67–69]

Recently, a few studies have reported that factors secreted from MSCs have therapeutic effect on liver regeneration. Injection of exosome-rich secretome from rat BM-MSCs reduced liver damages and increased albumin level in mice that underwent PHx.[70] Lee *et al*.[71] demonstrated that conditioned medium (CM) from lipopolysaccharide-preconditioned AD-MSC had higher amounts of HGF, vascular endothelial growth factor, TNF-α, and IL-6 compared with CM from untreated AD-MSC, and the cytokines-plentiful CM increased the number of proliferative cells in partially hepatectomized mice. Treatment CM obtained from human liver-derived MSCs (L-MSCs) stimulated hepatocyte proliferation by upregulating TNF-α, HGF, and PCNA expression in mice with PHx.[72] In addition, microvesicles released from human L-MSCs were shown to alleviate hepatocyte apoptosis by elevating cyclin A1 expression and improved hepatic regeneration in rats with PHx.[73] However, because the roles of MSCs and MSC-derived secretome in liver regeneration have not yet been fully investigated, further research is required to explore the beneficial effects of MSCs in liver restoration.

Conclusions

Liver regeneration is a process involving various cytokines and signaling pathways to restore lost liver mass.[37] If this process is compromised or delayed after liver resection, acute liver failure could develop, which may be life-threatening for the patient. Therefore, researchers are conducting studies on promoting liver regeneration by inducing hepatocyte proliferation, regulating metabolism, and transplanting MSCs. However, compared to research on liver regeneration in damaged tissue occurring as a result of CLD, studies on liver regeneration arising in the remnant liver after hepatectomy are limited. In addition, although the biological understanding of liver regeneration has greatly advanced to date, effective treatments for promoting liver regeneration are lacking because studies on clinical application are rare and the therapeutic effects and safety of these factors have not been verified. Therefore, more thorough research on factors involved in liver regeneration after hepatic resection is required to broaden our understanding and help discover and develop potential therapeutic targets to promote successful liver regeneration.

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HJ, CL, and MJL contributed to this paper with literature review and drafting the manuscript; YJ contributed to this paper with conception, review, drafting and editing the manuscript, and supervision. All authors have read and agreed to the published version of the manuscript.

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