

The concept of “domino” in liver and hepatocyte transplantation

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Abstract: Although orthotopic liver transplantation remains the only proven treatment for end-stage liver disease and inherited metabolic liver disease, its application has been limited by the scarcity of donor organs available for transplantation. Among feasible approaches developed to expand the donor organ pool, domino liver transplantation is a strategy in which explanted genetically defective livers of liver transplant recipients are used as grafts in other patients. Another promising therapeutic strategy is hepatocyte transplantation, an alternative to liver transplantation for certain groups of patients. However, the availability of primary hepatocytes is also hindered by the shortage of donor liver tissues. Against this background, domino hepatocyte transplantation, a strategy that utilizes the hepatocytes derived from the explanted livers of liver transplant recipients with noncirrhotic inherited metabolic liver diseases as the source of primary hepatocytes, may help increase the supply of liver cells available for transplantation. In this review, we focus on the *status quo* of domino liver transplantation and domino hepatocyte transplantation. We also describe recent innovative transplant strategies based on domino transplantation.

Keywords: domino hepatocyte transplantation, domino liver transplantation, inherited metabolic liver disease, primary hepatocyte

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Introduction

Since it was first performed for a 3-year-old child with biliary atresia in 1963,¹ liver transplantation (LT) has been increasingly used to treat patients with end-stage liver disease and inherited metabolic liver disease. With increasingly sophisticated transplantation surgical techniques, more extensive perioperative and postoperative management experience, and advancements in immunosuppressive agents, the long-term survival of liver transplant recipients has been significantly improved.^{2–4} Currently, LT is the only viable therapy for end-stage liver disease and inherited metabolic liver disease. However, the severe shortage of donor organs has hindered numerous patients from having access to LT, thereby leading to increased mortality in patients on the waiting list.⁵

To date, a few strategies have been developed to increase the supply of donor grafts for transplantation. Domino LT is one such strategy. It utilizes explanted livers procured from LT recipients with

monogenic hepatic diseases as grafts for other patients awaiting transplantation, to some extent alleviating the organ shortage.⁶ Alternative therapeutic approaches to LT are also being vigorously explored. Hepatocyte transplantation has been proposed as a potential alternative to LT for selected patients with acute liver failure (ALF) and inherited metabolic liver disease.^{7–9} However, the shortage of sources of donor liver cells has been a major obstacle in the clinical application of hepatocyte transplantation. Similar to the scenario in domino LT, explanted livers of LT recipients with noncirrhotic inherited metabolic liver diseases seem to be a promising source of high-quality hepatocytes for transplantation, namely domino hepatocyte transplantation.¹⁰

Domino liver transplantation

Nowadays, a growing number of patients with liver-based metabolic defects receive LT, either simply for life-saving, or for preventing neurological damage

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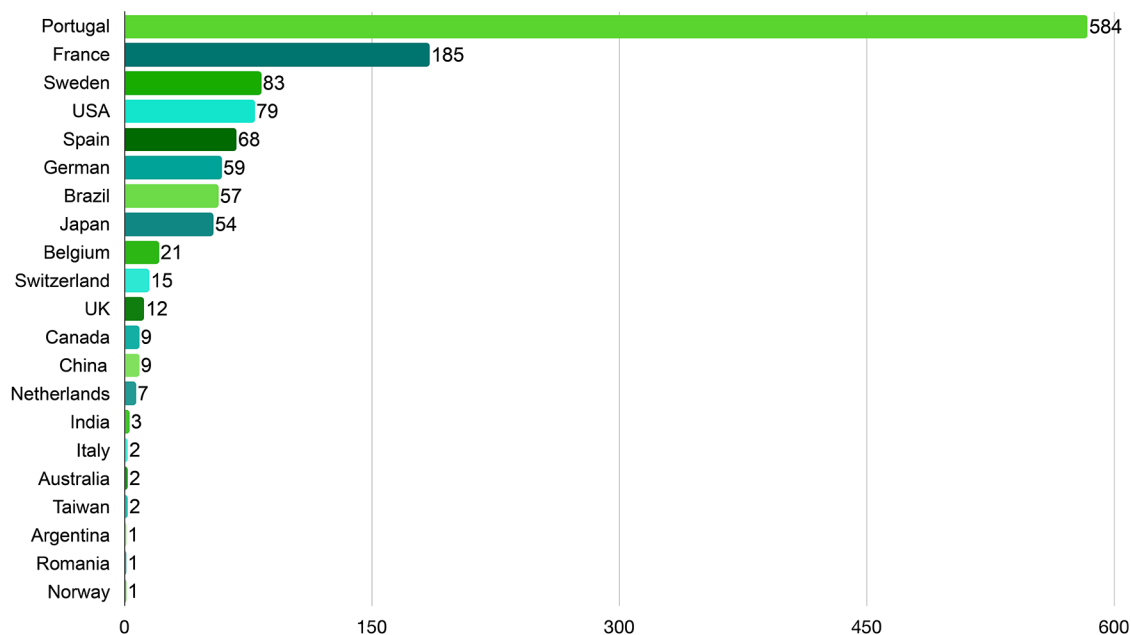


Figure 1. Reporting number of domino liver transplantation in the Domino Liver Transplantation Register until 31 December 2017.

and improving quality of life.^{11–13} With the increasing need for donor organs, the explanted liver during transplantation in one liver transplant recipient with monogenic liver disease, which would be simply sent for pathological examination, might be transplanted into a second recipient. This strategy is known as domino or sequential LT.^{14,15} Domino LT was first performed in Portugal in 1995 when an advanced oncological patient received a liver retrieved from a female adult LT recipient with familial amyloidotic polyneuropathy (FAP).¹⁵ Since then, the application of domino LT has greatly expanded the donor pool, enabling more specific patient groups to benefit from transplantation, thus shortening the overloaded waiting list.⁶

Domino liver donors

Generally, domino procedures can be performed with explanted livers from patients who have undergone LT for noncirrhotic inherited metabolic liver diseases, meanwhile their livers are anatomically and functionally normal except for some enzyme defects. According to the data in the Domino Liver Transplant Registry (<http://www.fapwtr.org/index.htm>), 1254 cases of domino LT on 1234 patients had been performed in 66 transplant centers in 21 countries and regions

up to 31 December 2017 (Figure 1). Explanted livers obtained from patients with FAP^{16–18} and maple syrup urine disease (MSUD)^{19–21} are the major sources of domino grafts. There are also other, less common, metabolic-diseased livers being used as domino grafts, including those from patients with acute intermittent porphyria, hereditary fibrinogen A α -chain amyloidosis, propionic acidemia, hyperhomocysteinemia, methylmalonic acidemia, familial hypercholesterolemia, primary hyperoxaluria, and hemophilia A (Table 1).^{22–37} It should be noted that not all liver grafts used in domino LT were associated with good recipient outcomes as some recipients developed early or late symptoms and even organ failure related to the underlying enzymatic defects.

Concerns regarding domino liver transplantation

The innate metabolic deficiency in the domino liver grafts raises the concern about the possibility of transmitting diseases from the donors to the recipients. Hence, despite excellent organ quality, not all explanted livers from patients with noncirrhotic inherited metabolic liver diseases are good candidates for domino LT. Taking the livers from patients with urea cycle diseases or thrombotic disorders as an example, these livers may rapidly

Table 1. The rare disease spectrum of the donors of domino liver transplantation.

Metabolic liver disease of donors	References	Year	Recipient		Diagnosis	Symptoms related to the domino donor liver	Outcome
			Age	Sex			
Acute intermittent porphyria	Dowman <i>et al.</i> ²²	2011	65	male	Hepatocellular carcinoma	axonal sensorimotor neuropathy	Died of sepsis related to surgical complications 32 days after transplantation
			43	male	Hepatocellular carcinoma	severe abdominal pain and symptoms of peripheral neuropathy, including leg weakness and sensory impairment	Alive, 13 months
			60	male	Hepatocellular carcinoma	N/A	Died of myocardial infarction secondary to profound intraoperative blood loss and graft dysfunction within 24 h after transplantation
Hereditary fibrinogen A α -chain amyloidosis	Stangou <i>et al.</i> ²³	2010	58–63 (n=4)	N/A	Hepatitis C, cryptogenic cirrhosis, or alcoholic cirrhosis, hepatocellular carcinoma	One with no evidence of de novo amyloid deposition up to 5 years;	One was alive at 5 years; one had normal liver and renal function at 2.5 years; two were lost to follow-up
Propionic acidemia	Moguile <i>et al.</i> ²⁴	2018	14	male	Fulminant hepatic failure	No symptoms with regular diet	Alive, two years
Hyperhomocysteinemia	Qu <i>et al.</i> ²⁵	2019	41	male	Acute liver failure following hemi-liver resection due to cholangiocarcinoma	Acquired hyperhomocysteinemia	Died of cholangiocarcinoma recurrence, 11 months
Methylmalonic acidemia	Khanna <i>et al.</i> ²⁶	2016	61	male	Primary sclerosing cholangitis and biliary cirrhosis	Elevated methylmalonate in blood and urine while receiving an unrestricted diet; no apparent symptoms	Alive, 9 months
Familial hypercholesterolemia	Popescu <i>et al.</i> ²⁷	2009	46	female	Hepatocellular carcinoma and hepatitis B-related cirrhosis	An elevated plasma cholesterol level; no signs of cardiovascular or atherosclerotic lesions	Alive, 7 years
	Liu <i>et al.</i> ²⁸	2010	60	male	Hepatocellular carcinoma	Plasma cholesterol level was slightly increased	Alive, 10 months

(Continued)

Table 1. (Continued)

Metabolic liver disease of donors	References	Year	Recipient		Diagnosis	Symptoms related to the domino donor liver		Outcome
			Age	Sex				
Primary hyperoxaluria	Golbus <i>et al.</i> ²⁹	2017	65	male	Primary sclerosing cholangitis and cirrhosis	Progressive atherosclerotic cardiovascular disease involving the arteries of proximal bilateral lower extremities, carotid arteries, and superior mesenteric artery	Alive, 7 years	
	Donckier <i>et al.</i> ³⁰	2001	69	male	Hepatitis C-related cirrhosis and multifocal hepatocellular carcinoma	Hyperoxalemia, hyperoxaluria, and renal insufficiency	Alive, 8 months	
	Casas-Melley <i>et al.</i> ³¹	2002	23-day-old	male	Fulminant hepatic failure caused by veno-occlusive disease	Hyperoxaluria; loss of differentiation between medulla and cortex of kidneys;	Re-transplantation, 4 months	
	Aziz <i>et al.</i> ³²	2005	57	female	End-stage liver disease secondary to chronic hepatitis C and alcohol abuse	Serum creatinine level rose steadily; bilateral increased echogenicity of the renal cortical parenchyma with prominent renal pyramids; elevated serum oxalate levels	Alive, 40 days	
Hemophilia A	Farese <i>et al.</i> ³³	2005	64	male	Cholangiocarcinoma	Marked increase of oxaluria; dialysis-dependent organ failure;	Died of bacterial pneumonia, 8 months	
	Franchello <i>et al.</i> ³⁴	2005	50	male	Cryptogenic cirrhosis and hepatocellular carcinoma	Renal function deteriorated; left renal stone and calcifications; increased oxalate and glycolate levels;	Re-transplantation, 3 months	
	Saner <i>et al.</i> ³⁵	2010	55–68 (n = 5)	N/A	Hepatocellular carcinoma, primary biliary cirrhosis, and hepatitis C-related cirrhosis	All five patients developed dialysis-dependent kidney failure;	Patient 1, 2, 4, 5: dead, 0.16– 11 months; Patient 3: re-transplantation, 12 days; alive, 20 months	
	Madeira <i>et al.</i> ³⁶	2009	69	male	Hepatocellular carcinoma and alcoholic cirrhosis	None; normal FVIII levels;	Alive, 110 days	
	Kurian <i>et al.</i> ³⁷	2020	65	male	alcoholic cirrhosis and hepatopulmonary syndrome	Slightly prolonged PTT immediately following transplant; no factor VIII deficiency and pathologic bleeding;	Died of unclear causes, three years	
N/A, not available; PTT, partial thromboplastin time.								

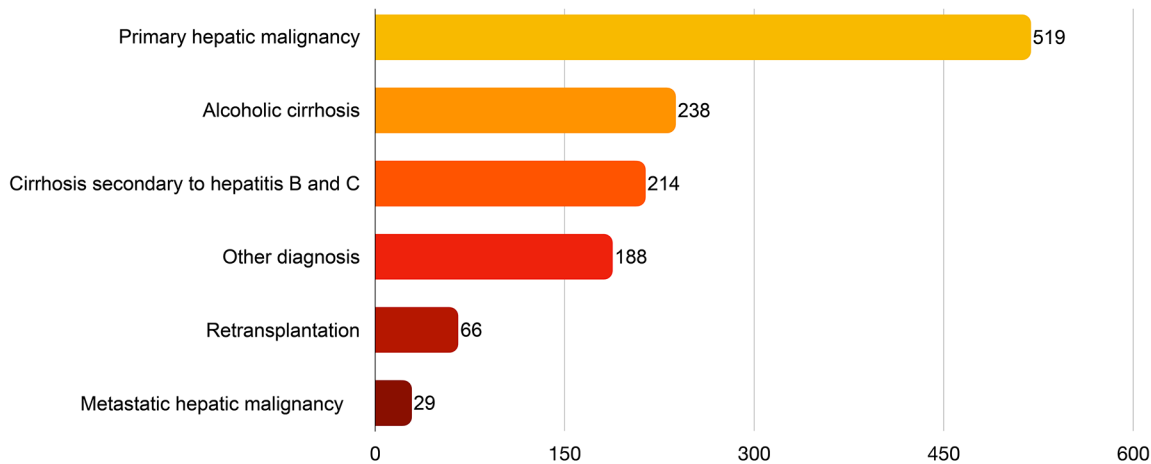


Figure 2. Indications for domino liver transplantation reported to the Domino Liver Transplantation Register until 31 December 2017.

result in metabolic disturbances associated with domino grafts and even life-threatening complications in the domino recipients. The ideal domino grafts should be explanted livers from patients with a systemic metabolic defect involving multiple organs, such as MSUD. The non-MSUD domino recipient has sufficient enzyme activity in extrahepatic tissues, which compensates for the genetic defect transmitted by the graft; thus protecting the domino recipient from the risk of disease transmission after LT.³⁸ Owing to the excellent organ quality comparable to living-related organs and limited risks of disease recurrence, such liver grafts can be widely applied without recipient restrictions. Recently, two large case series studies (involving 31 domino LT with MSUD liver grafts) showed that 30 recipients with various primary diseases were alive with good liver graft function, and the branched-chain amino acid concentrations were normal in all recipients with no metabolic decompensations.^{21,39}

However, domino LT, in which metabolically deficient grafts that may lead to the progressive development of acquired enzymatic deficiency in the recipients, should be limited to a small population of patients who: (1) have developed unresectable primary or metastatic liver malignancies and have an anticipated poor long-term prognosis, that is, the life expectancy of these potential domino recipients is estimated to be shorter than the interval until the development of metabolic symptoms; or (2) require emergent LT, and the metabolically abnormal liver

temporarily supports the recipient through the limited survival time or waiting period to permit a secondary LT (Figure 2).^{40,41} Several recent studies have found that the number of patients with acquired transthyretin amyloidosis following domino LT with FAP liver grafts is increasing, and the interval from transplantation to the development of amyloidosis is much shorter than expectations.^{18,42} To minimize the potential risk of complications related to metabolic deficiencies in recipients, the transplant team should have sufficient knowledge on the characteristics of such diseases, and careful selection is required for domino graft recipients. Furthermore, potential candidates for domino LT should be fully informed of the potential risks of disease transmission related to the domino liver grafts. More importantly, long-term intensive monitoring is necessary for all domino graft recipients after transplant.

Innovation in domino liver transplantation

In 2013, Zhu *et al.* performed the first cross-auxiliary double domino donor LT.⁴³ The first domino liver graft was from a 4-year-old child with Wilson's disease and the second graft was from a 3-year-old child with ornithine transcarbamylase deficiency (OTCD), which were successively implanted into a 32-year-old woman with FAP. Despite a markedly increased volume of the first domino liver graft that caused progressively elevated 24-h urinary copper excretion, this crisis was successfully contained by a percutaneous

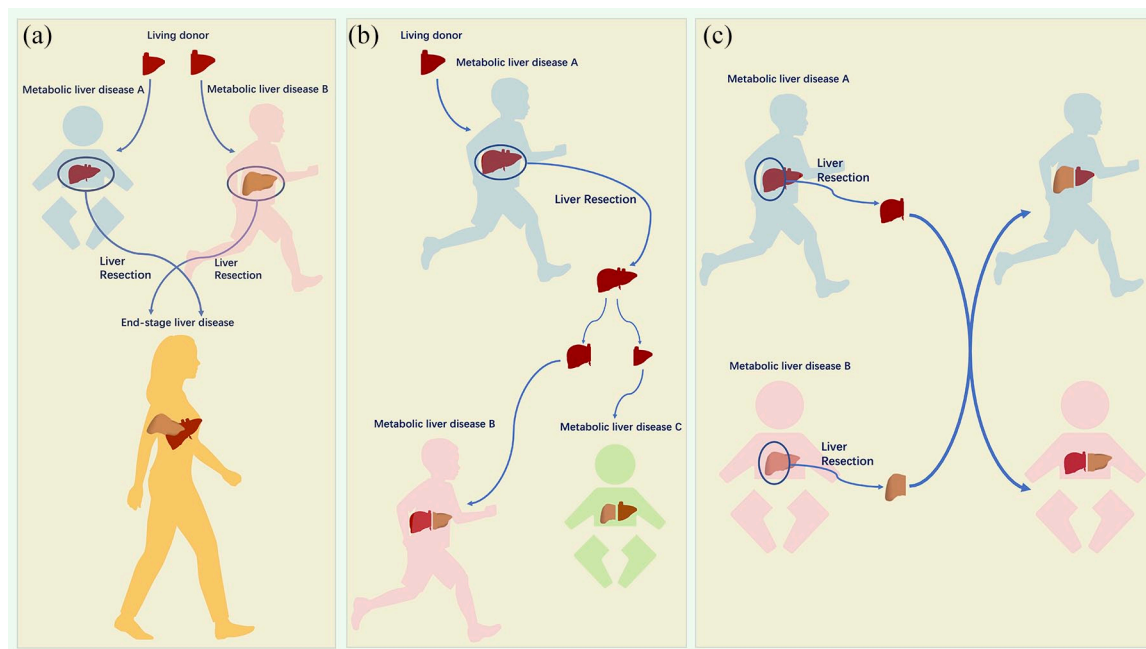


Figure 3. (a) cross-auxiliary double domino donor liver transplantation; (b) domino cross-auxiliary liver transplantation; (c) liver transplantation without donation.

transcatheter selective portal vein embolization. The recipient's hepatic function, blood ammonia, and 24-h urinary copper levels were normal 4 years after transplantation. It can be concluded that the two domino liver grafts with different noncirrhotic metabolic liver diseases could compensate for each other's metabolic defects and thus can be regarded as a completely well-functioning whole liver [Figure 3(a)]. Theoretically, the risk of developing early or late symptoms related to the underlying enzymatic defect in the single domino liver graft can be eliminated in this way. Notably, the balance of volume and portal blood flow between the two domino liver grafts is extremely critical for the maintenance of normal hepatic metabolic function in the recipient. The predominance of either domino liver graft could cause metabolic imbalance, thereby leading to the manifestations related to the missing enzyme in the dominant liver.

Since then, our team has developed the concept of "domino cross-auxiliary liver transplantation".⁴⁴ More specifically, a noncirrhotic inherited metabolic liver diseased liver graft was used for auxiliary partial orthotopic LT in another patient with an alternative type of noncirrhotic inherited metabolic liver disease. In that study,

six patients with inborn errors of metabolism received domino cross-auxiliary LT, and five patients achieved a favorable clinical outcome and quality of life after transplantation, whereas one patient died of multiple organ failure at 3 months post-transplant.⁴⁴ Similarly, in 2015, Govil and colleagues reported a case of domino auxiliary LT using the discarded liver from a patient with propionic acidemia as a domino graft in a patient with Crigler–Najjar Syndrome type 1; the recipient showed normal serum ammonia and amino acid profile on a normal diet with no manifestations of propionic acidemia after transplantation.⁴⁵ In the setting of domino cross-auxiliary LT, the residual native liver and the domino liver graft can achieve a mutual compensation for metabolic defects; thus, they function as a whole liver with a normal metabolic function within the same recipient [Figure 3(b)]. As mentioned above, the achievement of normal metabolic function in the domino recipient is based on the metabolic complementation and functional balance between the retained native liver and the domino graft. That is why special attention should be paid to preoperative pathophysiological matching, and both postoperative portal blood flow and liver regeneration monitoring are essential for this procedure. Other important considerations include compatible

blood groups, size-matched liver grafts, pathological examination of liver grafts, and post-transplant rejection monitoring.^{44,46}

With increasing experience and a better understanding of domino cross-auxiliary LT, in December 2018, Zhu *et al.* completed two special cases of domino cross-auxiliary LT, using the left lobes of one patient with hypermethioninemia and one patient with OTC deficiency as the domino liver grafts. After transplantation, the clinical prognosis of the two domino graft donors/recipients were favorable, with no manifestations related to either metabolic deficiency (unpublished data). It can be inferred that domino cross-auxiliary LT completed by the exchange of partial liver between two patients with different complementary noncirrhotic inherited metabolic liver diseases is practical. More importantly, LT without donation can be achieved in this way, which may rewrite the rulebook of LT in the future [Figure 3(c)].

Both cross-auxiliary double domino LT and domino cross-auxiliary LT will contribute to the improved utilization of explanted livers from patients with noncirrhotic inherited metabolic disorders. Thus, the organ donor pool can be further expanded. Notably, careful consideration of metabolic matching between recipients and donors is crucial for the successful application of these innovative and effective transplant strategies. In addition, accurate preoperative evaluation, sophisticated transplant doctors' surgical techniques, extensive perioperative management experience, and long-term close postoperative monitoring are especially important. Taking into account the potential risk of the above-mentioned procedures, it is necessary to ensure that informed consent is obtained from both the domino recipient and the donor. Of note, these innovative procedures are still far from extensive clinical application, and further studies are needed.

Primary hepatocyte transplantation

As a potentially promising alternative approach to LT, hepatocyte transplantation theoretically possess several significant advantages: (1) it is a minimally invasive procedure with relatively fewer costs and uncomplicated technical requirements; (2) from a piece of liver or a single whole liver, a sufficient number of hepatocytes could potentially be extracted, which would satisfy the needs

of multiple patients at the same time; (3) isolated hepatocytes can be cryopreserved to build a cell bank, and thus be available for patients in an emergency; and (4) the implanted hepatocytes only provide temporary hepatic metabolic support until recovery of the native liver or the availability of LT, and the recipients' native livers will remain in place to provide safety for recipients with ALF in case of cell graft dysfunction or to retain the possibility of receiving clinically feasible liver-based genetic therapy in the future for recipients with inherited metabolic liver diseases.^{10,47,48} Infusion of hepatocytes into the portal venous system, either by injection into a portal vein tributary or by intrasplenic injection, is the most widely used administration route. However, this carries a potential risk of bleeding, transient portal hypertension, sepsis, embolization of pulmonary capillary beds, and hemodynamic instability, in addition to possible rapid loss of cells, and the need for long-term immunosuppression.^{49,50} Emerging techniques including bioengineered humanized livers and alginate microencapsulated human hepatocytes can allow transplantation of a large number of functional liver cells, which provide long-term support for the failing liver, and may overcome the current limitations in existing approaches.^{51,52} Based on the relationship between donor and recipient, hepatocyte transplantation is classified into autologous and allogeneic transplantation.

Autologous hepatocyte transplantation

Autologous hepatocyte transplantation, in which donor hepatocytes are derived from the partial livers obtained from recipients themselves, was first performed by Mito *et al.* in 1992 in 10 patients suffering from acute exacerbation of chronic liver disease with autologous hepatocytes from partially resected livers.⁵³ They found that the transplanted hepatocytes survived and possessed hepatocellular function 1 month after transplant in eight recipients. As donor cells are isolated from the resected partial liver of the recipients themselves, autologous hepatocyte transplantation has the advantage of not requiring immunosuppression. However, the procurement of donor liver tissues may expose already vulnerable recipients to a high risk of intraoperative and perioperative complications. Furthermore, the viability and function of hepatocytes obtained from patients with chronic liver diseases are not optimal.⁵⁴ For this reason, autologous hepatocyte

transplantation may be more applicable in patients with inherited metabolic diseases, whose livers are structurally and functionally normal except for definite metabolic defects. These isolated genetically defective liver cells should be corrected by genetic strategies before transplantation. In the early 20th century, Grossman *et al.* reported that five patients with homozygous familial hypercholesterolemia were transplanted with autologous hepatocytes that had been *ex vivo* genetically corrected with recombinant retroviruses carrying the low-density lipoprotein receptor. Significant and persistent reductions in low-density lipoprotein were achieved in three of the five patients.^{55–57} Since then, the efficiency of *ex vivo* hepatocyte-directed gene therapy has mainly been verified in cellular and animal experiments, and there are still some impediments to this approach.^{58–60} Recently, Hickey *et al.* isolated autologous hepatocytes from pig models of hereditary tyrosinemia type 1 after partial hepatectomy. These hepatocytes were re-transplanted to the same pigs after using *ex vivo* gene therapy with lentiviral vectors, and the short- and long-term results showed the stable curative efficacy of genetically modified hepatocytes.⁶¹ Nevertheless, the effectiveness and safety of genetically corrected hepatocytes as well as the long-term metabolic consequences still require further confirmation before their application in clinical practice. In contrast, allogeneic hepatocyte transplantation may be more reliable in clinical practice.

Allogeneic hepatocyte transplantation

Allogeneic hepatocytes transplantation, using cells obtained from a different donor for transplantation, has been applied in clinical practice due to its significant advantages over autologous hepatocyte transplantation.^{8,62} First, this strategy circumvents the requirement of invasive surgical procedures for harvesting an adequate volume of liver from recipients and thus avoids the risk of mortality and morbidity in the recipients who are already debilitated by chronic liver diseases. Second, sufficient allogeneic hepatocytes can meet the needs of multiple treatments. However, a major drawback of allogeneic cells is the risk of rejection. This has led to the necessity for immunosuppression,⁶³ which may hamper the extensive clinical application of allogeneic hepatocyte transplantation. Another bottleneck is the shortage of a reliable and large-scale source of high-quality liver cells for transplantation. Currently, human primary hepatocytes

are mainly derived from the livers rejected for whole-liver transplantation for causes, including nonviral cirrhosis, high-grade steatosis, prolonged warm or cold ischemia times, or major parenchymal laceration.^{64,65} The quality of these available donor organs is poor in most cases, which is likely to compromise the yield, viability, and function of isolated hepatocytes. Besides, poor quality hepatocytes may diminish the clinical therapeutic effects of hepatocyte transplantation. Thus, alternative sources of liver cells are being actively sought.

Domino hepatocyte transplantation

Although stem cell-derived hepatocytes or mature hepatocytes generated from immortalized cell lines as well as hepatic progenitor cells seem to be a promising alternative to primary hepatocytes, there are still some concerns about the use of such derived ‘hepatocyte-like’ cells, including the risk of malignant tumorigenesis and whether these cells are capable of undertaking the full repertoire of hepatocyte functions.^{66–68} Primary hepatocytes obtained from donated human liver tissues currently remain the best cell source for liver cell-based therapy. Any approach which increases the availability of liver tissues suitable for hepatocyte isolation would thus directly improve the supply of primary hepatocytes.^{47,69,70} In this context, a new strategy in the area of hepatocyte transplantation has been explored using the domino approach [Figure 4(a)].

Domino hepatocytes in the experiment

In 2012, Bierwolf *et al.* evaluated primary hepatocytes isolated from explanted livers from three children with OTCD, carbamoyl phosphate synthetase deficiency, and primary oxalosis using *in vitro* experiments. They found that explanted livers from patients with congenital metabolic disorders could serve as an alternative cell source.⁷¹ Gramignoli *et al.* compared hepatocytes isolated from donor livers rejected for transplantation with those isolated from explanted livers of LT recipients with metabolic and other liver diseases in terms of cell viability, cell yield, plating efficiency, and hepatic metabolic activity.⁵⁴ They also found that hepatocytes isolated from discarded metabolically defective livers performed as well as or better than those isolated from organ donors. Taken together, these findings show that explanted livers obtained from LT recipients with monogenic hepatic diseases are morphologically

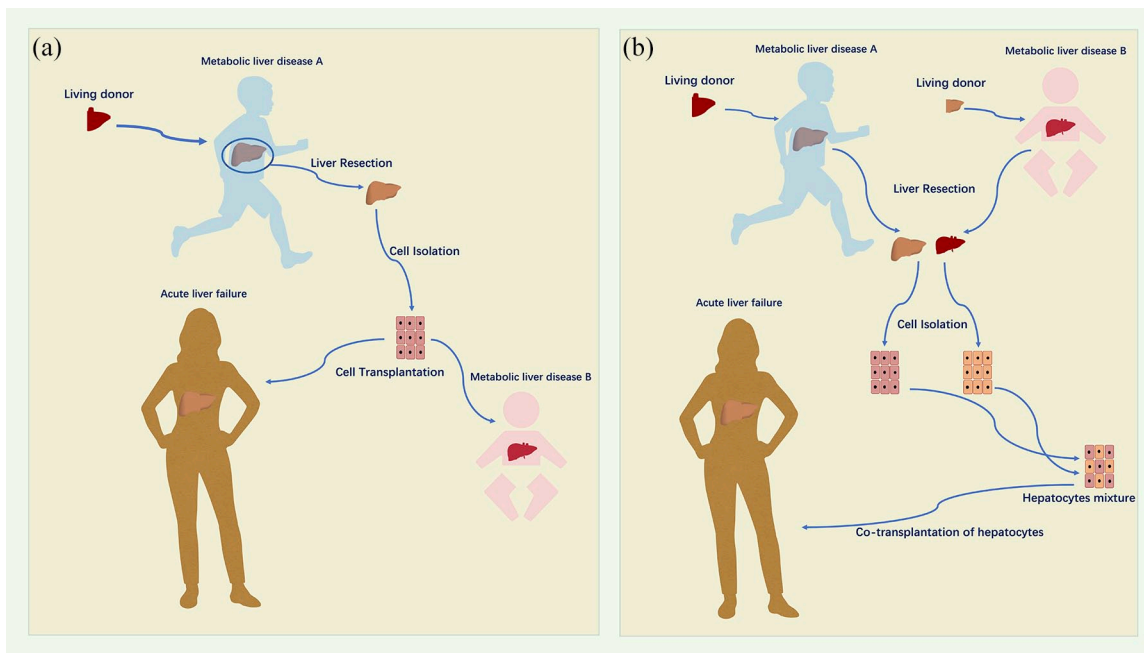


Figure 4. (a) Domino hepatocyte transplantation; (b) Cross-auxiliary double domino hepatocyte transplantation.

and biochemically normal except for specific enzymatic deficiency. Thus, these hepatocytes may be candidates for high-quality hepatocytes available for transplantation.

Domino hepatocyte transplantation in clinical practice

In 2012, Stéphanne *et al.* performed the first clinical domino hepatocyte transplantation in a 6-year-old boy with severe tetrahydrobiopterin nonresponsive phenylketonuria using hepatocytes isolated from the explanted liver from a 14-month-old liver transplant recipient with glycogen storage disease type 1b.⁷² Despite the time-limited metabolic-correcting effect of hepatocyte transplantation, early results were promising with blood phenylalanine levels returning within the therapeutic target and phenylalanine half-life decreased. More importantly, Stéphanne's team, for the first time, came up with the concept of "domino hepatocyte transplantation", similar to the concept of "domino cross-auxiliary liver transplantation".⁴⁴ In these domino hepatocytes, other hepatic functions are "normal", except for specific defective metabolic functions. Therefore, as long as the metabolic capabilities of the donor and the need of the recipient are carefully evaluated and matched, liver cells isolated from

explanted livers of patients with congenital metabolic disorders can be used for hepatocyte transplant procedures, namely domino hepatocyte transplantation.

Innovative concept of domino hepatocyte transplantation

In the setting of domino hepatocyte transplantation, the complementarity of the donor's metabolic capabilities and the recipient's metabolic need is extremely critical.⁵⁴ For patients with metabolic liver disease, the native liver remains in place. The transplanted hepatocytes are required to improve the single enzyme deficiency in the recipients;⁷³ thus, any liver cells carrying another complementary metabolic defect could theoretically be used for domino hepatocyte transplantation. As only a small portion (5–10%) of hepatocytes is infused into the recipient, the metabolic defect in the domino cells is unlikely to be transferred to the recipient. However, in patients with ALF, the metabolic defect of the candidate domino hepatocytes should be carefully considered. For example, hepatocytes isolated from donors with urea cycle disorders are considered unsuitable for patients with ALF because of the immediate need for ammonia metabolism in the ALF recipient. Under this

circumstance, similar to cross-auxiliary double domino LT,⁴³ cross-auxiliary double domino hepatocyte transplantation may be feasible [Figure 4(b)]. Co-transplantation of hepatocytes isolated from two types of metabolic-diseased livers enables the cells to compensate for each other's metabolic defects. And these mixed hepatocytes can be regarded as a mass of completely normal hepatocytes, but whether they could be applicable requires further research.

Domino liver transplantation versus domino hepatocyte transplantation

In the setting of domino LT, the entirety of the diseased liver is rapidly replaced with a metabolically deficient domino liver graft, and the enzymatic defect in the implanted liver is immediately transferred to the recipient. Therefore, the explanted liver from patients with hereditary metabolic diseases, such as urea cycle disorders, primary hyperoxaluria, and acute intermittent porphyria, which may rapidly cause serious symptoms or organ impairment related to the metabolic deficiency, is not recommended for domino LT.⁴¹ As hepatocyte transplantation only replaces a small portion of the liver, around 5–10% of the total liver mass in a single infusion, the probability of developing symptoms related to metabolic-diseased donor hepatocytes in the recipient is quite low.^{48,54} Therefore, it is theoretically feasible to use hepatocytes obtained from explanted livers of patients with various noncirrhotic inherited metabolic liver diseases for domino hepatocyte transplantation. On the other hand, the application of domino LT is limited to a small population of patients with unresectable liver malignancies who have a poor life expectancy or patients requiring urgent LT, while the recipients of domino hepatocyte transplantation mainly consist of selected patients with ALF and hereditary metabolic disorders, for whom the partial supply of “normally” functioning hepatocytes can be therapeutic.¹⁰

The utilization of explanted livers with metabolic deficiency, for either domino liver or hepatocyte transplantation, should be determined based on the need of recipients, the expected therapeutic effect, and the risk of metabolic disturbances caused by liver tissues with metabolic defects. Flexible choices for either domino liver or hepatocyte transplantation can maximize the utilization of metabolic-diseased livers, thereby benefiting

more patients with end-stage liver disease and inherited metabolic liver disease.

Conclusion

The number of available organs for transplant is insufficient to meet the needs of the growing waiting list. Theoretically, most explanted livers obtained from patients with noncirrhotic inherited metabolic liver diseases could be used for either domino liver or hepatocyte transplantation, instead of merely being sent for pathological examination. Domino LT and domino hepatocyte transplantation would help to alleviate the severe shortage of donor organs and offer effective treatment for more patients with terminal liver disease and inherited metabolic liver disease. Innovative strategies in domino liver and hepatocyte transplantation still warrant further studies.

Author contributions

Zhi-Jun Zhu and Guang-Peng Zhou contributed to the conception and design of the study. Guang-Peng Zhou undertook the literature search and wrote the manuscript. Li-Ying Sun supervised the study. All authors critically revised the manuscript and approved the final version of this manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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