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REVIEW

Immune and metabolic cross-links in the pathogenesis of comorbid non-alcoholic fatty liver disease

Stanislav Kotlyarov

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Abstract

In recent years, there has been a steady growth of interest in non-alcoholic fatty liver disease (NAFLD), which is associated with negative epidemiological data on the prevalence of the disease and its clinical significance. NAFLD is closely related to the metabolic syndrome and these relationships are the subject of active research. A growing body of evidence shows cross-linkages between metabolic abnormalities and the innate immune system in the development and progression of NAFLD. These links are bidirectional and largely still unclear, but a better understanding of them will improve the quality of diagnosis and management of patients. In addition, lipid metabolic disorders and the innate immune system link NAFLD with other diseases, such as atherosclerosis, which is of great clinical importance.

Key Words: Non-alcoholic fatty liver disease; Metabolism; Lipid metabolism; Lipid; Fat; Innate immune system; Pathogenesis

Core Tip: Non-alcoholic fatty liver disease (NAFLD) is an important medical and social problem. The development of NAFLD is closely related to the metabolic syndrome, which further increases attention to the problem. The pathogenesis of NAFLD is complex and involves closely intertwined metabolic and immune mechanisms, a better understanding of which will improve the effectiveness of measures to prevent and treat the disease. Lipid metabolism has multiple connections with the innate immune system, in which various liver cells are involved.

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INTRODUCTION

Interest in non-alcoholic fatty liver disease (NAFLD) has increased significantly in recent years, due to an increasing number of reports on its high prevalence and clinical significance[1]. Epidemiologic data show that the prevalence of NAFLD in the adult population ranges from 17% to 46%, but the data vary by region and depend on age, sex, and several other characteristics[2]. These negative epidemiologic findings are thought to be related to the high prevalence of metabolic diseases, such as obesity and diabetes mellitus, which is due to the effects of low physical activity and poor diet[3]. The links of NAFLD with the metabolic syndrome are attracting increasing attention from clinicians. Dyslipidemia, obesity, insulin resistance, and diabetes are important features of the metabolic syndrome and are closely related to NAFLD[4-6]. Indeed, the prevalence of NAFLD among obese adults is 80%-90%, approximately 30%-50% in patients with diabetes, and up to 90% in patients with hyperlipidemia[7].

Another problem associated with NAFLD is that the disease is often not diagnosed in a timely manner, as patients do not seek medical care for a long time. Most patients are asymptomatic or the symptoms are nonspecific, and patients may not pay enough attention to them. In addition, these patients often have comorbidities, the clinical picture of which may be more pronounced and of greater concern to patients. Atherosclerotic cardiovascular diseases are common in these patients, significantly affecting quality of life and prognosis[8-10]. It is important to note that accurate diagnosis of NAFLD is currently associated with a number of difficulties, primarily, the limited availability of modern diagnostic tools in the primary care setting. Thus, NAFLD is currently a growing burden on patients and healthcare systems.

NAFLD includes two morphological forms, non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH)[11,12]. At the same time, the diagnosis of NAFLD assumes the exclusion of secondary causes and significant alcohol consumption.

NAFLD is characterized by excessive fat accumulation in the liver, but the pathophysiology of this disorder involves complex mechanisms. According to the "two-hit hypothesis" model proposed in 1998 by Day *et al*[13], the "first hit" involves lipid accumulation in hepatocytes and development of steatosis, which is associated with the negative impact of obesity, type 2 diabetes, dyslipidemia and other metabolic risk factors on the liver[13-15]. The "second hit" leads to damage to the hepatocellular system and liver inflammation and is associated with the effects of oxidative stress and proinflammatory cytokines[13]. A growing body of evidence suggests that NAFLD develops as a result of a complex chain of events, many of whose links are cross-linked, consistent with the newly proposed "multiple parallel-hit" concept. Thus, insulin resistance, de novo lipogenesis, local and systemic inflammation, disorders in the structure of the gut microbiota, and oxidative stress play an important role in the pathophysiology of NAFLD and have crosslinks that involve different cells (Figure 1)[16]. Recent advances in the study of the mechanisms that contribute to the development and progression of NAFLD have led to a better understanding of the complex interplay between environmental factors, the gut microbiota, metabolism, and the innate immune system, which include both intrahepatic and extrahepatic events[17].

MOLECULAR MECHANISMS INVOLVED IN NAFLD PROGRESSION

The significance of metabolic disorders in the pathogenesis of NAFLD

The results of studies suggest that NAFLD exhibits a close bidirectional relationship with the metabolic syndrome[18]. The development of the metabolic syndrome may precede NAFLD or be a consequence of it[19,20]. NAFLD significantly increases the risk of metabolic syndrome and may also be considered an independent risk factor for some cardiovascular diseases[21-23]. Given that NAFLD is often combined with metabolic diseases such as obesity, type 2 diabetes, hyperlipidemia, and hypertension, it may have negative prognostic implications[24,25]. Thus, an overweight person is a typical NAFLD patient phenotype[26,27]. Moreover, body mass index and NAFLD show a strong correlation[27,28]. Interestingly, NAFLD also occurs in non-obese individuals, with the majority of these findings occurring in Asian countries, although they have been described worldwide[29-32]. Despite the phenotypic differences, NAFLD patients who were not obese had similar severity of histologic liver damage[33]. At the same time, NAFLD patients without obesity had a higher degree of fibrosis[34-37].

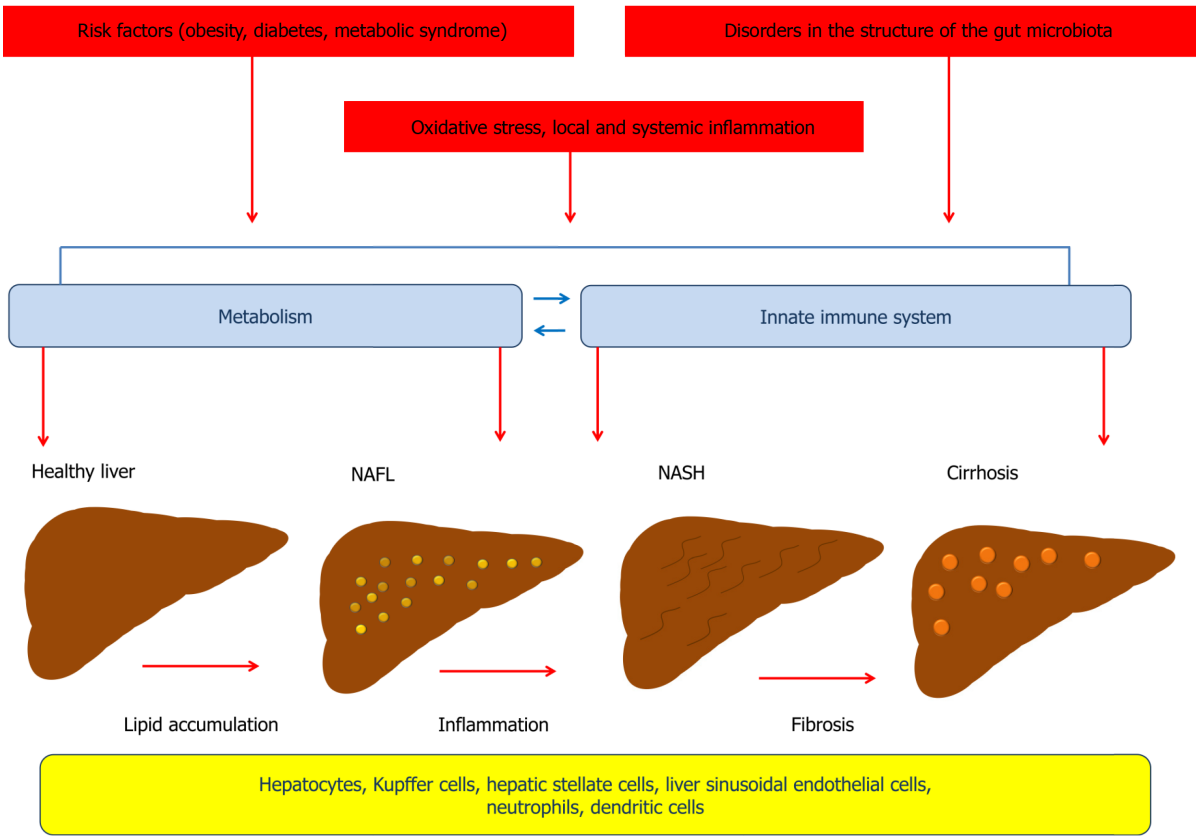

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Figure 1 Risk factors and links of non-alcoholic fatty liver disease pathogenesis. NAFL: Non-alcoholic fatty liver; NASH: Non-alcoholic steatohepatitis.

A key histological characteristic of NAFLD is the cellular accumulation of triglyceride (triacylglycerides, TAGs) containing lipid droplets[38-40]. TAG biosynthesis is carried out using fatty acids, which may enter the cells from the blood or be formed by de novo lipogenesis and endocytotic recycling of lipoprotein remnants[40,41]. In most cases, the main source of fatty acids used for TAG formation is absorption from the blood[41,42]. Interestingly, some data suggest that TAG accumulation per se is not harmful to hepatocytes and can even be considered as a certain protective mechanism against lipotoxicity induced by free fatty acids[43]. This is supported by the data that an excess of free fatty acids in nonfat cells can lead to their dysfunction and apoptotic death[44]. Moreover, levels of free fatty acids in the blood are related to the severity of NAFLD, with saturated fatty acids being more hepatotoxic than unsaturated fatty acids[45]. Thus, free fatty acids are important mediators of excessive lipid accumulation in the liver.

Studies have shown that monounsaturated fatty acids such as oleic or palmitoleic acids are less toxic than saturated fatty acids such as palmitic or stearic acids[46,47]. Long-chain saturated palmitate induces apoptosis in Chinese hamster ovary cells through a mechanism involving reactive oxygen species (ROS) and ceramide formation, which can enhance palmitate-induced apoptosis signals[43]. In turn, unsaturated fatty acids prevent palmitate-induced apoptosis by directing palmitate to triglyceride pools and removing them from pathways leading to apoptosis[43]. In doing so, reducing the ability of cells to synthesize triglycerides contributes to lipotoxicity[43]. The mechanism of this action may be related to the fact that palmitate is poorly incorporated into cellular triglyceride pools in the absence of additional signals, but the presence of unsaturated fatty acids can help direct palmitate toward triglyceride storage, thereby excluding palmitate from apoptotic pathways. Moreover, unsaturated fatty acids, which come both as additives to the medium, such as the addition of oleate, and as a result of the action of desaturase (*e.g.*, stearoyl-CoA desaturase), demonstrate this action[43]. Stearoyl-CoA desaturase-1 (SCD), known as fatty acid desaturase, is an enzyme that is expressed in the liver and is involved in the biosynthesis of monounsaturated fatty acids, primarily oleate and palmitoleate from corresponding saturated fatty acids. Decreased expression and activity of SCD1, leads to the intake of excessive amounts of saturated fatty acids, increasing their lipotoxic effects and the development of steatohepatitis and fibrosis[48,49]. Indeed, oleic acid has been shown to be more steatogenic but has less apoptotic effects than palmitic acid in hepatocyte cell cultures[50].

Increased fat in the liver correlates directly with changes in plasma saturated fatty acids and inversely with polyunsaturated fatty acids (PUFAs)[51]. Saturated fatty acids markedly induce fat deposition in

the liver and serum ceramides, whereas dietary PUFAs prevent fat accumulation in the liver and reduce ceramides and hyperlipidemia with excess energy intake in overweight people[51]. Higher concentrations of total ω-6 PUFAs and serum linoleic acid have been shown to be associated with lower odds of developing NAFLD in the future[52]. Meanwhile, ω-3 PUFAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may have a protective effect on the liver by reducing insulin resistance, reducing inflammation, and inhibiting apoptosis of hepatocytes[53].

These and other data allow us to expand our views on the features of metabolic processes in NAFLD, as well as NAFLD comorbid relationships. It has been shown that in NAFLD, regardless of the presence or absence of obesity, there is a high risk of coronary atherosclerosis, which contributes to the clinical picture[54]. It is widely known that NAFLD is associated with the development of atherosclerosis[55-57]. Moreover, NAFLD is associated with an increased risk of cardiovascular disease beyond that due to established risk factors[57]. Moreover, cardiovascular disease is the main cause of death in NAFLD patients[55].

NAFLD patients often have dyslipidemia along with other features of the metabolic syndrome. NAFLD patients have significantly elevated levels of oxidized low-density lipoprotein (LDL), and a significant association has been shown between LDL levels and the prevalence of NAFLD[58,59]. Elevated LDL levels within the normal range were associated with an increased risk of NAFLD[59]. In addition, there are important differences in LDL and high-density lipoprotein (HDL) subfractions in NAFLD patients. Liver fat has been shown to correlate more strongly with circulating HDL2 cholesterol and the ratio of HDL2 to HDL3 cholesterol than with total HDL cholesterol[60]. Patients with NASH had an increased number of small, dense LDL3 and LDL4 particles[61]. These changes may contribute to the increased risk of atherosclerosis and cardiovascular disease in these patients.

THE IMPORTANCE OF INNATE IMMUNITY IN THE PATHOGENESIS OF NAFLD

A growing body of evidence is increasing the understanding of the importance of the innate immune system in the development of NAFLD (Figure 2). The innate immune cells, which include Kupffer cells, neutrophils, dendritic cells (DCs), and natural killer (NK) cells, play an important role in the pathogenesis of NAFLD. Kupffer cells, which constitute 80% to 90% of the total macrophage population, are under physiological conditions a long-lived and self-renewing population[62]. Due to their location, they are central to innate immunity and are responsible for the rapid removal of exogenous particles such as lipopolysaccharide (LPS)[63-65]. Like other macrophages, Kupffer cells are also capable of detecting endogenous molecular signals resulting from homeostasis disruption[62].

Steatohepatitis is characterized by marked enlargement and aggregation of Kupffer cells in perivenular regions, with scattered large fat vacuoles found within Kupffer cells[66]. The contribution of macrophages originating from blood monocytes to this cell pool is not entirely clear, as there is currently no marker to distinguish them from resident macrophages[67].

Kupffer cells, which are resident macrophages of the liver, uptake large amounts of free fatty acids, which contributes to their proinflammatory activation. During inflammatory activation, Kupffer cells produce proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, which are important participants in the progression of inflammation and development of NASH[68]. Thus, free fatty acids mediate the link between lipid metabolism and the innate immune system[69-71].

It is important to note that Kupffer cells, like other macrophages, have complex immunometabolic regulation (Figure 3). It has been shown that a prolonged high-fat diet increased the number of Kupffer cells with a proinflammatory M1 phenotype producing proinflammatory cytokines. Saturated fatty acids promoted M1 polarization of Kupffer cells, whereas ω-3 PUFAs polarized Kupffer cells to the M2 phenotype, which was associated with activation of the NF-κB and PPAR-γ signaling pathways, respectively[72]. The proinflammatory M1 phenotype of macrophages is characterized by enhanced glycolysis and fatty acid synthesis, whereas the anti-inflammatory M2 macrophages use fatty acid oxidation[73].

It has been suggested that polarization of M2 Kupffer cells may protect against fatty liver disease. M2 macrophages have been shown to be predominant in individuals with limited liver lesions, corresponding to little hepatocyte apoptosis compared with patients with more severe lesions[74]. Interestingly, M2-induced apoptosis of M1 macrophages is one of the mechanisms regulating the balance between M1 and M2 macrophages[74].

It has been suggested that elevated levels of free fatty acids, resulting from their excessive intake with food or by release from adipose tissue during starvation, may be the main cause of TNF release from Kupffer cells, leading to hepatocyte steatosis. Toll-like receptor 4 (TLR4) is able to detect free fatty acids on Kupffer cells to detect excess and overload of fatty acids in the liver[75]. It is known that saturated fatty acids can participate in the activation of TLR4, a receptor of the innate immune system[76-78]. This action can be associated with both direct stimulation of the receptor, confirming the evolutionary connection with the structure of LPS, which is the receptor aimed at detecting. In addition, fatty acids can be incorporated into the phospholipids of the plasma membrane and thus influence their biophysical properties and function[77,79]. The saturation and length of the alkyl chain are important.

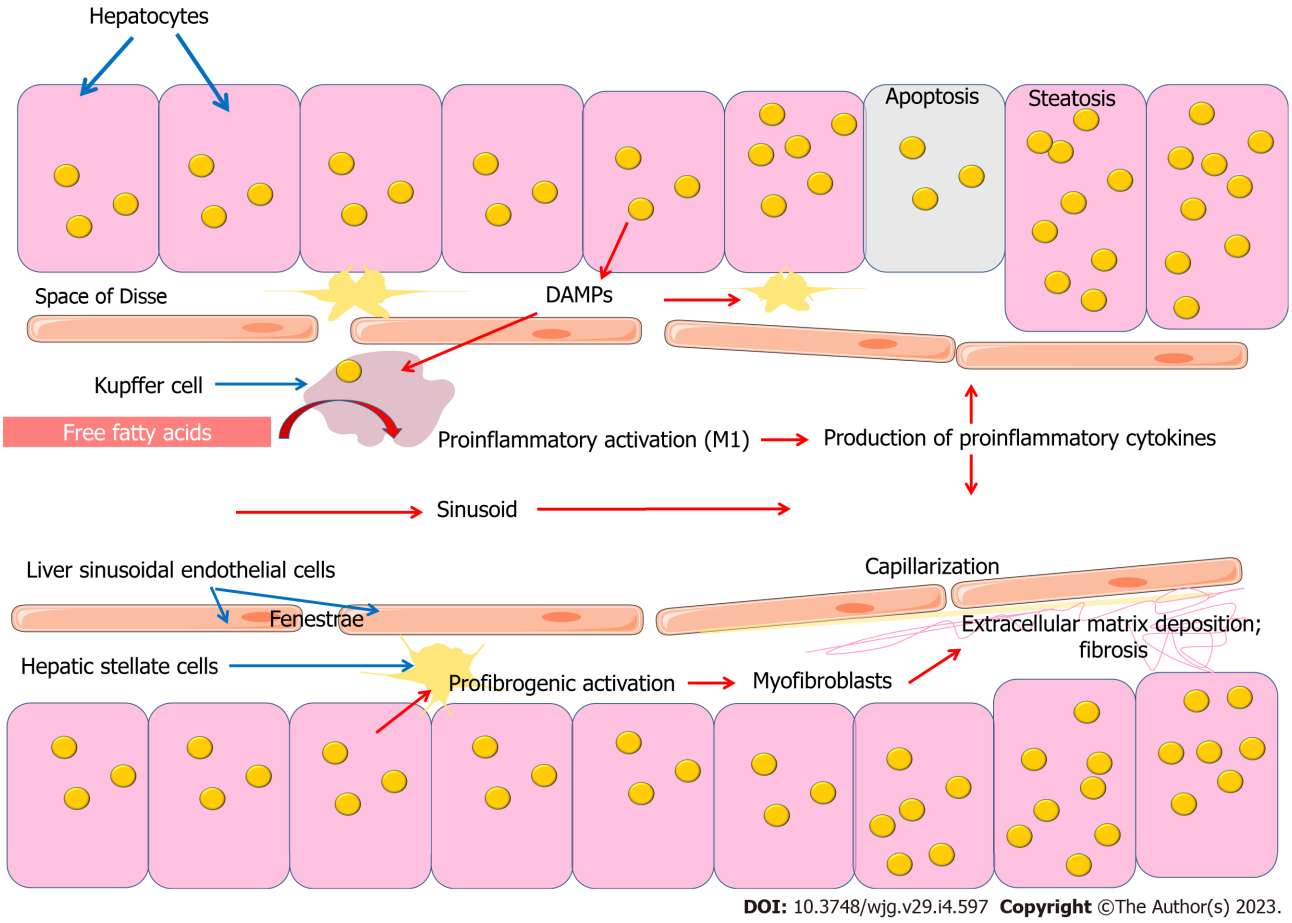

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Figure 2 Cellular mechanisms of non-alcoholic fatty liver disease pathogenesis. DAMPs: Damage associated molecular patterns.

By influencing the biophysical properties of the plasma membrane and the stability of lipid rafts in this way, the function of some membrane proteins can be regulated. It is suggested that unsaturated fatty acids contribute to a decrease in lipid ordering and the stability of lipid rafts, which may lead to anti-inflammatory effects, given the role of lipid rafts as platforms for the assembly and function of many signaling pathways. Thus, unlike saturated fatty acids, unsaturated fatty acids do not have the ability to activate TLR4. In addition, their effect on the biophysical properties of plasma membranes is opposite [77].

Unsaturated fatty acids can participate in the regulation of inflammation not only due to their biophysical properties. They are also precursors for the formation of many lipid mediators associated with inflammation. The family of lipid mediators called "specialized pro-resolving mediators" includes lipoxins, resolvins, protectins and maresins. They are formed enzymatically from ω-3 and ω-6 PUFAs such as arachidonic acid, EPA and DHA. Lipoxins are formed from arachidonic acid, E-series resolvins from EPA, and D-series resolvins, protectins and maresins from DHA[80].

Circulating maresin-1 (MaR1) levels were shown to be decreased in NAFLD patients, and a negative correlation between NAFLD and serum MaR1 concentrations was found[81]. MaR1 is mainly synthesized in M2-macrophages and plays an important anti-inflammatory role. It improves insulin sensitivity and eliminates adipose tissue inflammation[82]. In addition, MaR1 improves hepatic steatosis by inhibiting endoplasmic reticulum stress and lipogenic enzymes, and inducing autophagy *via* the AMP-activated protein kinase (AMPK) pathway[81,83,84]. Activation of Kupffer cells leads to M1 polarization and a decrease in the M2 phenotype, which corresponds to a decrease in maresin production and a decrease in their anti-inflammatory effect. Resolvin D1 (RvD1), which is an endogenous mediator produced from ω-3 DHA, reduced macrophage accumulation in adipose tissue and improved insulin sensitivity in obese and diabetic mice[85]. RvD1 shifted macrophages from an M1-to-M2-like anti-inflammatory phenotype, triggering the resolution process initiated by caloric restriction in obesity-induced steatohepatitis[86]. Protectin DX, derived from DHA, showed suppressive effects on inflammation and insulin resistance and improved hepatic steatosis by suppressing endoplasmic reticulum stress through AMPK-induced ORP150 expression[87].

On the other hand, the development of NAFLD correlates with an increase in serum eicosanoids. Moreover, profiling of plasma eicosanoids and other PUFA metabolites can differentiate NAFLD from NASH[88]. 11,12-dihydroxy-eicosatrienoic acid (11,12-diHETrE) was used as a biomarker to differ-

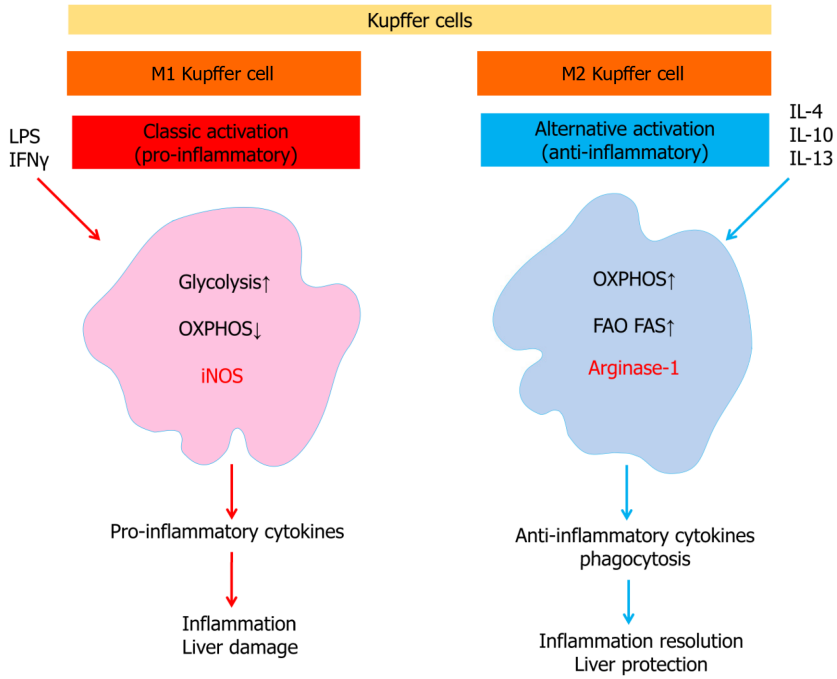

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Figure 3 Kupffer cell polarization. LPS: Lipopolysaccharide; FAO: Fatty acid oxidation; FAS: Fatty acid synthesis; IFN-γ: Interferon gamma; IL: Interleukin; iNOS: Inducible nitric oxide synthase; OXPHOS: Oxidative phosphorylation.

entiate NAFLD from NASH[88]. In another study, patients with NASH had significantly elevated levels of 9- and 13-HODE and 9- and 13-oxoODE, products of linoleic acid oxidation, compared with patients with steatosis[89]. Interestingly, patients with stage I NAFLD had lower plasma levels of 5-HETE, whereas patients with stage II steatosis had higher concentrations of 9-HODE[90].

Thus, lipid metabolites derived from fatty acids are involved in the development of NAFLD, which is an interesting topic for further research (Figure 2).

Hepatocellular accumulation of lipids can modulate the biological activity of Kupffer cells through a number of mechanisms. On the one hand, fat-saturated hepatocyte swelling changes the architecture of the sinusoidal network, reducing intrasinusoidal volume and microvascular blood flow. Disruption of microvascular blood flow also contributes to the involvement of sinusoidal endothelial cells, Kupffer cells, stellate cells and involvement of inflammatory cells and platelets[91]. Later developing fibrosing steatohepatitis with capillarization of the sinusoids, increases narrowing and distortion of the sinusoidal lumen, further limiting microvascular blood flow. In addition, leukocytes entering the narrowed sinusoids may adhere to the endothelium as a result of activation of the hepatic microvascular inflammatory response[91]. On the other hand, fat overload of hepatocytes causes lipotoxicity and the release of damage-associated molecular patterns (DAMPs), which can activate Kupffer cells and hepatic stellate cells (HSCs), promoting inflammation and fibrosis[92]. Lipid accumulation in hepatocytes has been shown to induce the release of factors that accelerate the activation and proliferation of HSCs and increase their resistance to apoptosis[93]. Conditioned medium from steatotic hepatocytes induced expression of the profibrogenic genes transforming growth factor (TGF)-beta, tissue inhibitor of metalloproteinase-1 (TIMP-1), TIMP-2 and matrix metalloproteinase-2, and expression of the NF-κB-dependent monocyte chemotactic protein-1 (MCP-1) in HSCs[93]. Thus, quiescent HSCs participate in the maintenance of liver architecture by maintaining the balance of extracellular matrix, while disruption of this balance, for example, due to metabolic disorders, leads to HSCs activation and fibrosis[94,95].

Hepatocytes exposed to apoptosis form apoptotic bodies, which are phagocytosed by HSCs and Kupffer cells, triggering a profibrogenic response due to transdifferentiation of HSCs into collagen-producing myofibroblasts[96]. Apoptotic cell uptake has been shown to stimulate Kupffer cell production of death ligands, including Fas ligand and TNF-alpha, which promotes inflammation and fibrogenesis[97].

An important pathogenetic mechanism involved in the pathogenesis of NAFLD is the role of the intestinal microbiota and a defect in the intestinal barrier caused by liver damage. Impaired gut barrier function is thought to accelerate translocation of enteric LPS, which activates proinflammatory signaling pathways and the release of related inflammatory factors in the liver[98]. Intestinal bacterial microflora and TLR4 have been shown to be involved in liver fibrogenesis[99]. *Escherichia coli* LPS can enhance liver damage in NAFLD by inducing macrophage and platelet activation through the TLR4 pathway [100]. Plasma endotoxin levels and inflammatory markers have been shown to be significantly higher in NAFLD compared with controls and to increase with the severity of hepatic steatosis[101]. Proinflam-

matory activity and immune imbalance associated with the pathophysiology of NAFLD may be related to gut dysbiosis[102]. For example, decreased Bacteroidetes and increased Firmicutes were observed in obese individuals[102]. Changes in gut microflora ratios may also increase endogenous ethanol production, which generally increases gut permeability, and contributes to translocation of endotoxins from the gut lumen into the portal bloodstream[102,103].

Another immunometabolic link between the gut microbiota and NAFLD, related to short-chain fatty acids (SCFAs), should also be noted[104,105]. SCFAs are formed by the gut microbiota during the fermentation of non-digestible fibers such as resistant starch, cellulose, and pectin[106]. SCFAs are used by colonic mucosal epithelial cells as an energy substrate, are involved in the regulation of a number of processes in the intestinal wall or enter the portal bloodstream, and may be involved in the formation of immunometabolic connections with other organs[107].

A growing body of evidence strengthens the understanding of the importance of SCFAs in inflammation. SCFAs act *via* receptors associated with the G-protein GPR43 and GPR41, also known as free fatty acid receptor (FFA)2 and FFA3, respectively[108-111]. In addition, SCFAs realize their action through inhibition of histone deacetylase (HDAC)[112,113].

Butyrate is well known for its anti-inflammatory properties and is of great clinical interest[107,114,115]. Through HDAC3 inhibition, butyrate can induce a metabolic switch of macrophages toward an anti-inflammatory M2 phenotype[112,113].

SCFAs are also known to affect the differentiation, recruitment and activation of neutrophils, DCs, macrophages and monocytes as well as T cells[116,117]. Butyrate is involved in the regulation of DC differentiation derived from human monocytes, keeping DCs in the immature stage[118].

In addition to their involvement in inflammation, SCFAs regulate lipid metabolism in the liver. Butyrate levels have been shown to decrease in NAFLD patients and mice with decreased estrogen levels, with butyrate administration attenuating liver steatosis[119]. Studies in rats fed a high-fat diet (HFD) have shown that butyrate increases β-oxidation of fatty acids, inhibits lipid synthesis and suppresses nuclear factor-kappa B and inflammation[120,121]. The addition of sodium butyrate protects mice from developing NASH. It is important to note that the metabolic role of SCFAs in liver function is rather complex[122]. In addition to attenuating hepatic steatosis, acetate, another SCFA derived from the microbiota, may conversely promote hepatic lipogenesis after excessive fructose intake[123,124].

A growing body of evidence strengthens the understanding that lipoproteins are part of an important transport mechanism that is utilized by the innate immune system. The mechanism of LPS elimination involves LPS disaggregation and binding to circulating lipoproteins, uptake of lipoprotein-associated LPS by the liver, and excretion of LPS with the bile[125,126]. This pathway, known as reverse LPS transport, involves lipoproteins as the main carriers of LPS in the plasma and includes the proteins LBP, BPI, phospholipid-transfer protein (PLTP), and cholesteryl ester transfer protein (CETP), which belong to the lipid transfer/LPS binding gene family (LT/LBP) and play different roles in LPS metabolism [126]. In addition, reverse cholesterol transport is at the beginning of the cross-talk between cholesterol metabolism and the innate immune system[126]. ABCA1, a key participant in reverse cholesterol transport also contributes to the efflux of LPS from macrophages[127]. HDL and other plasma lipoproteins have been shown to contribute to the release of LPS from the cell surface of monocytes[128].

Lipid transfer proteins (lecithin-cholesterol acyltransferase (LCAT), CETP, and PLTP) as well as hepatic and endothelial lipases remodel HDL in the bloodstream. CETP is part of a family of proteins including LPS-binding protein (LBP) and bactericidal permeability increasing protein (BPI) and may participate in the transport of LPS between lipoproteins for further utilization in the liver. CETP transports cholesterol esters from HDL to apoB-containing LDL and very low density lipoproteins (VLDLs).

Kupffer cells take up most of the LPS and can inactivate it by deacylation with acyloxyacyl hydrolase. Kupffer cells express high levels of class A scavenger receptors (SR-A), which bind oxidized low-density lipoproteins (LDL) and are also involved in LPS uptake[64,129]. SR-A expression is increased by oxidized LDL[130,131]. Importantly, in the liver, SR-A is also important for cell adhesion, suggesting a role for SR-A in the recruitment and retention of cells in various organs or in sites of pathological conditions, such as foci of inflammation or areas of atherosclerotic lesions[64]. In addition to Kupffer cells, SR-A types I and II are expressed in the liver on endothelial cells, which are less able to bind LPS [132].

Interestingly, plasma CETP predominantly originates from Kupffer cells, and plasma CETP levels predict the content of Kupffer cells in the liver in humans[133]. In addition, activation of Kupffer cells by LPS strongly decreases CETP expression[134]. LPS has been shown to activate resting Kupffer cells, resulting in decreased hepatic CETP expression and decreased CETP in plasma and increased HDL cholesterol levels[135]. Importantly, CETP inhibition improves HDL function but leads to liver obesity and insulin resistance in CETP-expressing transgenic mice on a HFD[136]. Information obtained in recent years has improved the understanding of the role of CETP in inflammation. Experimental evidence suggests that CETP in macrophages as well as in the liver prevents LPS interaction with TLR4, thereby reducing the inflammatory response[137]. Compared with wild-type mice, CETP mice showed a higher survival rate after polymicrobial sepsis. CETP mice had lower plasma IL-6 concentrations and decreased levels of hepatic TLR4 and acyloxyacyl hydrolase protein[137]. Species-specific differences in CETP expression should be noted[138]. In mice and rats, in contrast to humans, as well as primates,

rabbits, and hamsters, CETP is absent in plasma. Consequently, wild-type mice, have naturally low LDL and high HDL levels, in which up to 90% of cholesterol is transported and have low susceptibility to developing atherosclerosis. Transgenic mice expressing human CETP have increased reverse cholesterol transport, which is associated with increased clearance of apoB lipoproteins in the liver. They also show increased postprandial triglyceridemia, increased liver uptake of LPS, and increased survival in endotoxemia[139,140]. Transgenic expression of CETP in mice also reduces liver fat accumulation and improves insulin sensitivity in diet-induced obesity[141,142]. CETP has been shown to reduce liver TAG content in female mice through enhanced β-oxidation and to promote the synthesis and assembly of VLDL[142]. CETP inhibition in transgenic CETP-expressing mice disrupted TAG metabolic pathways, leading to liver TG accumulation and insulin resistance in diet-induced obese mice[136]. In addition, CETP inhibition by anacetrapib increased systemic and hepatic inflammation to a greater extent in obese mice[136].

Despite its weaker ability to bind LPS compared to LBP or BPI, CETP is associated with resistance to sepsis. Experiments with human CETP transgenic mice showed lower mortality after LPS administration compared to wild-type mice. The pathway involving CETP is of interest because it represents a cross-talk mechanism of reverse cholesterol transport and the innate immune system, in which LPS and cholesterol share common transport and utilization pathways[140].

Neutrophils, other important participants in the innate immune system, are also involved in the pathogenesis of NAFLD[143]. Given that inflammation is a key event that contributes to the progression of fatty liver dystrophy to NAFLD, these patients show significant neutrophil infiltration into the liver, often accompanied by increased expression of chemokines that promote neutrophil chemotaxis[144].

Neutrophils exhibit cross-links with HSCs. On the one hand, neutrophils activate HSCs through the production of ROS[145-147]. On the other hand, activated HSCs have been shown to support neutrophil survival by producing granulocyte-macrophage colony-stimulating factor and IL-15. This may serve as a positive direct loop contributor to liver damage and fibrosis under a HFD[147].

Interestingly, it has been shown that neutrophils in blood in patients with NASH had increased expression of receptors reflecting the preparation of neutrophils to migrate into tissue. In addition to preparation for migration, blood neutrophils in NASH were also functionally activated[148]. They were characterized by increased IL-8 production and had more than double the spontaneous oxidative burst. In analyzing these data, it was noted that neutrophils can not only move from the vascular lumen into extravascular tissues but can also move back into the bloodstream, through a process known as reverse transendothelial migration. Reverse transendothelial migration is of interest due to its possible interaction with the immune system[149]. However, its possible role in NAFLD has yet to be studied.

Thus, neutrophils play an important role in the development of inflammation and liver fibrosis[150]. On the other hand, neutrophils contribute to the spontaneous resolution of inflammation and liver fibrosis. Acting *via* miR-223, neutrophils act as resolving effector cells that induce the transition of proinflammatory macrophages to a restorative phenotype by suppressing NLRP3 inflammasome expression[151]. Another study in a diet-induced NASH mouse model also showed a phase-dependent contrasting role of neutrophils as triggers and pro-resolutive mediators of liver injury and fibrosis[150]. In addition to these findings, miR-223 was shown to be elevated in hepatocytes from HFD-treated mice and patients with NASH, which may be due to the fact that miR-223 can be transferred from neutrophils *via* the exosome. Moreover, miR-223 in hepatocytes acts as an anti-inflammatory molecule, directly affecting several inflammatory genes[152].

Thus, neutrophils play a complex multifaceted role in the pathogenesis of NAFLD, which is a promising topic for further research.

Liver DCs are a heterogeneous population of hepatic sinusoidal antigen-presenting cells[153,154]. DCs exist in mature or immature states and undergo maturation when exposed to immune or inflammatory signals such as microbial products and proinflammatory cytokines. DCs are involved in maintaining immune homeostasis and liver tolerance by promoting CD8+ T-cell elimination, as well as secreting anti-inflammatory cytokines that maintain the quiescent HSC state and promote TLR4 refractoriness to LPS. In addition, DCs regulate the number and activity of cells involved in the development of fibrosis and may play a role in the regression of liver fibrosis[155]. Dendritic cells can contribute to liver fibrosis regression by activating metalloproteinases and contribute to the homeostasis of NK cells, which are mainly antifibrogenic[154].

Natural killer cells are a heterogeneous multifunctional population of lymphoid cells located inside the sinusoidal space, where they can attach to endothelium and Kupffer cells[156]. A key factor determining the activity of these cells in NASH is their metabolic reprogramming.

Liver NK cells are part of the innate immune system and may play an important role in NAFLD. However, the regulation and function of NK cells in NAFLD remains controversial due to their different involvement at different stages of the disease. On the one hand, NK cells are active and may be useful in the early stages of fibrosis, when they contribute to TRAIL-mediated HSC death. On the other hand, NK cell involvement becomes detrimental when they lose their antitumor capacity, which may contribute to disease progression in later stages[156]. Indeed, metabolic reprogramming of NK cells in obesity limits the antitumor response, which is known as "metabolic paralysis"[157]. Overload of NK cells with lipids absorbed from the environment in obesity leads to metabolic defects that cause inhibition of the cytotoxic mechanism, resulting in loss of antitumor functions[157]. Overall, the available data suggest a

possible therapeutic potential for the regulation of NK cell function, which is a promising topic for further research.

ROLE OF RECEPTORS IN THE INNATE IMMUNE SYSTEM

The innate immune system relies on a large number of pattern recognition receptors (PRRs) to recognize both DAMPs and pathogen-associated molecular patterns. Toll-like receptors (TLRs) are the most well characterized representatives of PRRs. They are expressed in a variety of liver cells, including Kupffer cells, HSCs, hepatocytes, sinusoidal endothelial cells, and biliary epithelial cells[158-160]. A growing body of evidence reinforces the importance of TLRs in the pathogenesis of NAFLD[161]. TLR4 is of particular interest in connection with liver inflammation and fibrogenesis[158,162,163]. TLR4 is a receptor that detects the LPS of Gram-negative bacteria and is widely known for its role in various diseases.

TLR4 is expressed on all types of liver cells, including Kupffer cells, HSCs, and hepatocytes. Under normal conditions, hepatic cells express minimal TLRs, indicating a high tolerance of the liver to TLR ligands[164]. At the same time, receptor expression in the liver is associated with inflammation and fibrosis[164]. TLR4 plays a central role in Kupffer cell activation by responding to LPS. LPS is considered a potent inducer of hepatic inflammation. It promotes the production of TNF-α in Kupffer cells, which is a mediator of inflammation in the pathogenesis of NAFLD[165]. In addition, LPS can activate HSCs, and Kupffer cells can enhance this process by producing TGF-β and making HSCs more sensitive to TGF-β[164]. Despite the fact that Kupffer cells are the main targets for LPS in the liver, it is HSCs that contribute to TLR4-dependent fibrosis[99]. In addition, modulation of TGF-β signaling along the TLR4-MyD88-NF-κB axis provides a link between proinflammatory and profibrogenic signals[99]. Numerous data support the involvement of HSCs as central mediators of hepatic fibrosis. Activation of TLR4 in quiescent HSCs enhances chemokine secretion and induces Kupffer cell chemotaxis and inhibits the TGF-β pseudoreceptor Bambi, which increases HSCs sensitivity to signals induced by TGF-β and enables unrestricted activation by Kupffer cells[99]. A significantly reduced expression of the Bambi gene in HSCs was seen when incubated with the TLR4 LPS ligand[166].

It was found that a diet high in cholesterol leads to the accumulation of free cholesterol in HSCs, which promotes TLR4 signaling by increasing TLR4 levels in the membrane and can suppress Bambi gene expression. As a consequence, TGF-β signaling in HSCs was enhanced, leading to HSCs activation and progression of liver fibrosis[166].

ENDOTHELIAL CELL INVOLVEMENT IN THE IMMUNE SYSTEM IN THE LIVER

Endothelial cells, which form the inner membrane of blood vessels, play an important role in the functioning of the barrier between blood and tissues. Endothelium is characterized by heterogeneity and plasticity due to phenotypic specialization of different tissue types. This endothelial specialization can provide dense connections necessary for functioning of histo-tissue barriers, or on the contrary can promote infiltration and extravasation of molecules and particles circulating in the bloodstream due to fenestrated endothelium in the liver and kidneys[167]. Given that the liver is a highly vascularized organ (accounting for 20% of cardiac output), hepatic sinusoidal endothelial cells constitute a significant proportion of the total number of liver cells[168]. Liver sinusoidal endothelial cells (LSECs) have a unique morphological phenotype characterized by a combination of numerous fenestrae and lack of a basement membrane, which provides open access for dissolved substances between the sinusoidal blood and the Disse space (Figure 2). LSECs are involved in regulation of the liver microenvironment and act as the liver's first protective barrier. An important functional phenotypic feature of hepatic sinusoidal endothelial cells is their high endocytic capacity[169]. These cells are capable of absorbing and removing soluble macromolecules from the portal venous blood in addition to Kupffer cells located on the lumen side of the endothelium[168].

Disruption of the LSECs phenotype is a critical step in the liver fibrosis process (Figure 2). Capillarization, in which there is a lack of fenestration of hepatic sinusoidal endothelial cells and formation of an organized basal membrane, precedes fibrosis and contributes to HSC activation[169]. Vascular endothelial growth factor (VEGF) produced by hepatocytes and HSCs has been shown to be a key regulator of the LSEC phenotype[169-173]. The maintenance of the fenestrated LSEC phenotype is provided by the action of VEGF through a nitric oxide (NO)-dependent and NO-independent pathway [169-171]. In this case, VEGF, which is produced by hepatocytes or stellate cells, promotes NO formation from LSECs *via* endothelial nitric oxide synthase (eNOS)[171].

A growing body of evidence supports the important role of the endothelium in vascular biology. Endothelial cells can detect changes in blood flow and are involved in the regulation of hemodynamics and inflammation through the production of several bioactive substances. Endothelial production of NO is the best known way to regulate vascular hemodynamics. Nitric oxide is an important signaling molecule that is at the crossroads between the regulation of vascular hemodynamics and innate

immunity[174]. Importantly, NO demonstrates active involvement in the regulation of inflammation in the vascular wall, which is important in the development of atherosclerosis. Endothelial NO actively regulates the innate immune response involved in atherogenesis by regulating macrophage and lymphocyte uptake and vessel wall migration *via* adhesion molecules[174].

Nitric oxide synthesis in the endothelium is carried out by a specific constitutive eNOS isoform. Mechanical stimulation of endothelial cells by blood flow triggers a complex chain of events involving numerous cellular mechanosensors and enzymes, leading to activation of eNOS[175]. eNOS is expressed in LSECs and produces small amounts of NO, which maintain intrahepatic sinusoidal vascular tone and hemodynamics in the liver. Another isoform of nitric oxide synthase, inducible NOS (iNOS) is expressed in various liver cells, including LSECs, hepatocytes, Kupffer cells, HSCs and other immune cells[176-178]. LPS induces iNOS expression and NO production and increases caveolin-1 and decreases eNOS phosphorylation[179].

It should be noted that while the NO produced by eNOS has a hepatoprotective effect by inhibiting inflammatory activation of Kupffer cells, the NO produced by iNOS, in contrast, promotes NAFLD [180]. iNOS produces significantly more NO than eNOS, which can have negative effects. This is due to the cytotoxicity of NO in high concentrations. In particular, peroxynitrite (ONOO-) can damage a wide range of cellular molecules[181]. Interestingly, peroxynitrite can affect cyclooxygenase (COX)-1 and COX-2 activity depending on the concentration[182,183]. It has been suggested that NO can interact directly with COX, for example *via* S-nitrosylation, causing an increase in its enzymatic activity[184, 185]. Thus, NO production has closely overlapping connections with innate immunity. These and other data suggested a role for COX enzymes as important endogenous receptor targets for NO functions [186]. COX-2-mediated inflammation is important for insulin resistance associated with obesity and fatty liver dystrophy. Daily aspirin intake was associated with less severe histologic signs of NAFLD and NASH and a reduced risk of fibrosis progression over time[187].

Importantly, eNOS activity is decreased in pathological conditions, whereas iNOS activity is increased. Decreased NO production in LSECs causes endothelial cell capillarization and HSCs activation. This leads to deposition of extracellular matrix, proliferation of HSCs, increased intrahepatic resistance and impaired sinusoidal blood flow[180].

Thus, the function of NO is related to the maintenance of liver cell function. NO derived from eNOS protects against liver disease, whereas NO derived from iNOS has a proinflammatory effect[180]. When mice were fed a HFD, a decrease in liver NO was shown to precede the onset of liver inflammation through the NF-κB pathway as well as impaired insulin signaling at the IRS-1 and phospho-Akt levels. Thus, an important physiological role of endothelial NO has been shown to limit obesity-associated inflammation and impaired insulin signaling in hepatocytes and Kupffer cells *via* the NO/cGMP-dependent protein kinase (PKG)/ vasodilator-stimulated phosphoprotein (VASP) pathway as part of a cross-talk mechanism with metabolic disturbances associated with obesity[168].

LSECs exhibit a proinflammatory phenotype during the progression of NAFLD to NASH. It is characterized by surface overexpression of adhesion molecules such as ICAM-1, VCAM-1, and VAP-1 (AOC3) and production of proinflammatory molecules such as TNF-α, IL-6, IL-1, and MCP1 (CCL2)[188,189]. Interestingly, LSECs and HSCs are involved in maintaining each other's differential phenotype. On the one hand, VEGF-A production by either HSCs or hepatocytes supports LSECs differentiation[170]; on the other hand, fenestrated LSECs prevent HSCs activation and promote the conversion of activated HSCs to a dormant state. However, LSECs lose this effect when they are undifferentiated or have a capillarized phenotype[171,190].

Thus, LSECs play an important role in liver immunology and the development of NAFLD. In contrast to hepatocytes, free fatty acids such as palmitic acid and oleic acid inhibit LPS-induced production of proinflammatory chemokines in LSECs and inhibit inflammatory cell recruitment. These findings suggest a potentially protective role for LSECs in the liver with excess free fatty acids, as in NAFLD [191].

A growing body of evidence suggests that the role of lipid metabolism in endothelial cell function is not only as a structural or energetic substrate, but also as a participant in cell mechanobiology. In doing so, lipids are at the intersection of chemo- and mechanobiological signaling pathways.

CONCLUSION

NAFLD is a widespread disease whose clinical and pathophysiological links are only beginning to be understood. TAG accumulation in hepatocytes in NAFLD results from a complex chain of events and is complicated in nature, involving many exogenous and endogenous factors. Obesity and impaired lipid metabolism are considered to be the key links in the development of NAFLD. Moreover, impaired fatty acid metabolism is one of the central events in the pathogenesis of NAFLD due to their involvement not only as an energy substrate or their structural function in cells, but also due to their connection with the innate immune system. Lipid metabolism has multiple cross-links with the innate immune system, and these links are important in the pathogenesis of NAFLD.

Analysis of the data allows us to emphasize the need for a better study of the multifaceted role of lipid metabolism and its disorders as a link in the complex chain of processes underlying the development of NAFLD.

The pathogenesis of NAFLD is an important target for further research, among which immunometabolic cross-linkages can be considered as one of the promising directions. Immunometabolic regulation of cells and intercellular connections at different stages of liver disease development can be a significant target for therapeutic intervention. In addition, the immune and metabolic axes that link the liver to other organs are also of research and clinical interest. There is a growing understanding that the gut microbiota is an important participant in immune and metabolic processes not only in the gut, but also in other organs. There is also interest in information on the cross-linkages of lipid-transport function and innate immunity, which have evolutionarily conservative roots and link a number of diseases that mutually influence their natural history.

In summary, NAFLD is a complex multifaceted disease whose keys are still unknown to clinicians and researchers, but a better understanding of metabolic and immune cross-linkages will improve patient diagnosis and treatment approaches.

FOOTNOTES

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