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Review

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Lipid metabolism in liver transplantation: from challenge to chance

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Abstract

In the past 20 years, liver transplantation has become one of the few effective treatments for various end-stage liver diseases. With the development of surgical methods and equipment, ischemia/reperfusion injury (IRI) and rejection have become the main factors affecting prognosis. Due to the use of detection methods such as metabolomics, surprising findings revealed that some significant lipid metabolism disorders are associated with liver transplantation. Moreover, the fatty liver, as an important part of the marginal donor organ, is severely affected by imbalances derived from the preexisting lipid metabolism turbulence. In other words, the lipid metabolism remodeling present in conventional liver transplantation is more severe and intricate in nonalcoholic fatty liver. This paper aims to review the recent 20 years of research on lipid metabolism in liver transplantation, especially the different molecular targets and signaling pathways involved in IRI, acute rejection, and chronic

rejection. Through a comprehensive review and analysis of the literature, we outline the research status and forward motion, which provides both a valuable reference substance for future research and a theoretical summary for the prevention and treatment of lipid metabolism disorders during liver transplantation.

Keywords: Lipid metabolism, liver transplantation, arachidonic acid, rejection, oxidative stress

INTRODUCTION

Liver transplantation (LT) is a crucial treatment for end-stage liver disease[1,2]. However, the shortage of donor livers limits the feasibility of LT and the survival rate[3]. To solve this problem, the use of fatty livers as marginal donors is highly important for expanding the donor pool[4]. Studies have shown that fatty liver, due to its increased sensitivity to ischemia/reperfusion injury (IRI), may lead to a more severe inflammatory response and tissue damage after transplantation[5,6]. Although this risk can be weakened through the appropriate selection of recipients, more research is necessary to improve the utilization of donor livers[7,8].

Lipid metabolism disorders, the main pathological feature of fatty liver[9,10], are closely associated with poor outcomes in LT patients[11-13]. Lipid metabolism is an indispensable part of physiological status, including energy supply, organ protection, and biofilm composition[14-16]. There is a cross-relation between products from lipid metabolism and core signaling pathways activated in LT[17-19]. The importance of lipid metabolism in LT has been gradually realized in recent years, but there is still insufficient evidence to clarify this issue.

We used three literature search systems, namely PubMed, the Wiley Online Library, and Elsevier ScienceDirect, to search for studies about lipid metabolism and LT. A total of 137 articles were included. The two stages that may correlate with lipid metabolism in LT are IRI and acute rejection[20-23]. Hepatic IRI is characterized by aseptic inflammation, whereas acute rejection is the stage outcome of a series of immune responses. In this review, we describe key molecules that regulate lipid metabolism in LT and analyze their correlative signaling characteristics. In addition, the effects of several immunoregulatory drugs were evaluated given their impact on lipid metabolism. The interaction between lipid metabolism and oxidative stress should be carefully considered.

In summary, drawing upon clinical, translational, and basic research findings, we have deduced several potential directions and viable strategies for the burgeoning field of lipid metabolism research in LT.

LIPID METABOLISM AND LIVER ISCHEMIA-REPERFUSION INJURY

Arachidonic acid

Arachidonic acid (AA) is widely present in the phospholipids of the cell membrane as a necessary unsaturated fatty acid[24]. The metabolites of AA, including prostaglandins (PGs), leukotrienes, and thromboxane, regulate multiple molecular events that are closely associated with hepatic IRI. Intriguingly, despite belonging to similar metabolite pathways, they sometimes play contrary roles in hepatic IRI[25]. PGs have precise protective effects in disparate models[26]. Specifically, prostaglandin E (PGE) serves as a barrier against IRI damage in the liver. Monoacylglycerol lipase (MAGL) hydrolyses the endocannabinoid 2-arachidonoylglycerol to generate the AA precursor pool for prostaglandin production. PGE can promote liver blood perfusion, inhibit platelet aggregation, and reduce oxidative stress levels[27] [Table 1].

Table 1. Research on liver transplantation, lipid metabolism and signaling pathways

Title	Journal	Year	Category	Target molecule	Signaling pathway	Serial number
Monoacylglycerol lipase controls endocannabinoid and eicosanoid signaling and hepatic injury in mice	*Gastroenterology*	2014	Article	MAGL	Endocannabinoid, eicosanoid	27
Chemical composition of hepatic lipids mediates reperfusion injury of the macrosteatotic mouse liver through thromboxane A(2)	*Journal of Hepatology*	2011	Article	TXA2	-	29
Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation	*Nature Neuroscience*	2012	Article	MAGL	Endocannabinoid, prostaglandin	37
Substance P-regulated leukotriene B4 production promotes acute pancreatitis-associated lung injury through neutrophil reverse migration	*International Immunopharmacology*	2018	Article	LTB4	PKC/MAPK	38
Expression of a cyclo-oxygenase-2 transgene in murine liver causes hepatitis	*Hepatology*	2005	Article	COX-2	NF-κB	40
Acute atorvastatin is hepatoprotective against ischaemia-reperfusion	*Liver International*	2015	Article	Atorvastatin	NF-κB	41
Ferroptosis: an iron-dependent form of nonapoptotic cell death	*Cell*	2012	Article	GPX4	Ferroptosis	49
Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice	*Nature Cell Biology*	2014	Article	Gpx4	Ferroptosis	50
Arachidonic acid activates NLRP3 inflammasome in MDSCs via FATP2 to promote post-transplant tumour recurrence in steatotic liver grafts	*JHEP Reports*	2023	Article	NLRP3 inflammasome, FATP2	NLRP3 inflammasome	53
Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis	*Journal of Hepatology*	2022	Article	NLRP3 inflammasome, gasdermin D	Pyroptosis	54
In situ repurposing of dendritic cells with CRISPRCas9-based nanomedicine to induce transplant tolerance	*Biomaterials*	2019	Article	CRISPR/Cas9	-	63
MARC1 downregulation reduces hepatocyte lipid content by increasing beta-oxidation	*Clinical and Molecular Hepatology*	-	Article	1-Mar	Beta-oxidation	82
Hepatic deficiency in transcriptional cofactor TBL1 promotes liver steatosis and hypertriglyceridemia	*Cell Metabolism*	2011	Article	TBL1	PPARα lipid metabolism	83
NAFLD causes selective CD4(+) T lymphocyte loss and promotes hepatocarcinogenesis	*Nature*	2018	Article	ROS	-	104
PPARα is down-regulated following liver transplantation in mice	*Hepatology*	2003	Article	PPARα	-	105
GTPBP8 mitigates NASH by depressing hepatic oxidative stress and mitochondrial dysfunction via PGC-1α	*Free Radical Biology and Medicine*	2024	Article	GTPBP8, PGC-1α	Oxidative stress, mitochondrial dysfunction	107
Elevated sensitivity of macrosteatotic hepatocytes to hypoxia/reoxygenation stress is reversed by a novel defatting protocol	*Liver Transplantation*	2015	Article	ROS	Oxidative stress	108

NASH: Nonalcoholic steatohepatitis; MAGL: monoacylglycerol lipase; TXA2: thromboxane A2; LTB4: leukotriene B4; COX-2: cyclo-oxygenase-2; Gpx4: glutathione peroxidase 4; NAFLD: nonalcoholic fatty liver disease; ROS: reactive oxygen species; PPARα: peroxisome proliferator-activated receptor α; MDSCs: myeloid-derived suppressor cells.

Another metabolic pathway, the lipoxygenase (LOX) pathway, which generates bioactive mediators such as leukotrienes and thromboxane, is related to AA. Prostanoids, including PGs and thromboxanes (TXs), are formed through the cyclooxygenase (COX) pathway, leukotrienes, and lipoxins (LXs) by the action of 5-LOX. Although eicosanoids are usually associated with proinflammatory responses, nonclassic eicosanoids,

such as LX, have anti-inflammatory and proresolving properties. These mediators are nonnegligible in the immune response in hepatic IRI[28].

The activation of the AA metabolic pathway also depends on the phase divergence of liver disease. For example, patients diagnosed with nonalcoholic fatty liver disease (NAFLD) exhibit high AA levels in the liver, leading to overactivation of the AA metabolic pathway and the production of bioactive lipid mediators. The excessive accumulation of these factors exacerbates the degree of inflammation, promotes the deterioration of oxidative stress, and eventually exacerbates hepatic IRI[29].

Mitogen-activated protein kinase and nuclear factor kappa-B signaling pathways

Mitogen-activated protein kinase (MAPK) and nuclear factor kappa-B (NF-κB) are inextricably related to each other during hepatic IRI[30,31]. Research in recent years has revealed that they are connected to the AA. Metabolites of AA can activate MAPK and NF-κB directly and contribute to inflammatory conditions in the liver. Given these findings, we summarize the signaling pathways involved in the past few years [Figure 1].

MAPK

The MAPK signaling pathway contains several subfamilies, such as ERK, JNK, and p38[32-34]. These different subunits are often activated via phosphorylation and are widely involved in liver damage, oxidative stress, and early acute rejection disease (EAD)[35,36]. Some lipid mediators generated from the AA metabolic pathway are reported to mobilize MAPK. This might constitute a pivotal approach for lipid metabolites to participate in hepatic IRI, that is, to regulate immune responses by affecting core inflammatory signals.

Previous studies have shown that the AA metabolite thromboxane A2 (TXA2) has the potential to launch the p38 subunit by binding to specific receptors[37]. This process then intensifies hepatic inflammation and cellular apoptosis. Similarly, leukotriene B4 (LTB4), another AA metabolite, can activate both ERK and p38. As a result, infiltration of neutrophils is increased, resulting in increased hepatic inflammation[38]. In addition, MAPK activation is usually affected by multiple factors in hepatic IRI[39]. Individual metabolites might have limited effects on core molecular events, so a joint analysis such as metabolomics involving diverse lipid metabolites is necessary.

NF-κB

Lipid metabolites derived from AA metabolism activate molecules associated with the NF-κB signaling pathway, which reinforces cytokine release and liver damage. Decades after the correlation between inflammation and tumors was revealed, the relationship between inflammation and metabolism came into sight.

A previous study revealed that PGE2 activates the NF-κB signaling pathway, which induces the release of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in the liver[40]. However, several PGs are known to support LT, particularly during the recovery phase following LT. For example, prostaglandin E1 infusion may prevent arterial spasm in LT[41]. Based on the above findings, the underlying mechanism of the PGs in LT still needs more evidence. As NF-κB signaling regulates both inflammation and regeneration, it sometimes has different functions even in the same model. This heterogeneity is consistent with particular stages of the disease and diverse upstreams.

Additionally, thromboxane B2 (TXB2) has also been investigated in hepatic IRI. Previous studies have shown that atorvastatin can reduce TXB2 levels and inhibit NF-κB, thereby mitigating the inflammation caused by liver IRI[42]. The primary disease of the liver significantly influences the degree of activation of the

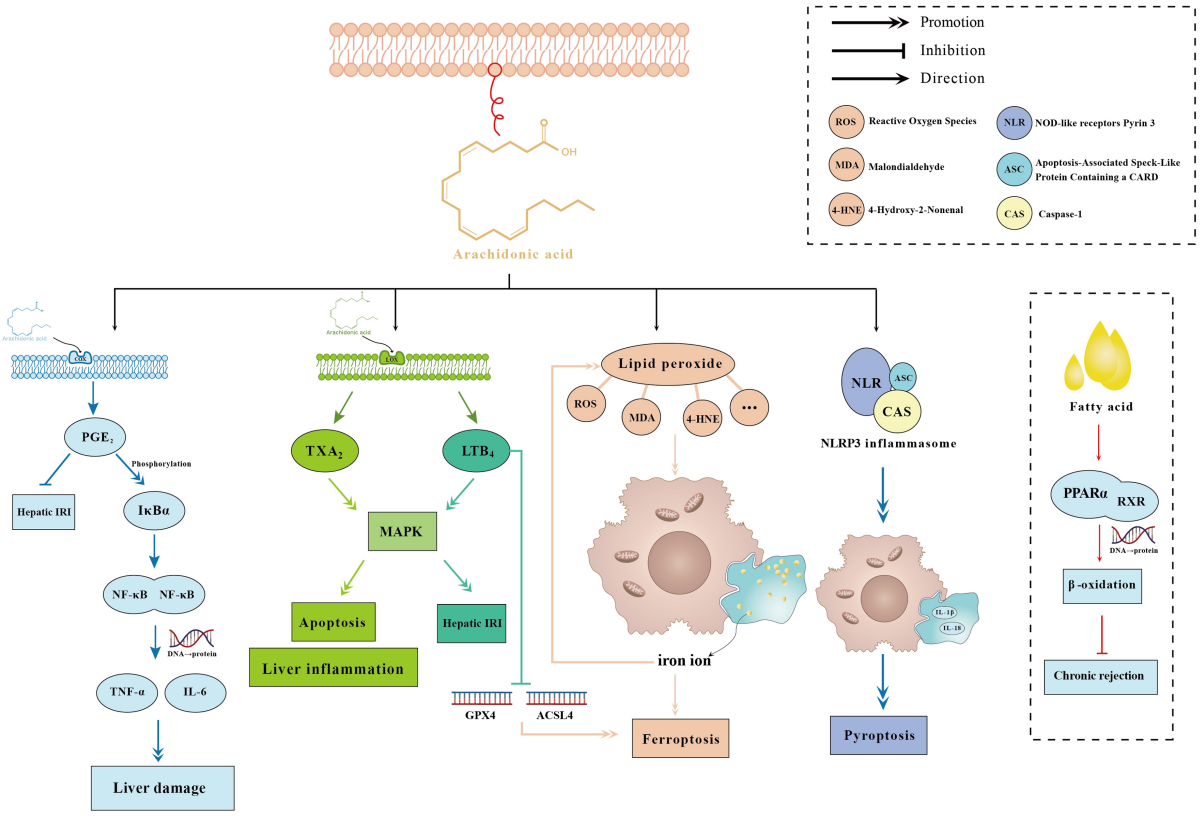

Figure 1. Lipid metabolism signaling pathways in liver transplantation.

NF-κB signaling pathway, increasing the complexity of hepatic IRI and the severity of liver damage[43]. Notably, the determination of primary disease during LT is an emerging area due to the shortage of donor livers, especially in older livers and fatty livers, which tend to cause the receptors to produce a stronger immune response[4,5,44].

Ferroptosis and pyroptosis

Ferroptosis and pyroptosis are two vital processes of programmed cell death in hepatic IRI[45,46]. The AA metabolic pathway and its metabolites are intimately associated with the onset of ferroptosis and pyroptosis[47,48].

Ferroptosis

Ferroptosis, a form of cell death dependent on iron, is characterized by lipid peroxidation and iron ion accumulation[49]. During IRI, products of lipid peroxidation are generated through the AA metabolic pathway and then trigger ferroptosis. Lipid peroxidation by the AA pathway directly impairs the stability and integrity of liver cell membranes, eventually leading to membrane rupture and the release of iron ions. Iron ions act as catalysts and further aggravate lipid peroxidation reactions, thus creating a vicious cycle[50]. In addition, some lipid mediators in the AA metabolic pathway can directly mediate gene expression related to ferroptosis and accelerate the ferroptosis process[51].

During hepatic IRI, the occurrence of ferroptosis is not solely determined by the AA metabolic pathway. As with other types of programmed death, multiple factors might be involved in the regulation of ferroptosis. The primary disease of the liver partially determines the fate of hepatic cells after IRI[52]. In addition to liver

parenchymal cells, whether and how ferroptosis progresses in nonparenchymal cells and immune cell activation are largely unexplored.

Pyroptosis

Pyroptosis is characterized by cell swelling, membrane pore formation, and the release of inflammatory cytokines[53]. For pyroptosis, some AA mediators have the ability to activate the NLRP3 inflammasome, which is currently considered an inherent signal of pyroptosis. AA can activate the NLRP3 inflammasome in myeloid-derived suppressor cells (MDSCs) via FATP2 to promote posttransplant tumor recurrence in steatotic liver grafts[54]. Hepatocyte pyroptosis and inflammasome release induce stellate cell activation and liver fibrosis, suggesting the bridge role of pyroptosis among different hepatic cells[55]. The current research on the role of pyroptosis in lipid metabolism after LT is not limited to parenchymal cells and has made great progress. This finding is quite different from the initial reports of Kupffer cells as the main target in hepatic IRI.

From another perspective, gasdermin D (GSDMD) is currently considered the main functional subunit of pyroptosis in LT, but some studies have not screened other family proteins, which might omit some subtle mechanisms[56].

LIPID METABOLISM AND REJECTION

Rejection post-LT poses an inevitable challenge for every liver transplant recipient. Interestingly, IRI and lipid metabolism also play significant roles in rejection processes following LT.

Acute rejection

Acute rejection is a common complication in the early posttransplant period after LT and manifests as impaired graft function, tissue damage, and poor prognosis[57-59]. Acute rejection is thought to be associated with lipid metabolism remodeling. Moreover, LT patients are procedurally treated with immunosuppressant drugs for acute rejection, which probably influences lipid metabolism as a nonnegligible side effect[20,60,61].

Lipid metabolism remodeling during acute rejection

Acute rejection after LT is one of the primary problems[62,63]. Owing to the activation of immune cells, including T cells and macrophages, in the graft, a substantial amount of cytokines and chemokines are released, causing direct damage to the graft and remodeling lipid metabolism[64-66].

Tacrolimus-induced lipid metabolism perturbations

Tacrolimus (TAC), as the first-line drug for immunosuppressive therapy, exerts certain effects on lipid metabolism[67,68] [Table 2]. Studies have shown that in patients undergoing adult-to-adult living donor liver transplantation (AALDLT), higher blood concentrations of TAC are associated with hyperlipidemia in the early postoperative period. The potential mechanism might involve the activation of immune cells, leading to the release of inflammatory factors, which in turn injures lipid metabolism. This can partially explain the elevation of total cholesterol (TC) and triglyceride (TG) levels and the decrease in high-density lipoprotein cholesterol (HDL-C) levels[69]. Given that, the tandem effects of inflammation and lipid metabolism seem to require further elucidation.

Ethanol-induced oxidative stress and lipid metabolism disturbance

Ethanol is reported to be involved in acute rejection. A previous study revealed that ethanol consumption by donors prior to LT causes oxidative stress after the transplantation of fatty livers, thereby disturbing the graft and generating microcirculation disturbances. In this situation, Kupffer cells and neutrophils are redeployed by oxidative stress and then facilitate the production of free radicals[70].

Table 2. Influence of the application of immunosuppressants after liver transplantation on lipid metabolism

Category	Name	Effect
CNIs	Tacrolimus	Reduces total cholesterol and triglycerides levels, potentially lowering the risk of cardiovascular disease
	Cyclosporine A	Elevates blood lipid levels, including cholesterol and triglycerides
Antiproliferative gents	Mycophenolate mofetil	Generally has a neutral or mildly beneficial effect on lipid metabolism, with no significant increase in lipid levels
mTOR inhibitors	Sirolimus (rapamycin)	Can increase cholesterol and triglyceride levels, but may have a beneficial effect on reducing the progression of atherosclerosis in some patients
	Everolimus	Similar to sirolimus, may increase lipid levels but with potential cardiovascular protective effects in certain contexts
Corticosteroids	Dexamethasone	Increases blood lipid levels, including cholesterol and triglycerides, contributing to an increased risk of cardiovascular disease
Circular RNA	circFOXN2	Alleviates dyslipidemia induced by tacrolimus and dexamethasone by reducing FASN mRNA stability and modulating lipid metabolism

CNIs: Calcineurin inhibitors; FASN: fatty acid synthase.

Application of immunosuppressant drugs

Impact of TAC and cyclosporine a on lipid metabolism

To prevent acute rejection, a prolonged immunosuppressive strategy is necessary for most LT patients. Some of these drugs have complicated synergistic effects on lipid metabolism[71,72]. TAC and cyclosporine A are widely administered immunosuppressants. Studies indicate that the utilization of TAC is related to lower levels of TC and TG after LT, which might reduce the risk of cardiovascular disease. Moreover, cyclosporine A is associated with elevated blood lipid levels[73]. As powerful immunosuppressive drugs, their ability to modulate lipid metabolism has far-reaching effects on direct and indirect targets, and what we observe might be some macroscopic results from synergistic actions.

Therapeutic potential of circFOXN2 in managing dyslipidemia

Another study revealed that circFOXN2 can alleviate dyslipidemia induced by TAC and dexamethasone (Dex). Specifically, a decreased circFOXN2 level is correlated with an increase in fatty acid synthase (FAS). The overexpression of circFOXN2 can reverse TC, TG, FASN, and sterol regulatory element-binding transcription factor 2 (SREBP-2) levels[74]. These findings suggest that circFOXN2 might serve as a potential therapeutic target for managing dyslipidemia in LT patients receiving TAC and Dex.

Combination therapy for minimizing adverse effects on lipid metabolism

Combination therapy is often used to mitigate the adverse effects of immunosuppressants in the clinic. Strategies integrating mTOR inhibitors with TAC or mycophenolate mofetil (MMF) could reduce the dosage of single drugs, thereby minimizing interference with lipid metabolism[75].

Chronic rejection

Chronic rejection, a long-term complication following LT, primarily presents as durable degeneration of graft function, fibrosis, and vascular pathology[76-78]. Compared with acute rejection, chronic rejection has a more enduring and intricate influence on lipid metabolism.

Long-term transition in lipid metabolism during chronic rejection

In the context of chronic rejection, ongoing inflammation and fibrosis of the graft result in aberrant expression of enzymes and ligands that interfere with lipid metabolism. Studies have shown that patients

with chronic rejection exhibit persistent elevations in TC, TG, and LDL-C, along with decreased HDL-C[79]. This lipid metabolism disorder could be explained by macrophage infiltration, increased oxidative stress, and dysregulation of lipid metabolism-associated genes in the transplanted organ.

Both the immune system and the metabolic system might be damaged by chronic rejection. A previous study demonstrated that patients with chronic rejection suffer from insulin resistance and abnormal glucose metabolism. Insulin resistance inhibits fatty acid oxidation and ketogenesis but promotes fat synthesis and deposition. Excessive glucose metabolism might lead to the accumulation of intermediate products of lipid metabolism, further worsening lipid metabolism disorders in renal transplantation[80]. However, more studies are needed on fatty LT to clarify the relationship between insulin resistance and chronic rejection in fatty LT patients, which is a potential research direction for the future. Moreover, in 2023, disulfide death induced by glucose starvation was discovered; for example, the donor liver suffers glucose deprivation during ischemia, and the low glucose level of the living donor decreases graft survival[81]. Thus, this new form of programmed death may be comprehensively explored in the context of LT and lipid metabolism[82,83].

Regulation of lipid metabolism in delaying chronic rejection

Considering the connection between lipid metabolism and chronic rejection, regulating lipid metabolism may constitute another strategy for preventing chronic rejection.

Regulation of fatty acid oxidation

Fatty acid oxidation is vital for lipid metabolism stability[84]. Increasing fatty acid β-oxidation can decrease fat production and accumulation, thus improving lipid metabolism. Research has shown that peroxisome proliferator-activated receptor α (PPARα) can stimulate the β-oxidation of fatty acids, reduce liver fat, and delay chronic rejection[85]. PPARα agonists such as fenofibrate and clofibrate are being further investigated for the treatment of lipid metabolism disorders in chronic rejection. In addition, lipase inhibitors also improve liver lipid levels/utilization and insulin sensitivity, which affects the outcomes of patients with LT[86,87].

Cholesterol metabolism

Inhibition of cholesterol synthesis and promotion of cholesterol excretion improve graft dysfunction caused by lipid metabolism instability[88-90]. Statins are commonly administered as lipid-lowering drugs in the clinic and inhibit the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, subsequently restricting cholesterol synthesis. According to some studies, statins can simultaneously remit blood lipids and liver fibrosis[91]. However, further research is needed to demonstrate its benefits and potential side effects in chronic rejection.

Other molecules

Sterol regulatory element-binding proteins (SREBPs) are a cluster of important transcription factors that control lipid synthesis and metabolism. Recent findings suggest that the upregulation of SREBPs, especially SREBP2, is indispensable in lipid metabolism disorders induced by TAC. CircFASN inhibited miR-33a, thus weakening SREBP expression and fat synthesis and deposition. These consequences collectively improve lipid metabolism disorders induced by TAC[92]. Liver X receptors (LXRs) are nuclear receptors that coordinate cholesterol metabolism and inflammation. Mobilization of LXRs contributes to cholesterol excretion, immune adjustment, and hepatic stellate cell deactivation[93]. T0901317, an LXR agonist, has been investigated in the study of chronic rejection. The causal relationship between lipid metabolism and chronic rejection appears to be variable for some of the multiconnotative molecular threads involved. Concurrently, the establishment of a chronic rejection model costs much more than the acute rejection and IRI models do.

Potential interventions

When exploring the regulation of lipid metabolism in chronic rejection, several potential treatments have demonstrated significant protective effects in various organ transplantations and IRI and may contribute to chronic rejection after LT. MAGL inhibitors have been shown to effectively prevent IRI in lung transplantation[94]. Another study demonstrated that inhibition of lipolysis improves the survival of transplanted fat grafts by ameliorating lipotoxicity and inflammation[95]. Similarly, the lipase inhibitor atglistatin preserves myocardial function following cardiac ischemia[96].

LIPID METABOLISM AND OXIDATIVE STRESS

Oxidative stress in the donor liver can directly impair liver function. Although the harmful effects of oxidative stress on the whole process of LT have been studied for many years, its association with lipid metabolism has gradually been recognized.

Association between lipid peroxidation and oxidative stress

Some papers argue that lipid peroxidation serves as an intermediary agent between lipid metabolic disorders and oxidative stress. In the case of fatty liver, the peroxidation of polyunsaturated fatty acids under oxidative stress generates a series of highly reactive molecules, including reactive oxygen species (ROS). Together with lipid peroxidation products such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), these toxic factors give rise to structural impairment and dysfunction in cells. The accumulation of these metabolites could, in turn, exacerbate oxidative stress[97] [Table 3].

Studies have demonstrated that oxidative stress accelerates inflammation and cell death, particularly under conditions of fatty liver and IRI. ROS formation increases the formation of MDA and 4-HNE, damaging cellular components. On this basis, the interaction between lipid metabolism disorders and oxidative stress creates favorable conditions for lipid peroxidation[98].

Energy metabolism is crucial for both lipid metabolism and oxidative stress, and its disturbance has substantial implications. The Cori and Krebs cycles are reported to intensify oxidative stress and lipid peroxidation. Research on the primary nonfunction of fatty liver allografts has shown that defects in lactate transport and utilization can result in the build-up of lactate and related metabolites, possibly exacerbating oxidative stress and lipid peroxidation[99]. This relationship might need further elaboration, especially in the case of product crossover among different types of metabolism.

During LT, cold storage of the liver is necessary in some cases, and latent adverse conditions such as temperature fluctuations and insufficient oxygen supply are responsible for the increase in lipid peroxidation levels. The oxidative stress derived from organ preservation can directly lead to extensive cell damage and uncontrollable immune responses[100,101]. Even rats with mild fatty liver exhibit severe lipid peroxidation and oxidative stress after cold preservation[102]. At present, although several reports of ischemia-free cases exist, researchers might still pay attention to improving the conditions of organ preservation for a long time because of cost and technical limitations[103,104].

ROS directly target polyunsaturated fatty acids in the cell membrane, triggering a chain reaction that produces massive amounts of lipid peroxidation substances. This process leads to severe cell membrane damage, resulting in compromised integrity and the leakage of intracellular components. Consequently, it can induce alterations in protein structure and cause DNA damage, ultimately exacerbating oxidative stress[105-108].

Table 3. Pathophysiological process after liver transplantation: the interaction between lipid metabolism and the immune response

Molecular event	Key findings	Mechanisms
IRI	- Increased lipid metabolism disorders	- AA metabolites regulate inflammatory responses
	- AA metabolites (PGs, leukotrienes, thromboxanes) play crucial roles	- MAPK and NF-κB pathways mediate cellular responses to injury
	- MAPK and NF-κB signaling pathways activated	- Ferroptosis and pyroptosis induced by lipid peroxidation
Acute rejection	- Lipid metabolism remodeling	- Immune cell activation leads to cytokine release, affecting lipid metabolism
	- Immunosuppressant drugs (e.g., tacrolimus, cyclosporine A) influence lipid metabolism	- Immunosuppressants have varied effects on lipid profiles
	- Increased levels of TC and TG, decreased HDL-C	- Ethanol-induced oxidative stress disturbs lipid metabolism
Chronic rejection	- Persistent lipid metabolism disorders	- Ongoing inflammation and fibrosis interfere with lipid metabolism
	- Increased TC, TG, LDL-C, decreased HDL-C	- Insulin resistance and abnormal glucose metabolism exacerbate disorders
	- Fibrosis and vascular pathology	- Fatty acid oxidation, cholesterol metabolism, and other molecular pathways involved
Oxidative stress and lipid peroxidation	- Lipid peroxidation serves as an intermediary between lipid metabolic disorders and oxidative stress	- ROS targets polyunsaturated fatty acids, initiating lipid peroxidation
	- Increased ROS, MDA, and 4-HNE levels cause cell damage	- Peroxidation products damage cell structures and function
	- Lipid peroxidation modifies mitochondria, exacerbating oxidative stress	- Mitochondrial membrane permeability altered, leading to cell death

AA: Arachidonic acid; PGs: prostaglandins; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-κB; ROS: reactive oxygen species; MDA: malondialdehyde; 4-HNE: 4-hydroxynonenal; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; IRI: ischemia/reperfusion injury; TC: total cholesterol; TG: triglycerides.

In addition, lipid peroxidation modifies mitochondria, which are energy factories, as they are the primary site of ATP production and a considerable source of generated ROS. Lipid peroxidation can directly attack the mitochondrial membrane, thus altering its permeability and leading to ROS production. Lipid peroxidation also activates the mitochondrial permeability transition pore (MPTP), a key trigger for cell apoptosis and necrosis, subsequently exacerbating hepatocyte death in LT[109-112].

Lipid metabolism disorders exacerbate oxidative stress

Lipid metabolism abnormalities in LT manifest in various forms, including enhanced fatty acid synthesis, TG aggregation, and low-density lipoprotein (LDL) oxidation. These processes interact to form a complex network that promotes ROS generation and exacerbates oxidative stress. This phenomenon has been widely explored in the context of fatty liver disease[97,113,114].

Reports certify that specific preservation solutions and adjuvants could mitigate liver injury caused by lipid metabolism disorders and oxidative stress by enhancing antioxidant defense and reducing inflammation. Preservation solutions such as HTK, UW, and IGL-2 have been demonstrated to reduce injury in steatotic livers[115]. This provides a potential option for future cold storage for the donation of fatty liver. Research has focused mainly on improving traditional preservation solutions that have not been specific for fatty liver in the past ten years, and there is a lack of revolutionary next-generation products on the market.

Abnormal fatty acid synthesis is a prominent manifestation of lipid metabolism disorders. Under LT, hypoxia and hypothermia coupled with the stress response can increase the level of FAS. This event results in excessive lipid accumulation[21,115].

TG are key molecules in lipid metabolism disorders that intensify oxidative stress. As a main substance of lipid metabolism, superfluous fatty acids, which are deposited as TG, disrupt the dynamic balance of mitochondrial metabolic processes, resulting in increased ROS and oxidative stress[116,117]. Due to the effects of organ preservation and IRI, the amount of TG is clearly increased. This condition can reshape the liver energy supply and impair patient outcomes.

LDL oxidation is another mechanism that exacerbates oxidative stress. LDL is easily oxidized under oxidative stress conditions, thereby generating oxidized low-density lipoprotein (ox-LDL). Ox-LDL is capable of activating immune cells and releasing cytokines[118,119]. Although few studies have investigated the oxidative stress of LDL in LT, its impacts on lipid metabolism regulation in other organs have been confirmed. Appropriate strategies for LDL are expected to be potential tactics for fatty donor livers.

Regulation of oxidative stress on lipid metabolism

Notably, oxidative stress exerts an inverse effect on lipid metabolism. Alleviation of oxidative stress can improve lipid metabolism in the liver. A traditional Chinese medicinal formula has been shown to remit fatty acid oxidation by upregulating peroxisome proliferator-activated receptors (PPARs), thus reducing lipid accumulation in the liver. This formula, through its antioxidant properties, has the potential for use in the treatment of NAFLD[120]. Stimulation with PPAR can increase the oxidative decomposition of fatty acids and diminish lipid accumulation. In contrast, the elevation of beta-oxidation of fatty acids under PPAR initiation may increase ROS[105,107,121].

Pinolenic acid, a natural compound discovered in pine nut oil, has also been found to coordinate lipid metabolism. Pinolenic acid can decelerate lipid synthesis and oxidative stress induced by oleic acid through the AMPK/SIRT1 signaling pathway. It inhibits the expression of lipid synthesis-related genes such as FAS and leads to increased antioxidant defense and improved lipid metabolism imbalance[122].

More importantly, the impact of oxidative stress on mitochondria could disrupt lipid metabolism. Oxidative stress impairs the mitochondrial membrane and disrupts respiratory chain complexes, paving the way for decreased ATP synthesis and increased ROS. These alterations further induce mitochondrial fusion, fission, and autophagy[105,123-125].

Potential interventions

The relationship between lipid metabolism and oxidative stress is complex, but there are still several potential mechanisms and interventions that can be explored in the future.

One promising approach is the administration of antioxidants, such as vitamin E and N-acetylcysteine, which can scavenge ROS and thereby reduce lipid peroxidation[126,127]. The utilization of dietary supplements rich in antioxidants, such as omega-3 fatty acids, has shown promise in reducing oxidative stress and lipid peroxidation[128]. These interventions hold great potential in improving the outcomes of LT by mitigating the adverse effects of lipid peroxidation.

DISCUSSION

The role of lipid metabolism in LT presents both challenges and opportunities for the development of novel therapeutic strategies. Through an in-depth review of studies, we can more fully understand how lipid metabolism affects the diverse stages of LT. This discussion focuses on three major issues commonly encountered in LT - IRI, rejection, and oxidative stress - which are explored in detail.

The remodeling of lipid metabolism in LT is a phenomenon that cannot be ignored. As early as the Suzuki score was proposed, the accumulation of lipid droplets was included in the pathological criteria. LT and subsequent immunosuppressive therapy have a profound impact on lipid metabolism[129,130]. IRI is a decisive challenge in the early stages of LT[131]. AA metabolites, including PGs, leukotrienes, and TXs, are crucial in regulating molecular events during hepatic IRI, yet their mechanisms of action are diverse and occasionally contradictory[29,48,54,132,133]. PGE has shown marked effects in protecting the liver from IRI damage by promoting liver blood perfusion, inhibiting platelet aggregation, and reducing oxidative stress levels[27]. However, other metabolites, such as TXA2 and LTB4, may exacerbate liver inflammation and apoptosis by initiating the MAPK and NF-κB signaling pathways[29,38]. This dual role of metabolites requires a deeper understanding of the internal mechanisms for more precise regulation.

In addition, lipid metabolism is critical in rejection. Both acute rejection and chronic rejection impair the function and cell structure of the transplanted liver, along with lipid metabolism disorders[134,135]. The effects of immunosuppressants on lipid metabolism have often been overlooked. TAC strongly influences lipid metabolism[73]. Studies have shown that TAC can lead to abnormalities in lipid metabolism and further endanger the transplanted liver by increasing oxidative stress and inflammatory responses[69]. In chronic rejection, the relationship between fibrotic processes and lipid metabolism has not been confirmed, but its correlation has been reported[136-141].

Oxidative stress and lipid metabolism closely interact in LT[98,107,142,143]. In fatty LT, oxidative stress promotes the peroxidation of polyunsaturated fatty acids to produce a series of highly reactive molecules and lipid peroxidation products, including ROS, MDA, and 4-HNE. These molecules further alter cell structure and function[100,109,118]. Moreover, abnormal lipid metabolism in the liver, manifested by increased fatty acid synthesis, TG accumulation, and LDL oxidation, can also increase oxidative stress levels[97,113,114]. Identifying the common factors among these elements represents a future research direction.

In addition to their direct ramification, lipid metabolism and oxidative stress also regulate the outcome of LT by influencing cell destiny. Ferroptosis and pyroptosis are highly important in LT[20,45,144,145]. Lipid peroxides produced by the AA metabolic pathway can erode the stability and integrity of liver cell membranes, leading to membrane rupture and iron ion release, triggering iron death[146]. LTB4 can also initiate pyroptosis by activating the NLRP3 inflammasome, causing cell swelling, membrane pore formation, and the subsequent release of inflammatory cytokines[147]. New modes of death continue to be discovered, and the main target cells will be the first focus.

In special populations, such as obese individuals, elderly patients, and pregnant women, more factors often need to be considered during LT. Abnormal lipid metabolism in obese patients may exacerbate IRI and rejection post-transplantation, whereas the decline in physiological functions in elderly patients and the unique physiological state of pregnant women may also significantly impact transplantation outcomes and postoperative recovery[148]. Therefore, for these special populations, further in-depth research on the role of lipid metabolism in LT is needed, and more personalized and refined treatment strategies need to be developed.

The liver is the main execution organ of lipid metabolism and is closely related to other physiological processes, including glucose metabolism[149,150]. In addition to surgical means, systemic measures are necessary. In the preoperative phase, a thorough assessment of lipid metabolism indicators allows for the timely identification of potential abnormalities, suggesting appropriate intervention measures. During surgery, efforts are made to optimize organ preservation techniques and conditions, minimizing the impact of lipid peroxidation and oxidative stress on the transplanted liver. Postoperatively, personalized immunosuppressive therapy and nutritional support plans are tailored to each patient's unique needs, ensuring the maintenance of normal lipid metabolism.

In the future, we need to further refine our research directions. Specifically, future studies could focus on elucidating the underlying mechanisms of the AA metabolic pathway in the long-term dysregulation of lipid metabolism post-LT, as well as developing novel intervention strategies targeting this pathway to improve graft function. Moreover, identifying new targets capable of effectively inhibiting lipid peroxidation and oxidative stress during chronic rejection post-LT is crucial.

In summary, lipid metabolism faces such challenges during LT. As an immunologically privileged organ, immunization protocols for other organs sometimes have some reference value for the liver. Moreover, the expanded use of some drugs has yielded unexpected benefits for lipid metabolism. The shortage of donor organs is a global problem. It is still under discussion whether there is a need for refined subdivision criteria for marginal donor livers, especially for fatty liver and elderly donor liver, including distinct coping approaches for every type.

CONCLUSION

This review identifies potential targets, underlying mechanisms, and future directions by analyzing common problems closely related to lipid metabolism in LT. Fatty liver, an important component of marginal donor livers, has self-evident importance. Addressing lipid metabolism disorders, the core issue in fatty LT, is crucial for improving the quality of life and outcomes of patients.

DECLARATIONS

Authors' contributions

Wrote the initial draft and revised the manuscript: Zhang Y
Conducted the literature search, compiled relevant studies, and assisted in drafting the manuscript: Wang R
Performed data analysis, prepared tables/figures, and interpreted results: Liu X
Reviewed the clinical implications and edited the manuscript: Ye Y
Developed methodology and conducted critical appraisal: Pu S
Conducted additional literature search and wrote specific sections: Zong K
Coordinated team collaboration and facilitated communication: Yang E
Reviewed the manuscript for scientific accuracy and suggested revisions: Li S
Assessed the clinical relevance and contributed to the discussion on future research directions: Huang Z
Supervised the overall project and finalized the manuscript: Wu Z

Availability of data and materials

Not applicable.

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Conflicts of interest

Huang Z is a Junior Editorial Board member of the Journal of *Metabolism and Target Organ Damage*. Huang Z was not involved in any steps of the editorial process, including reviewer selection, manuscript handling, or decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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