Cyclin D1 in the Liver: Role of Noncanonical Signaling in Liver Steatosis and Hormone Regulation

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Background: Cyclin D1 is an important protein for cell cycle progression; however, functions independent of the cell cycle have been described in the liver. Cyclin D1 is also involved in DNA repair, is overexpressed in many cancers, and functions as a proto-oncogene. The lesser-known roles of Cyclin D1, specifically in hepatocytes, impact liver steatosis and hormone regulation in the liver.

Methods: A comprehensive search of PubMed was conducted using the keywords Cyclin D1, steatosis, lipogenesis, and liver transplantation. In this article, we review the results from this literature search, with a focus on the role of Cyclin D1 in hepatic lipogenesis and gluconeogenesis, as well as the impact and function of this protein in hepatic steatosis.

Results: Cyclin D1 represses carbohydrate response element binding protein (ChREBP) and results in a decrease in transcription of fatty acid synthase (FAS) and acetyl-coenzyme A carboxylase (ACC). Cyclin D1 also inhibits peroxisome proliferator-activated receptor gamma (PPARγ) which is involved in hepatic lipogenesis. Cyclin D1 inhibits both hepatocyte nuclear factor 4 alpha (HNF4α) and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1α) and represses transcription of lipogenic genes FAS and liver-type pyruvate kinase (Pklr), along with the gluconeogenic genes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase).

Conclusion: Cyclin D1 represses multiple proteins involved in both lipogenesis and gluconeogenesis in the liver. Targeting Cyclin D1 to decrease hepatic steatosis in patients with nonalcoholic fatty liver disease or alcoholic fatty liver disease may help improve patient health and the quality of the donor liver pool.

Keywords: Cyclin D1, fatty liver, gluconeogenesis, hormones, lipogenesis, liver, liver transplantation

INTRODUCTION

The liver is the major site for nutrient synthesis as well as carbohydrate, lipid, glucose, and drug metabolism. Liver injury resulting from trauma, surgical excision, viral infection, chronic alcoholism, and/or poor diet causes hepatocyte turnover and elicits cellular programs leading to liver regeneration. Viral infections (hepatitis B and C),1,6 as well as alcoholic fatty liver disease and nonalcoholic fatty liver disease (NAFLD),7-10 trigger chronic inflammation with persistent activation of liver regeneration pathways that can progress to cirrhosis and fibrosis, requiring curative liver transplantation. Despite advancements in hepatitis C viral (HCV) therapy, patients with HCV may still progress to HCV cirrhosis, requiring liver transplantation. Although the number of HCV patients requiring liver transplantation has stabilized and should decline, the prevalence of NAFLD and nonalcoholic steatohepatitis (NASH) continues to rise. The net effect is a continuous rise in the number of patients on the liver transplant wait list while the donor liver pool remains stable. Although extended criteria donor livers, such as those of advanced age, with liver macrosteatosis, or procured after cardiac arrest, may help address this deficit, these grafts have a higher risk of acute graft dysfunction and graft failure compared to donor livers meeting standard criteria and deemed suitable for transplantation.11-13 Grafts with prevalent macrosteatosis are particularly at risk for graft failure. The obesity epidemic and the rising prevalence of NAFLD will increase the frequency of steatosis in donor liver procurements. Biomarkers that capture the failure risk associated with donor steatosis will be required, particularly because the percentage of macrosteatosis may not reliably predict failure risk.

The process of organ procurement, preservation, and transplantation causes ischemia/reperfusion injury, leading to inflammation and hepatocyte turnover.14 In the healthy liver, this process triggers stellate cell activation and hepatocyte proliferation, ultimately stabilizing liver function postsurgery in the transplant recipient.15-22 Sequential biopsies of a patient undergoing partial orthotopic liver transplantation demonstrated continuous hepatocyte proliferation that eventually restored the patient’s original liver mass 14 months after transplantation.23 Steatotic hepatocytes, containing intracellular lipid droplets, have a lower threshold for ischemic injury...
and a dampened proliferative response postinjury that contribute to greater necrotic injury and extended recovery periods in transplanted steatotic donor livers.24

Signaling pathways that trigger proliferation in hepatocytes converge upon Cyclin D1, the gatekeeper into the cell cycle. Cyclin D1 plays an instrumental role in liver regeneration, as evidenced by studies of small-for-size vs half-size grafts. Small-for-size grafts resulting in graft failure had limited induction of Cyclin D1, while half-size grafts that regenerates to restore original liver volume contained a nearly 8-fold higher induction of Cyclin D1.25 Further, impaired liver regeneration in steatotic rats following ischemia/reperfusion injury was attributed to delayed induction of Cyclin D1 compared to healthy controls.26 Studies have described several cell cycle–independent functions of Cyclin D1, including lipid and carbohydrate metabolism and hormone regulation. Deficits in nonessential amino acids trigger Cyclin D1 repression and impaired hepatocyte regeneration.27

In this review, we briefly cover the canonical pathway of Cyclin D1 in cell cycle progression and its overexpression in some cancers. The majority of this article reviews the noncanonical pathways of Cyclin D1 in the liver regarding carbohydrate and lipid metabolism, hormone regulation, and the progression from simple to severe liver steatosis.

CYCLIN D1 PROTEIN STRUCTURE

Cyclin D1 contains multiple domains and motifs that activate and/or repress numerous proteins in the liver involved in steatosis and hormone regulation. Cyclin D1 belongs to the highly conserved D-type cyclin family, originally identified as universal cell cycle regulators.28 Cyclin D1 is encoded by the gene CCND1, located on the long arm of chromosome 11 at position 13.3, and spans 13,388 bases.29,30 The CCND1 gene contains 5 exons translated to 295 amino acids with a molecular weight of 33.7 kDa.31

The N-terminal consists of a retinoblastoma (Rb) binding domain and an LXCXE motif that some researchers maintain is required for the phosphorylation of Rb. This domain and motif are also found in other D-type cyclins, Cyclin D2 and D3. Reports conflict as to whether the LXCXE motif is required for Rb phosphorylation.32-35 The cyclin box, located near the center of the protein, functions as the binding location for cyclin-dependent kinase 4 and 6 (CDK4 and CDK6). Point mutation in the 112th residue of Cyclin D1, switching from a lysine to a glutamic acid (K112E mutant), and CDK6. Point mutation in the 112th residue of Cyclin D1, located near the center of the protein, functions as the repressor domain, located within amino acids 142-253, is involved in repression of multiple proteins, including androgen receptor and hepatocyte nuclear factor 4 alpha (HNF4α).36 Following the repressor domain is the LLXXLL motif that binds to the steroid receptor coactivator-1 (SRC-1).37 Last is the PEST sequence, a proline-, glutamate-, serine-, and threonine-rich region through which Cyclin D1 is targeted for degradation through proteolysis.40 An array of domains and motifs in Cyclin D1 allows complex interactions and the functional diversity required for its important canonical role in cell cycle progression.

THE CANONICAL PATHWAY OF CYCLIN D1 IN THE CELL CYCLE

The mechanisms of the interactions and function of Cyclin D1 and its binding partners in cell cycle progression from the G1 to the S phase, as well as its interactions with CDK4, have been thoroughly characterized and reviewed.28,41,42 Genes encoding D-type cyclins become activated and are further induced at the beginning of the G1 phase in response to mitogen stimulation.28,43,44 During this phase, Cyclin D1 translocates to the nucleus and remains as a static protein bound to an immobile complex.31 In the nucleus, Cyclin D1 assembles with its catalytic partners CDK4 or CDK645-50 and targets its primary substrate, the nuclear protein Rb.31,51,52

Rb is the principal transcriptional repressor for many of the genes required to progress from G1/S transition through S phase, positioning Rb as a central target for phosphorylation and inactivation downstream of several mitogenic signaling pathways.53,54 During the G0 phase, Rb binds to and represses E2F transcription factors blocking gene transcription necessary for S phase initiation and DNA replication, thus preventing progression through the cell cycle.28,33,55 Rb inhibits transcription of the E2F-responsive promoters through enlistment of histone deacetylases (HDACs) to block E2F activity at the Cyclin E promoter.56-60 Cyclin D1-CDK4 phosphorylates Rb, disrupting the repression of E2F by Cyclin E-CDK2, enabling cell cycle progression.61 Cyclin D1 activates the kinase of Cyclin E-CDK2 by a second mechanism that also blocks cell cycle progression. This noncatalytic function sequesters Cip/Kip cell cycle inhibitors.62 Cip/Kip proteins p21Cip1 or p27Kip1 interact with cyclin/CDK complexes to deter kinase activity and repress cell cycle progression.63 Cyclin D1 accumulates in the nuclei and disappears once the cell enters S phase and DNA replication begins.64 Cyclin D1 is targeted for degradation by phosphorylation of residue Thr286 by glycogen synthase kinase-3 beta (GSK3β).65-66 This phosphorylation stimulates association with chromosome maintenance 1 protein and facilitates the nuclear export of Cyclin D1 to the cytoplasm.65 Once exported, phosphorylated Cyclin D1 is ubiquitinated and degraded by the 26S proteasome.64-67 Because of the important role of Cyclin D1 during the G1/S cell cycle transition, Cyclin D1 expression and localization are tightly regulated in the cell.

REGULATION OF CYCLIN D1 DURING THE CELL CYCLE

In the G1 phase, Cyclin D1 expression and assembly with CDK4 are regulated by the Ras-Raf1-MEK-ERK kinase cascade.68-73 Induction of CCND1 transcription is activated through mitogen-induced Ras signaling and ERK.74 The CCND1 promoter can also be transactivated by signal transducer and activator of transcription (STAT) proteins, early growth response protein-1 (Egr-1), nuclear factor-kappa B (NF-κB), cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), β-catenin, and JunB.75-79 Through this signaling pathway, mitogen-activated protein kinases (MAPKs) induce Cyclin D1-CDK4 assembly, and overexpression of p41MAPK stimulates Cyclin D1 promoter activity.80 Withdrawal of mitogen signals stops Ras signaling and CCND1 transcription.81 Degradation of Cyclin D1 by nuclear exclusion and proteolysis through GSK3β are controlled and prevented by Ras activation (Figure 1). Ras signaling in collaboration with phosphatidylinositol-3-OH (PI3K) downregulates GSK3β through its activity on the c-Akt proto-oncogene product (Akt), inhibiting the rate of Cyclin D1 turnover.82 The PI3K-Akt-GSK3β
Cyclin D1 is involved in activating hepatocyte proliferation, restoring liver mass after partial hepatectomy. In hepatocytes, Cyclin D1 retains its canonical pathway in cell cycle progression as mentioned above. Hepatocytes account for 70% of the cells in the liver and are normally quiescent. However, upon liver injury, as in the case of liver transplantation or in livers that undergo resection, hepatocytes become primed and enter the cell cycle in efforts to restore liver mass. Increased levels of Cyclin D1 were detected in human liver biopsies following transplantation. Ccn1d1 expression also increased in both mice and rats following 70% partial hepatectomy in efforts to restore liver mass. Cyclin D1 overexpression is sufficient to cause proliferation in hepatocytes both in vitro and in vivo. In rat primary hepatocytes stimulated with insulin, the expression of Cyclin D1 coincided with DNA synthesis, confirming the role of Cyclin D1 in hepatocyte cell cycle progression.

Regulation of Lipogenesis and Gluconeogenesis Through Cyclin D1 in the Liver

The liver is the primary site of lipid and glucose metabolism. In recent years, new functions for Cyclin D1 in the liver have emerged, particularly in regulating lipogenesis and gluconeogenesis. Cyclin D1 regulates transcription of genes involved in lipid metabolism and the sensing/processing of carbohydrates and amino acids in mouse hepatocytes. In fasting mice, an overall decrease in both mRNA and protein expression of Cyclin D1 is observed, with levels increasing upon food intake. In primary rat hepatocytes, nonessential amino acid starvation inhibited cell proliferation and resulted in undetectable Cyclin D1; however, overexpression of Cyclin D1 in these starved hepatocytes resulted in proliferation. Additionally, in hepatocytes, minimal essential medium (MEM) amino acids increased Ccn1d1 expression significantly more than nonessential amino acids. These results indicate that nutrient availability can impact the functions of Cyclin D1 in the liver. Nutrient availability is particularly important in donor livers, as time after procurement can dramatically affect nutrient availability which could potentially affect Cyclin D1 levels and have an impact on graft failure. In our laboratory, Cyclin D1 was elevated in the livers of rats with >90% macrosteatosis and resulted in death after partial hepatectomy (unpublished data). The alternatively spliced isoform, Cyclin D1b, was found in nuclear fractions of macrosteatotic livers that showed slow recovery after partial hepatectomy (unpublished data). The exact role of Cyclin D1 in these fatty livers and how it may contribute to liver failure after partial hepatectomy remain under investigation. Further evidence of the importance of Cyclin D1 in liver disease has been validated in animals with increasing steatosis in NAFLD and NASH. The drug metformin has been used to treat NAFLD, resulting in inhibition of Cyclin D1 and decreased gluconeogenesis in the liver. However, studies of Cyclin D1 in human hepatocytes are lacking, with the majority of experiments having been performed in mice and rats.

Regulation of Lipogenesis by Cyclin D1

Hepatic de novo lipogenesis is the process of generating fatty acids from excess acetyl-coenzyme A (CoA) subunits from the catabo-
lism of carbohydrates. These lipids are stored in hepatocytes and exported as needed via very low density lipoproteins. Glucose is primarily taken up by the liver after feeding, and excess carbohydrates are converted and stored as triglycerides. Glucose is the primary driver for lipogenesis; however, fructose also promotes lipogenesis in the liver as reviewed elsewhere. De novo lipogenesis in hepatocytes is transcriptionally regulated by the carbohydrate response element binding protein (ChREBP). ChREBP is phosphorylated and bound to the protein 14-3-3, rendering it inactive in the cytoplasm. Mediators of glycolysis activate ChREBP via dephosphorylation and dissociation with 14-3-3. Once activated, ChREBP interacts with max-like factor x (Mix) and is translocated to the nucleus to activate transcription of lipogenic genes such as fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC). Cyclin D1 repressed transcription of ChREBP in a manner that was dependent on the CDK4 binding domain through interactions with the first 492 amino acids of ChREBP. Cyclin D1 also repressed lipogenic gene transcription, particularly FAS and ACC in hepatocytes in the presence of glucose. This repression resulted in decreased lipogenesis and could be beneficial in decreasing fat accumulation in the liver as a treatment for NAFLD when glucose is present. A 2016 report showed that activation of CDK4 induced NAFLD in mice fed a high-fat diet, while inhibiting CDK4 reduced the level of hepatic steatosis in mice fed a high-fat diet. Additionally, elevated expression of ACC and FAS is activated by certain ligands such as fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC). Cyclin D1 also decreased in fasting mice, and this downregulation is likely due to enhancement of lipogenic gene transcription by Cyclin D1. Cyclin D1 increases after refeeding. In the presence of glucose, Cyclin D1 represses lipogenesis through 2 modes of action: through prevention of PPARγ and HNF4α binding ACC and therefore has potential utility in the treatment of NAFLD.

Hepatocyte Nuclear Factor 4 Alpha Repression Through Interactions With Cyclin D1. Cyclin D1 interacts with HNF4α, a master regulator in hepatocytes. HNF4α is required for normal liver development, and HNF4α knockout mice do not express functional levels of hepatocyte-specific gene programs, resulting in incomplete liver maturation. HNF4α also promotes the transcription of the following apolipoproteins: A1, AII, B, CII, and CIII. These proteins form complexes involved in delivering fatty acids into cells. The role of HNF4α in cell proliferation and cancer has been reviewed elsewhere. HNF4α binds to fatty acids; however, evidence suggests this interaction increases HNF4α stability rather than augments transcriptional activity. Therefore, HNF4α prevents binding to the promoter regions of the lipogenic genes FAS and liver-type pyruvate kinase (Pklr), thereby repressing their transcription in hepatocytes. This observation was reversed in knockdowns of Cyclin D1 in hepatocytes. HNF4α is also involved in the transcription of gluconeogenesis such as glycogen synthase, phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase (G6Pase). These results confirm the involvement of Cyclin D1 in repressing gluconeogenesis in the presence of glucose. Cyclin D1 represses lipogenesis through 2 modes of action: through prevention of PPARγ and HNF4α binding ACC and therefore has potential utility in the treatment of NAFLD.

Cyclin D1 Repression of Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha. The hepatic gluconeogenesis regulator peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC1α) interacts with Cyclin D1. PGC1α transcriptionally activates oxidative phosphorylation and regulates carbohydrate metabolism. PGC1α also triggers lipogenesis by promoting expression of apolipoproteins AIV, B, CII, and CIII. PGC1α is strongly induced in fasting mice, leading to transcriptional programs promoting gluconeogenesis through G6Pase and PEPCK. CREB also induces expression of PGC1α in hepatocytes. CREB inhibits PGC1α through phosphorylation, targeting PGC1α for proteasomal degradation. CREB is also Ras-dependent, as Akt can inactivate GSK3β through phosphorylation. GSK3β is active in fasting animals, but it becomes inactivated upon refeeding through phosphorylation via insulin/Akt signaling, while expression of Ccnd1 and Cyclin D1 increases after refeeding. In the presence of insulin and GSK3β, Cyclin D1 is sequestered in the nucleus. Cyclin D1 represses PGC1α in a manner that is CDK4-dependent. Following Cyclin D1 exportation from the nucleus by GSK3β, PGC1α translocates to the nucleus and activates transcription of G6Pase and PEPCK in the absence of glucose (Figure 1). Because PGC1α regulates its own expression, repression of PGC1α by Cyclin D1 also decreases PGC1α mRNA expression.

In mouse hepatocytes stimulated with insulin, Cyclin D1-CDK4 becomes activated and phosphorylates GCN5. GCN5 is an acetyltransferase and when phosphorylated binds to and acetylates PGC1α (Figure 2), decreasing its promoter binding capabilities and thus decreasing gluconeogenic gene expression through G6Pase and PEPCK repression. Lee et al showed that upon refeeding in mice, Ccnd1 expression increased in the liver. In a study published in 2014, Bhalla et al demonstrated that PEPCK,
G6Pase, and PGC1α mRNA expression decreased in the livers of refed mice. Chemical inhibition or depletion of CDK4 led to an increase in gluconeogenesis genes (PEPCK and G6Pase) and glucose production in primary hepatocytes, providing evidence that the process is dependent on CDK4. Amino acids, and not insulin, were found to increase Ccnd1 expression in hepatocytes. Perhaps lower levels of Cyclin D1 may be found in patients with high glucose levels, resulting in increased gluconeogenesis.

**Summary.** The interaction between PGC1α and HNF4α are required for PEPCK and G6Pase transcription. PGC1α and HNF4α both trigger apolipoprotein expression significantly more together than either protein alone. Figure 2 provides an overview of Cyclin D1 in hepatocytes with glucose. Lipogenesis inhibition through PGC1α and ChREBP by Cyclin D1 requires CDK4, while HNF4α inhibition requires the repressor domain located upstream of the CDK4 binding site. Thus, in the presence of glucose and insulin, Cyclin D1 binds to and activates CDK4 in the nucleus. Cyclin D1-CDK4 can then repress PGC1α and through the repressor domain of Cyclin D1, inhibit HNF4α and PPARγ function. As a result, lipogenesis and storage of lipids are inhibited. The question then becomes what turns Cyclin D1-CDK4 to cell cycle progression vs inhibiting lipogenesis? If the cell is trying to regenerate because of liver injury, lipogenesis will be inhibited to convert all processes for cellular division to repair liver tissue. Interestingly, after 70% partial hepatectomy in rats, PPARγ expression increased at 48 hours, while DNA synthesis peaked at 24 hours. Cyclin D1 protein levels increased 24-72 hours after partial hepatectomy in rats, likely revealing that during liver injury, some mechanisms are in place to ensure that hepatocyte proliferation occurs.

**Cyclin D1 Activation of Estrogen Receptor and Repression of Androgen Receptor in the Liver**

Cyclin D1 controls hormone metabolism in the liver. In cultured hepatocytes, Cyclin D1 is upregulated upon stimulation with epithelial growth factor. Hepatocytes naturally express estrogen receptor alpha (ERα) and androgen receptor. Particularly in the livers of rats, differences in the number of estrogen receptors vary between males and females as well as between prepubescent and adult females. The number of estrogen receptors on the surface of adult female rat livers is estimated to be one-third of the number present in the uterus. For estrogen to activate transcription of genes, estrogen receptors in the livers of adult female rats require high levels of estrogen for nuclear relocationization. In breast cancer cells, Cyclin D1 activates genes containing estrogen receptor elements through estrogen receptors in a manner that is independent of CDK and Rb binding and the presence of estrogen, as well as independent of phosphorylated ERα. Cyclin D1 directly interacts with ERα and recruits SRC-1 family coactivators to ERα for activation through a leucine-rich motif (Figure 3). Zwijsen et al showed that mutations in the leucine-rich motif abolished direct interactions of Cyclin D1 with SRC-1 and prevented ERα activa-
 powdered ingredients, while the females did not when fed a high-fat diet. 

In this experiment, male mice fed a high-fat diet developed steatosis, while the females did not. Studies conflict on whether antiestrogen compounds affect this interaction, which seems to be cell-type dependent. In the breast cancer cell line T47D, the antiestrogens hydroxyltamoxifen and ICI 182780 did not inhibit Cyclin D1 activity of estrogen responsive element (ERE)–containing genes, while sterol carrier protein 2 (SCp2) inhibition was observed. 

The C-terminus is important for Cyclin D1 interaction with ERα, as mutations in amino acids 254 and 255 negate Cyclin D1 interactions with ERα. 

Zwijsen et al demonstrated that estrogen could induce proliferation in vitro in hepatocytes. After a partial hepatectomy, antiestrogens have been shown to reduce the number of ERα and proliferation of hepatocytes. Additionally, arsenic-induced hepatocellular carcinoma in mice induced both Cyclin D1 and ERα expression. In the male mouse liver, hepatic Cyclin D1 expression was linked to increases in serum estradiol levels, estrogen-dependent gene expression, and decreased androgen-dependent gene expression. Overexpression of either Cyclin D1 or Cyclin D1b led to the downregulation of steroid 5α-reductase, an enzyme that converts testosterone into androgen and dihydrotestosterone. Interestingly, overexpression of Cyclin D1b induced the expression of 3β-hydroxysteroid dehydrogenase type 2, a protein involved in steroidogenesis, while Cyclin D1 did not.

Cyclin D1 is also involved in androgen receptor inhibition. Cyclin D1 contains a repressor domain between residues 142-253 that is required for interactions with androgen receptor in the human prostate adenocarcinoma cell line LNCaP. Additionally, the Cyclin D1b isoform reduced androgen receptor regulation, although this isoform retained the repressor domain and the ability to recruit HDACs. Less work has been done looking into the role of Cyclin D1 and sex hormones in hepatocytes. Cyclin D1 may be involved in enhancing estrogen-dependent genes while decreasing androgen-dependent genes. Estrogen has been suggested to play a protective role in the liver by inhibiting apoptosis after ischemia/reperfusion injury. Furthermore, hepatic androgen receptor knockout male mice developed steatosis, while the females did not when fed a high-fat diet. Additionally, men with liver diseases who underwent liver resection developed feminization syndrome, which may be linked to increased Cyclin D1 and estrogen-dependent genes. Although aberrant expression of Cyclin D1 could increase estrogen-dependent gene expression, implications for the development and progression of steatosis remain to be investigated. However, these studies strongly suggest Cyclin D1 expression can influence hormone levels and hormone signaling pathways in the liver.

CONCLUSION

Cyclin D1 has many diverse functions in the liver. Aside from the canonical pathway in cell proliferation, Cyclin D1 is involved in the repression of lipogenesis and gluconeogenesis through the interactions of multiple groups of proteins. Extended criteria donors with hepatic steatosis are on the rise, along with an increase in the number of patients on the wait list. Current methods to improve this imbalance include decreasing hepatic steatosis or preventing damage during ischemia/reperfusion. Reversing hepatic steatosis in patients can improve the quality of the donor liver pool and increase the number of livers used for transplantation. Cyclin D1 may prove to be an excellent target to reduce lipogenesis in fatty livers through its repression of PPARγ and HNF4α in the induction of lipogenic genes. Because of the functions of Cyclin D1 in hepatic proliferation, targeting Cyclin D1 could also improve liver regeneration after liver transplantation. Further studies are necessary to determine how Cyclin D1 functions in steatotic livers.

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