pISSN 2287-2728
eISSN 2287-285X

CMH

Review

http://dx.doi.org/10.3350/cmh.2015.21.1.7
Clinical and Molecular Hepatology 2015;21:7-13

Clinical implications of advances in liver regeneration

Yong Jin Kwon[1], Kyeong Geun Lee[2], and Dongho Choi[2]

[1]Department of Surgery, Hallym University College of Medicine, Kangnam Sacred Heart Hospital, Seoul, Korea; [2]Department of Surgery, Hanyang University College of Medicine, Seoul, Korea

Remarkable advances have been made recently in the area of liver regeneration. Even though liver regeneration after liver resection has been widely researched, new clinical applications have provided a better understanding of the process. Hepatic damage induces a process of regeneration that rarely occurs in normal undamaged liver. Many studies have concentrated on the mechanism of hepatocyte regeneration following liver damage. High mortality is usual in patients with terminal liver failure. Patients die when the regenerative process is unable to balance loss due to liver damage. During disease progression, cellular adaptations take place and the organ microenvironment changes. Portal vein embolization and the associating liver partition and portal vein ligation for staged hepatectomy are relatively recent techniques exploiting the remarkable progress in understanding liver regeneration. Living donor liver transplantation is one of the most significant clinical outcomes of research on liver regeneration. Another major clinical field involving liver regeneration is cell therapy using adult stem cells. The aim of this article is to provide an outline of the clinical approaches being undertaken to examine regeneration in liver diseases. **(Clin Mol Hepatol 2015;21:7-13)**

Keywords: Liver regeneration; Hepatectomy; Liver transplantation

INTRODUCTION

The liver possesses the specific competence to return to a constant size within a short period after injury.[1,2] We can observe this clinically in the form of regeneration after liver resection or liver transplantation, and after toxic liver injury. Liver regeneration involves hyperplasia of all the cell types of the liver. In humans, hepatocyte replication generally starts within a day of major hepatectomy, and replication of non-parenchymal cells, such as endothelial cells, Kupffer cells, and biliary cells begins somewhat later.[3] Intensive research on liver regeneration has been carried out for several years (Table 1). But the molecular signals responsible for maintaining an original liver volume are unclear. However it stands to reason that the liver keeps up a delicate balance between cell loss and excess growth.[4] Remarkable advancements that are directly relevant to clinical problems have been made in our understanding of liver regeneration. Moreover new experimental approaches have provided us much more information of hepatic failure and liver regeneration.[5] The aim of this review is to survey recent progress in understanding liver regeneration. Greater understanding will lead to safer operations on living donors and on patients with huge or multiple liver masses. Furthermore it should provide to the development of new treatment strategies and diagnostic procedures for various liver diseases.

Abbreviations:

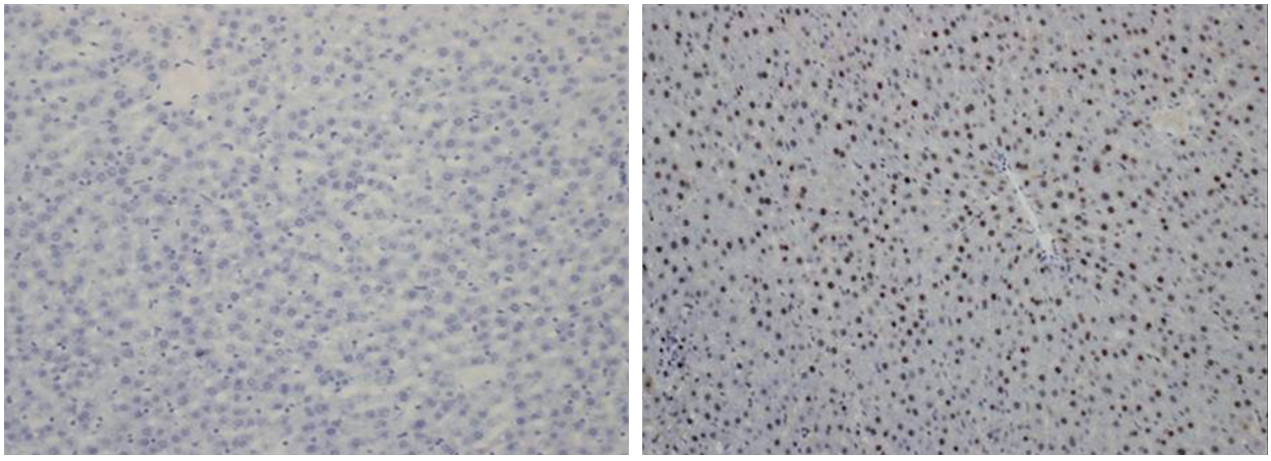
ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; EGF, epidermal growth factor; HGF, hepatocyte growth factor; IL-6, interleukin-6; ISGLS, international study group of liver surgery; PHLF, post-hepatectomy liver failure; POD, post-operative day; PVE, portal vein embolization; PVO, portal vein occlusion; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha

Corresponding author : Dongho Choi
Department of Surgery, Hanyang University College of Medicine,
222 Wangsimni-ro, Seongdong-gu, Seoul 133-791, Korea
Tel. +82-2-2290-8448, Fax. +82-2-2281-0224
E-mail; crane87@hanyang.ac.kr

Received : Jan. 30, 2015 / **Accepted :** Feb. 16, 2015

Table 1. Chronological overview of liver regeneration research

Year	First author	Contents
2011[44]	Mortensen	Animal research on liver regeneration
2010[45]	Kandilis	Variable cell types and topographic differences
2007[2]	Michalopoulos	Molecular aspects of liver regeneration
2006[1]	Fausto	Molecular mechanism of liver regeneration
2004[46]	Black	Molecular aspects of liver regeneration
2004[47]	Zimmermann	Regulatory steps of liver regeneration
2001[48]	Kountouras	Liver regeneration after hepatectomy
2000[49]	Diehl	Molecular aspects of liver regeneration
1997[50]	Kay	Molecular aspects and clinical applications of liver regeneration
1996[51]	Taub	Genetic aspects of liver regeneration
1996[52]	Diehl	Signal regulation during liver regeneration
1991[53]	Fausto	Variable growth factors in liver
1990[54]	Leffert	Molecular aspects of liver regeneration
1990[55]	Michalopoulos	Molecular aspects of liver regeneration
1986[56]	Alison	Molecular aspects of liver regeneration



Ki-67 (–) Ki-67 (+)

Figure 1. Ki-67 immunostating for regenerating rat liver following 2/3 liver resection. Ki-67 positive hepatocytes indicating hepatoctyes are proliferating after hepatectomy. Most of hepatocytes are stained with Ki-67.

MECHANISM OF LIVER REGENERATION

After liver resection, the residual liver responds by undergoing hyperplasia (Fig. 1).[1] Upon partial hepatectomy, non-diving mature hepatocytes quickly reenter the cell cycle. Throughout proliferation, liver recover its own volume. There are two main proposals concerning the physiological triggers for liver regeneration.[6] One is that the increased energy demand per unit liver volume after partial hepatectomy generates an early stress signal.[7] The other is that liver regeneration is triggered by altered hemodynamic factors. Although there is a definite correlation between blood flow and liver regeneration, the definite role of blood flow in liver regeneration remain unclear.[6] Similar liver regeneration can be initiated after several different hepatic injuries including viral and toxic hepatitis.

Standard liver regeneration

Usually hepatocytes are non-dividing (G0 phase) in the normal liver. After liver injury, they enter the G1 phase. Tumor necrosis

http://dx.doi.org/10.3350/cmh.2015.21.1.7

Table 2. Cytokines and growth factors engaged in liver regeneration

Cytokine	Function
Tumor necrosis factor α (TNF-α)	After partial hepatectomy, expression of TNF-α is induced in Kupffer cells. It vitalize the transcription factor, nuclear factor κB (NF-κB). The latter is an potent regulator of initiation of liver regeneration.
Interleukin-6 (IL-6)	IL-6 is increased after partial hepatectomy and serum levels are elevated soon after hepatectomy. It is mainly secreted by Kupffer cells and the LPS/MyD88 pathway regulate its expression.
Hepatocyte growth factor (HGF)	After partial hepatectomy, serum HGF level increase intensively within 1-3 hours. HGF activates receptor tyrosine kinase c-Met. It is a major hepatocyte mitogen.
Epidermal growth factor (EGF) family	EGF activates EGFR/ErbB1, HER2/ErbB2, HER3/ErbB3 and HER4/ErbB4. It provoke hepatocyte proliferation and is significant for survival after partial hepatectomy.
Fibroblast growth factors (FGFs)	FGFs activate FGF receptors (FGFR) 1–4.
Vascular endothelial growth factor (VEGF)	VEGF controls angiogenesis and lymphangiogenesis by activating three receptor tyrosine kinases (VEGFR1-3).
Insulin-like growth factors (IGFs)	IGF-I and IGF-II are strong mitogens. They bind to six insulin-like growth factor binding proteins (IGFBPs).
Transforming growth factor β (TGF-β)	TGF-β activates heteromeric receptor complexes containing type I and type II transmembrane receptors. It is a powerful suppressor for variable types of epithelial cells.
Activins	Activins activate heterodimeric receptor complexes consisting of type I and type II receptors. Activin A has a potential role in terminating the liver regeneration.

factor α (TNF-α) and interleukin-6 (IL-6) are released from Kupffer cells, and these contribute to the initiation of the cell cycle (G0 to G1) by binding to their receptors.[8,9] Several factors for instance hepatocyte growth factor (HGF), epidermal growth factor (EGF), and transforming growth factor α (TGF-α) are thought to initiate the G1 to S transition.[10] These factors stimulate DNA replication and mitosis by binding to their corresponding receptors.[11] TGF-β1 is a noted inhibitor of hepatocyte proliferation.[12] In the normal liver, growth factors and TGF-β have agonistic effects. At the begining of regeneration, the HGF signal is more powerful than that of TGF-β, whereas at the termination of regeneration, the original balance is restored.[13] Activin is an inhibitor of liver regeneration that selectively suppress hepatocyte proliferation. When the liver volume returns to its own size, activin A, apoptosis and other factors may terminate the regeneration process.[14] Table 2 summarizes the properties of various cytokines and growth factors engaged in liver regeneration.[15] Shear stress is the powerful stimuli for liver regeneration. After liver resection, the increased portal vein flow past hepatocytes or sinusoidal endothelial cells initiates regeneration and regulates the size of the liver. Shear stress on the endothelial cells is the powerful impetus for regeneration, liver volume regulation, and growth, as well as atrophy.[16] Hemodynamic factors increase the shear stress in the liver, and nitric oxide (NO) is secreted. NO then initiates the liver regeneration cascade.[17]

Oval cell-mediated liver regeneration

Oval cells are detected after partial hepatectomy when hepatocyte proliferation is suppressed in the rat or mouse models. It is very difficult to find oval cell mediated liver regeneration in the chronic liver disease patients. Their origin is unclear, but there is considerable evidence that they derive from the biliary component.[18] Unlike in standard liver regeneration, in oval cell-medicated regeneration there is no hepatocyte proliferation. When hepatocyte proliferation is constrained, bile duct cells reproduce and expand into many oval cells. Gene expression in these cells has characteristics of both biliary cells and hepatocytes. The oval cells transform into a hepatocyte phenotype.[19]

CLINICAL APPLICATIONS OF LIVER REGENERATION

Recent research for liver regeneration is focused on human liver disease treatment especially for various hepatectomy for chronic liver disease and hepatic tumors. For these innovative researches on liver regeneration, hepatectomy outcomes have markedly improved over recent decades.[20] However post-hepatectomy liver failure (PHLF) remains one of the most dangerous and life-threat-

ening complications of hepatectomy, and takes place in up to 10% of cases.[21] A number of different criteria are used for PHLF. One of the most frequently used in clinical practice is the 50-50 criterion that combines a PT index <50% and serum total bilirubin >50 μmol/L (>2.9 mg/dL) on post-operative day (POD) 5.[22] In 2011, the International Study Group of Liver Surgery (ISGLS) described the three grades of PHLF.[23] This kind of criteria could be established because of marked increase of understanding of clinical aspect of liver regeneration potential in chronic liver disease patients.

Portal vein embolization

Portal vein embolization (PVE) is the best example of how liver regeneration research has influenced clinical application. PHLF is associated with a small relative residual liver volume.[24] Two-stage liver resection after portal vein occlusion (PVO) is one of the best strategies for volume manipulation.[3] PVE was first described by Kinoshita in 1980s.[25,26] In general, two approaches exist for portal vein occlusion: radiological PVE and surgical portal vein ligation (PVL). After liver injury, various activated growth factors are carried from the intestine to the liver. These factors run through the portal flow, not the hepatic artery, and induce a number of molecular and cellular changes.[27] PVO induces apoptosis in the same side lobe, and proliferation of the opposite side lobe.[28] PVE is indicated only if there is a high risk of a small relative residual liver volume after hepatectomy.[29] There are no universal guidelines. Schindl et al. observed a relationship between liver dysfunction score and relative residual liver volume, and they identified a critical minimum relative residual liver volume of 26.6% that was needed to avoid serious hepatic dysfunction.[24] In normal livers, if the size of the liver remnant is likely to exceed 30% of the original volume, hepatectomy can be performed safely. In cirrhotic livers, the threshold is 50% based on our current practice and available data.[3]

Living donor liver transplantation

Living donor liver transplantation is state of the art of liver regeneration research. Even though wonderful clinical outcomes from Asian large volume centers, there are still obstacles to be overcome. In 2008, Ghobrial et al. examined donor morbidity following living donor liver transplantation. Overall complications were 38% (148 donors had a total of 220 complications). According to the Clavien grading system, there were 48% grade 1 complications, 47% grade 2, <4% grade 3 and 1.4% grade 4 (leading to death).[30] For donor safety, it is necessary to minimize the size of the graft. However, graft size is positively related to recipient prognosis, and a balance between the two must be maintained. In terms of donor safety and recipient prognosis, research on liver regeneration is essential for improving clinical outcomes.

Small-for-size graft syndrome

Understanding about liver regeneration has been made some progress for treating small-for size graft syndrome following living donor liver transplantation. Small-for-size graft syndrome is defined as long-lasting cholestasis and refractory ascites.[31] Long-lasting cholestasis is defined as total bilirubin >10 mg/dL on POD 14, and refractory ascites is defined as an amount of ascites of >1 L/day on POD 14 or >500 mL/day on POD 28.[32]

In 2008, Ikegami et al. summarized the reason of small-for-size syndrome and outlined potential solutions. The former involved graft size, quality, and flow as graft-related factors, and portal hypertension and the severity of the liver disease as recipient-related factors. Right lobe grafts, auxiliary transplants, and dual graft transplants were described as strategies for overcoming insufficient graft size. For poor graft quality, use of younger donors and donor diet programs for steatosis were possible strategies. Various shunt and graft operations were considered for excessive inflow and insufficient outflow drainage. Larger grafts and appropriate flow were considered ways of dealing with poor general recipient condition.[33]

Associating liver partition and portal vein ligation for staged hepatectomy

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) refers to in situ splitting and iatrogenic portal vein obliteration aimed at inducing rapid liver hypertrophy; it was first introduced by Hans Schlitt in 2007.[34] Schnitzbauer et al. performed PVL with in situ splitting in 2012. This approach induced median hypertrophy of 74%, and yielded results superior to PVL or PVE alone.[35] Knoefel et al. demonstrated that ALPPS offered an chance for curative hepatectomy even after PVE had failed and had resulted in insufficient growth of the liver remnant (Fig. 2).[36]

Stem cells and liver regeneration

In 2007, Takahashi et al. generated pluripotent stem cells from adult human fibroblasts.[37] This approach could lead, in the fore-

http://dx.doi.org/10.3350/cmh.2015.21.1.7

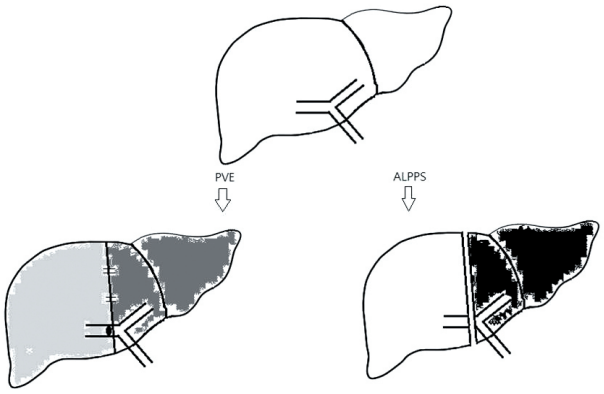


Figure 2. Portal vein embolization (PVE) versus associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). PVE is radiological method, and so less invasive. However a shunt is opened in the liver. ALPPS is more invasive than PVE, because surgery is needed, but complete isolation is achieved.

seeable future, to a remarkable change of therapeutic strategy in the area of cell-based therapies for life-threatening liver diseases. Recently there have been clinical trials of transplantation of mature hepatocytes, but the long-term effect is uncertain. If we can get over these problems, we will use variable stem cells, such as autologous induced pluripotent stem cells, mesenchymal stem cells, and endogenous hepatic stem/progenitor cells, as possible materials for transplantation.[38]

RECENT TRENDS AND FUTURE PERSPECTIVES

Tissue engineering can be a useful therapeutic option that combines cells, biological scaffolds and active molecules.[39] Three-dimensional (3-D) scaffolds play a critical role in tissue engineering by regulating cell functions and inducing the formation of new tissues and organs. They supply adequate space for the transplanted cells, as well as physical and biological signals that promote adhesion, migration, proliferation and differentiation, and they also gather the cells that have proliferated, and released matrices, into functional tissues and organs.[40] In 2010, Ott et al. created an artificial biological lung from decellularized lungs. They made these lungs by detergent perfusion and succeeded in generating scaffolds that contained vasculature, airways and alveoli without cell. Thereafter they were able to successfully transplant the regenerated artificial lungs into the orthotopic position.[41] In 2010, Uygun et al. demonstrated the architecture of a decellularized 3-D liver, as well as its functional vasculature and the original matrix composition. Furthermore, they achieved recellularization of the graft in vitro. This artificial liver was viable on its own.[42] In 2013, Takebe et al. constructed a functional human organ from pluripotent stem cells. They generate functional human liver with vasculature from human induced pluripotent stem cells by transplantation of liver buds created *in vitro*.[43] 3-D printing refers to a variety of processes for making three-dimensional objects from a 3D models or other electronic data sources primarily through an additive process in which successive layers of material are laid down under computer control. In the near future, we should be able to generate bioprinted livers using 3D printing technology.

CONCLUSIONS

Liver regeneration has been well known for centuries, and in recent decades we have begun to understand its mechanism. Recent researches have focused on understanding liver regeneration after liver resection and liver transplantation. The use of innovative approaches could change strategies for treating liver dysfunctions such as PHLF and small-for-size graft syndrome. Liver regeneration has numerous applications. The use of PVO should permit the removal of large volumes of liver tissue with a diminished risk of liver failure. Hepatocyte transplantation could repopulate the liver of patients with inborn error metabolism. Moreover, regenerative therapy could provide innovative support for living donor transplantation. In the near future, we will be able to make artificial livers constructed from an individual's own cells. This would be the perfect way to support liver transplantation without the need for immunosuppressant drugs. In conclusion, the research of liver regeneration provides new strategies for the detection and treatment of a variety of liver diseases.

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Fausto N, Campbell JS, Riehle KJ. Liver regeneration. Hepatology 2006;43:S45-53.
2. Michalopoulos GK. Liver regeneration. J Cell Physiol 2007;213:286-300.
3. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. N Engl J Med 2007;356:1545-1559.

4. Duncan AW, Dorrell C, Grompe M. Stem cells and liver regeneration. Gastroenterology 2009;137:466-481.
5. Duncan AW, Soto-Gutierrez A. Liver repopulation and regeneration: new approaches to old questions. Curr Opin Organ Transplant 2013;18:197-202.
6. Abshagen K, Eipel C, Vollmar B. A critical appraisal of the hemodynamic signal driving liver regeneration. Langenbecks Arch Surg 2012;397:579-590.
7. Crumm S, Cofan M, Juskeviciute E, Hoek JB. Adenine nucleotide changes in the remnant liver: An early signal for regeneration after partial hepatectomy. Hepatology 2008;48:898-908.
8. Yamada Y, Kirillova I, Peschon JJ, Fausto N. Initiation of liver growth by tumor necrosis factor: deficient liver regeneration in mice lacking type I tumor necrosis factor receptor. Proc Natl Acad Sci U S A 1997;94:1441-1446.
9. Mohammed FF, Khokha R. Thinking outside the cell: proteases regulate hepatocyte division. Trends Cell Biol 2005;15:555-563.
10. Pediaditakis P, Lopez-Talavera JC, Petersen B, Monga SP, Michalopoulos GK. The processing and utilization of hepatocyte growth factor/scatter factor following partial hepatectomy in the rat. Hepatology 2001;34:688-693.
11. Zheng ZY, Weng SY, Yu Y. Signal molecule-mediated hepatic cell communication during liver regeneration. World J Gastroenterol 2009;15:5776-5783.
12. Apte U, Gkretsi V, Bowen WC, Mars WM, Luo JH, Donthamsetty S, et al. Enhanced liver regeneration following changes induced by hepatocyte-specific genetic ablation of integrin-linked kinase. Hepatology 2009;50:844-851.
13. Michalopoulos GK. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. Am J Pathol 2010;176:2-13.
14. Oe S, Lemmer ER, Conner EA, Factor VM, Leveen P, Larsson J, et al. Intact signaling by transforming growth factor beta is not required for termination of liver regeneration in mice. Hepatology 2004;40:1098-1105.
15. Bohm F, Kohler UA, Speicher T, Werner S. Regulation of liver regeneration by growth factors and cytokines. EMBO Mol Med 2010;2:294-305.
16. Sato Y, Tsukada K, Hatakeyama K. Role of shear stress and immune responses in liver regeneration after a partial hepatectomy. Surg Today 1999;29:1-9.
17. Schoen JM, Wang HH, Minuk GY, Lautt WW. Shear stress-induced nitric oxide release triggers the liver regeneration cascade. Nitric Oxide 2001;5:453-464.
18. Roskams TA, Theise ND, Balabaud C, Bhagat G, Bhathal PS, Bioulac-Sage P, Brunt EM, et al. Nomenclature of the finer branches of the biliary tree: canals, ductules, and ductular reactions in human livers. Hepatology 2004;39:1739-1745.
19. Michalopoulos GK. Liver regeneration: alternative epithelial pathways. Int J Biochem Cell Biol 2011;43:173-179.
20. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236:397-406.
21. Jaeck D, Bachellier P, Oussoultzoglou E, Weber JC, Wolf P. Surgical resection of hepatocellular carcinoma. Post-operative outcome and long-term results in Europe: an overview. Liver Transpl 2004;10:S58-63.
22. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg 2005;242:824-828.
23. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713-724.
24. Schindl MJ, Redhead DN, Fearon KC, Garden OJ, Wigmore SJ, Edinburgh Liver S, et al. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut 2005;54:289-296.
25. Kinoshita H, Sakai K, Hirohashi K, Igawa S, Yamasaki O, Kubo S. Preoperative portal vein embolization for hepatocellular carcinoma. World J Surg 1986;10:803-808.
26. Makuuchi M, Takayasu K, Takuma T, Yamazaki S, Hasegawa H, Nishiura S, et al. Preoperative transcatheter embolization of the portal venous branch for patients receiving extended lobectomy due to the bile duct carcinoma. J Jpn Soc Clin Surg 1984;45:14-20.
27. Yokoyama Y, Nagino M, Nimura Y. Mechanisms of hepatic regeneration following portal vein embolization and partial hepatectomy: a review. World J Surg 2007;31:367-374.
28. Madoff DC, Abdalla EK, Vauthey JN. Portal vein embolization in preparation for major hepatic resection: evolution of a new standard of care. J Vasc Interv Radiol 2005;16:779-790.
29. Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. Br J Surg 2006;93:1091-1098.
30. Ghobrial RM, Freise CE, Trotter JF, Tong L, Ojo AO, Fair JH, et al. Donor morbidity after living donation for liver transplantation. Gastroenterology 2008;135:468-476.
31. Soejima Y, Taketomi A, Yoshizumi T, Uchiyama H, Harada N, Ijichi H, et al. Feasibility of left lobe living donor liver transplantation between adults: an 8-year, single-center experience of 107 cases. Am J Transplant 2006;6:1004-1011.
32. Soejima Y, Shimada M, Suehiro T, Hiroshige S, Ninomiya M, Shiotani S, et al. Outcome analysis in adult-to-adult living donor liver transplan-

http://dx.doi.org/10.3350/cmh.2015.21.1.7

tation using the left lobe. Liver Transpl 2003;9:581-586.
33. Ikegami T, Shimada M, Imura S, Arakawa Y, Nii A, Morine Y, Current concept of small-for-size grafts in living donor liver transplantation. Surg Today 2008;38:971-982.
34. Zhang GQ, Zhang ZW, Lau WY, Chen XP. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): a new strategy to increase resectability in liver surgery. Int J Surg 2014;12:437-441.
35. Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255:405-414.
36. Knoefel WT, Gabor I, Rehders A, Alexander A, Krausch M, Schulte am Esch J, et al. In situ liver transection with portal vein ligation for rapid growth of the future liver remnant in two-stage liver resection. Br J Surg 2013;100:388-394.
37. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007;131:861-872.
38. Kakinuma S, Nakauchi H, Watanabe M. Hepatic stem/progenitor cells and stem-cell transplantation for the treatment of liver disease. J Gastroenterol 2009;44:167-172.
39. Langer R, Vacanti JP. Tissue engineering. Science 1993;260:920-926.
40. Hoshiba T, Lu H, Kawazoe N, Chen G. Decellularized matrices for tissue engineering. Expert Opin Biol Ther 2010;10:1717-1728.
41. Ott HC, Clippinger B, Conrad C, Schuetz C, Pomerantseva I, Ikonomou L, et al. Regeneration and orthotopic transplantation of a bioartificial lung. Nat Med 2010;16:927-933.
42. Uygun BE, Soto-Gutierrez A, Yagi H, Izamis ML, Guzzardi MA, Shulman C, et al. Organ reengineering through development of a transplantable recellularized liver graft using decellularized liver matrix. Nat Med 2010;16:814-820.
43. Takebe T, Sekine K, Enomura M, Koike H, Kimura M, Ogaeri T, et al. Vascularized and functional human liver from an iPSC-derived organ bud transplant. Nature 2013;499:481-484.
44. Mortensen KE, Revhaug A. Liver regeneration in surgical animal models - a historical perspective and clinical implications. Eur Surg Res 2011;46:1-18.
45. Kandilis AN, Koskinas J, Tiniakos DG, Nikiteas N, Perrea DN. Liver regeneration: focus on cell types and topographic differences. Eur Surg Res 2010;44:1-12.
46. Black D, Lyman S, Heider TR, Behrns KE. Molecular and cellular features of hepatic regeneration. J Surg Res 2004;117:306-315.
47. Zimmermann A. Regulation of liver regeneration. Nephrol Dial Transplant 2004;19 Suppl 4:iv6-10.
48. Kountouras J, Boura P, Lygidakis NJ. Liver regeneration after hepatectomy. Hepatogastroenterology 2001;48:556-562.
49. Diehl AM. Cytokine regulation of liver injury and repair. Immunol Rev 2000;174:160-171.
50. Kay MA, Fausto N. Liver regeneration: prospects for therapy based on new technologies. Mol Med Today 1997;3:108-115.
51. Taub R. Liver regeneration 4: transcriptional control of liver regeneration. FASEB J 1996;10:413-427.
52. Diehl AM, Rai RM. Liver regeneration 3: Regulation of signal transduction during liver regeneration. FASEB J 1996;10:215-227.
53. Fausto N. Growth factors in liver development, regeneration and carcinogenesis. Prog Growth Factor Res 1991;3:219-234.
54. Leffert HL, Koch KS, Lu XP, Brenner DA, Karin M, Skelly HF, et al. Cellular and molecular biology of hepatocyte growth, regeneration and gene expression. Adv Second Messenger Phosphoprotein Res 1990;24:352-358.
55. Michalopoulos GK. Liver regeneration: molecular mechanisms of growth control. FASEB J 1990;4:176-187.
56. Alison MR. Regulation of hepatic growth. Physiol Rev 1986;66:499-541.