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Altered macrophage function and its impact on fatty liver disease

Disfunción de macrófagos y su impacto en la enfermedad del hígado graso

Luis José Pinto-García,* Nayelli Nájera,‡ José Javier Flores-Estrada,§ Fernando Javier Cáceres-Carranza¶

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* Internal Medicine Specialist. Comprehensive Cardiometabolic Research Laboratory. Instituto Politécnico Nacional. Mexico City, Mexico. ORCID: 0000-0003-2863-8412
‡ PhD. Comprehensive Cardiometabolic Research Laboratory. Instituto Politécnico Nacional. Mexico City, Mexico. ORCID: 0000-0002-6869-8762
§ PhD. Research division. Hospital Juárez de México. Mexico City, Mexico. ORCID: 0000-0002-7029-7036
¶ Physician. Asociación de Educación Médica Hondureña. Honduras. ORCID: 0000-0002-6824-2781

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ABSTRACT

Nonalcoholic Fatty Liver Disease (NAFLD) is a prevalent global disease, affecting at least a third of the world population and having an estimated prevalence that could be greater than 50% in Mexico. NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis, generally associated with metabolic disorders such as obesity, type 2 diabetes, and cardiovascular disease. Kupffer cells are specialized hepatic macrophages essential for liver health and immune regulation but become pathogenic in NAFLD and contribute to liver inflammation and fibrosis through cytokine secretion and signaling pathways such as the nuclear factor kappa light chain enhancer of activated B cells (NF-κB) and the Peroxisomes Proliferators Activated Receptors Gamma (PPAR-γ). Chronic macrophage activation in NAFLD is influenced by factors such as saturated fatty acids, leading to polarization of the M1 phenotype and promoting inflammation. Currently, there are no FDA-approved drugs specifically targeting macrophage dysfunction. However, several therapeutic approaches are under investigation that may indirectly influence macrophage activation and further polarization to suppress inflammation and prevent disease progression. Promising strategies include modifying this macrophage polarization and targeting specific signaling pathways. Targeting chemokines such as the chemokine ligand 16 (CXCL16) also can potentially reduce liver inflammation and steatohepatitis. Targeting hepatic macrophage activation offers a promising approach for mitigating NAFLD progression.

RESUMEN

La enfermedad del hígado graso no alcohólico (NAFLD, por sus siglas en inglés) es una enfermedad global prevalente, que afecta al menos a un tercio de la población mundial y tiene una prevalencia estimada que podría ser mayor al 50% en México. La NAFLD varía desde la esteatosis simple hasta la esteatohepatitis no alcohólica (NASH, por sus siglas en inglés), fibrosis y cirrosis, generalmente asociadas con trastornos metabólicos como obesidad, diabetes tipo 2 y enfermedad cardiovascular. Los macrófagos juegan un papel crítico en la NAFLD, contribuyendo a la inflamación, fibrosis y progresión de la enfermedad. Las células de Kupffer, macrófagos hepáticos especializados, son esenciales para la salud del hígado y la regulación inmunológica, pero se vuelven disfuncionales en la NAFLD. Exhiben un comportamiento dinámico, responden a diversos estímulos y contribuyen a la inflamación y fibrosis del hígado a través de la secreción de citocinas y vías de señalización como el factor nuclear potenciador de la cadena ligera kappa de las células B activadas (NF-κB) y el receptor gamma activado por el proliferador de peroxisomas (PPAR-γ). La activación crónica de los macrófagos en la NAFLD está influenciada por factores como los ácidos grasos saturados, lo que lleva a la polarización del fenotipo M1 y promueve la inflamación. Actualmente, no existen medicamentos aprobados por la FDA que se dirijan específicamente a la disfunción de los macrófagos. Sin embargo, se están investigando varios enfoques terapéuticos que pueden influir indirectamente en la activación de los macrófagos y una mayor polarización para suprimir la inflamación y prevenir la progresión de la enfermedad. Las estrategias prometedoras incluyen la modificación de esta polarización de los macrófagos y la focalización en vías de señalización específicas. La focalización de quimiocinas como la quimiocina ligando 16 (CXCL16) también puede reducir potencialmente la inflamación hepática y la esteatohepatitis. La focalización de la activación de los macrófagos hepáticos ofrece un enfoque prometedor para mitigar la progresión de la NAFLD.

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Abbreviations:

Ω-3 PUFA = Ω-3 Polyunsaturated Fatty Acids.
CVC = Cenicriviroc.
CXCL16 = Chemokines such as the Chemokine Ligand 16.
DAMPs = Danger-Associated Molecular Patterns.
FFAs = Free Fatty Acids.
GLP-1 RAs = Glucagon-Like Peptide-1 Receptor Agonists.
HSCs = Hematopoietic Stem Cells.
IFN-γ = Interferon-γ.
IL = Interleukin.
iNOS = Inducible Nitric Oxide Synthase.
LCM = Liver Capsular Macrophages.
LPS = Lipopolysaccharides.
M1 = Classically Activated Macrophages.
M2 = Alternatively Activated Macrophages.
MCP-1 = Monocyte Chemoattractant Protein-1.
M-CSF = Macrophage Colony-Stimulating Factor.
MoMFs = Monocyte-Derived Macrophages.
NAFLD = Nonalcoholic Fatty Liver Disease.
NASH = Nonalcoholic Steatohepatitis.
NF-Kb = Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells.
OCA = Obeticholic Acid.
oxLDL = Oxidized Low-Density Lipoproteins.
PAMPs = Pathogen-Associated Molecular Patterns.
PPAR-δ = Peroxisome Proliferator-Activated Receptor Delta.
PPAR-γ = Peroxisomes Proliferators Activated Receptors Gamma.
PRRs = Pattern Recognition Receptors.
ROS = Reactive Oxygen Species.
TGF-β = Transforming Growth Factor-beta.
TLRs = Toll-Like Receptors.
TNF-α = Tumor Necrosis Factor-α.

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is a prevalent condition globally, affecting almost a third of the population worldwide. It is recognized as the most common liver disease in Western countries. Mexico is a country prone to this condition due to its population having several risk factors; the estimated prevalence of the disease could surpass 50%.[1] NAFLD encompasses a spectrum of liver conditions, from simple steatosis to Non-Alcoholic Steatohepatitis (NASH), fibrosis, and cirrhosis.[2] The disease is associated with metabolic dysregulation and can progress to severe complications such as hepatic cirrhosis and hepatocellular carcinoma.[3]

The prevalence of NAFLD is rising globally, with estimates suggesting that around 25 to 30% of the world population is affected by the disease.[4] Lifestyle factors such as physical inactivity and poor dietary habits contribute to the increasing prevalence of NAFLD.[5] Furthermore, the disease is closely associated with other metabolic disorders like obesity, type 2 diabetes, and cardiovascular diseases,[6] which are, in turn, risk factors for NAFLD, including obesity, insulin resistance, dyslipidemia, and hypertension.[7]

In NAFLD, macrophages are involved in inflammation, fibrosis, and disease progression to more severe stages.[8] The disease is characterized by hepatic steatosis, where macrophages contribute to the inflammatory response within the liver, leading to the development of NASH and fibrosis.[2] Additionally, macrophages regulate metabolic homeostasis in NAFLD, highlighting their importance in the pathogenesis of the disease.[8]

PHYSIOLOGY AND NORMAL FUNCTION OF MACROPHAGES IN THE LIVER

The liver contains three main populations of macrophages: Kupffer cells, which make up 80-90% of the body's total macrophage population, and Liver Capsular Macrophages (LCM), recently identified on the outer surface of the liver.[7] Kupffer cells are the only resident population of macrophages in the liver and play a crucial role in defending against pathogens and resolving inflammation; they are long-lived, self-renewing, and do not typically require recruitment from the bloodstream. Kupffer cells are strategically located in the liver sinusoids, allowing them to monitor blood flow from the gastrointestinal tract. This unique positioning enables them to efficiently phagocytose (engulf) pathogens, dead cells, and debris that enter the liver. Besides their role in pathogen clearance, Kupffer cells are critical for maintaining tolerance to harmless substances absorbed from the gut and modulating immune responses. They help suppress excessive inflammation under normal conditions but can also become polarized to release pro-inflammatory cytokines when pathogens or liver damage are detected. Their ability to regulate inflammation is central

to preventing chronic liver injury. Meanwhile, LCM unlike Kupffer cells, which handle internal immune surveillance, LCMs are believed to serve as a first line of defense against infections that breach the liver capsule from the peritoneal cavity. The third non-resident population is called monocyte-derived macrophages (MoMFs), which migrate into the liver during injury, infection, or inflammation in response to signals like cytokines and chemokines released. Unlike long-lived and self-renewing Kupffer cells, monocyte-derived macrophages are recruited for temporary responses to acute conditions.[7]

Development and differentiation of macrophages in the liver

The origin of Kupffer cells has been a subject of scientific inquiry. Research indicates that Kupffer cells have a unique developmental pathway, distinct from Hematopoietic Stem Cells (HSCs). Studies suggest that Kupffer cells can be derived from yolk sac-specific progenitor cells,[9] which settle in the hepatic sinusoids and can persist in adult mice independently of HSCs.[10] However, the debate over the origin and cell kinetics of Kupffer cells continues, with some researchers arguing for a monocytic origin while others support the idea of self-replication.[11]

Kupffer cells exhibit a heterogeneous nature, with different subsets demonstrating distinct functional properties. Both Kupffer cells and macrophages of monocytic origin can express a wide range of cytokines. While monocytic macrophages are typically more associated with the production of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-18, Kupffer cells can also produce these cytokines under specific conditions. Conversely, both cell types have the potential to express anti-inflammatory cytokines, including IL-10, TGF-β, IL-4, and IL-13, depending on their activation state. The hepatic microenvironment plays a crucial role in shaping the development and function of these cells, particularly through the influence of the Macrophage Colony-Stimulating Factor (M-CSF), which supports their survival and proliferation.[12]

While Kupffer cells originate from the fetal yolk sac and are embryonically derived and self-renewing, liver LCM are derived from infiltrated bone marrow-derived monocytes/macrophages and are replenished from blood monocytes in the steady state.[13,14] These macrophages are identified as F4/80+ cells beneath the liver surface, distinct from F4/80+ monocytes, indicating a different cell type.[15]

MoMFs in the liver originate from bone marrow-derived Ly-6C high monocytes that are recruited into the liver in response to acute and chronic injuries. These monocytes are primarily attracted via the CCL2-CCR2 axis, where they differentiate into hepatic Ly-6C+[16] with either pro-inflammatory or anti-inflammatory functions based on the local environment.[17]

Kupffer cells have unique morphological features. They include vacuoles containing membrane-bound granules, increased lysosomes in the cytoplasm, crystal clefts and lipid droplets, and multiple cytoplasmic extensions. These features enable the cells to patrol the sinusoidal lumen effectively.[18,19] Additionally, they express a variety of surface receptors, including pattern recognition receptors such as Toll-Like Receptors (TLRs), scavenger receptors, and complement receptors. When activated, these cells exhibit specific histopathological changes such as karyomegaly and increased phagocytic activity.[20]

Role in liver homeostasis, metabolism, and interaction with other hepatic cells

Kupffer cells, as the only liver-resident macrophages, play a crucial role in maintaining liver homeostasis through their interactions with other hepatic cells, particularly hepatocytes. These interactions are essential for responding to various stimuli, such as sensing necrotic cells and inducing the production of chemokines like CXCL1 in hepatocytes. Additionally, Kupffer cells contribute to liver injury in conditions like endotoxemia, where their communication with hepatocytes is a key factor.[21,22]

Moreover, Kupffer cells are responsible for most of the phagocytic activity in the liver, as evidenced by the predominantly localization of nanoparticles in them.[23] They are also involved in lipid metabolism and have been implicated in modulating hepatocyte lipid metabolism, contributing to hepatic steatosis in response to high-fat diets. Kupffer cells can internalize

and degrade oxidized low-density lipoproteins (oxLDL), playing a role in both lipid homeostasis and the prevention of atherosclerosis.[24] Kupffer cells can also activate stellate cells through the secretion of Transforming Growth Factor-beta (TGF-β), leading to extracellular matrix deposition and fibrogenesis.[25]

Kupffer cells can be identified by the expression of CD68, prominently found on their surface and within their cytoplasm, as well as by the upregulation of CD14, particularly in response to lipopolysaccharide (LPS) exposure. Additionally, these cells exhibit heterogeneous surface expression of M1 and M2 markers, including iNOS and CD206, reflecting their functional diversity.[26-30]

ALTERATION OF MACROPHAGE FUNCTION IN FATTY LIVER DISEASE

NAFLD is a multifaceted disorder marked by the pathological accumulation of lipids within hepatocytes. This condition encompasses a spectrum that ranges from benign hepatic steatosis to more severe NASH, which poses significant risks for the development of liver fibrosis, cirrhosis, and HCC. The pathogenesis and progression of NAFLD are driven by a complex interplay of genetic predispositions, environmental influences, and metabolic dysregulation, reflecting the intricate nature of this disease.[31]

Insulin resistance and dysregulated lipid metabolism are closely linked and play central roles in the development of the disease. Insulin resistance causes an increase in the release of free fatty acids from adipose tissue into the bloodstream. The liver then takes up these FFAs, storing them as triglycerides or undergoing de novo lipogenesis, a process that is also promoted by insulin resistance. In a state of insulin resistance, the liver's ability to control lipid metabolism becomes impaired. Normally, insulin inhibits hepatic glucose production and encourages lipid oxidation, but in insulin-resistant conditions, this regulation is disrupted. This leads to an increase in lipogenic pathways, resulting in excessive triglyceride synthesis, while fatty acid oxidation is reduced due to concurrent mitochondrial dysfunction. This imbalance between lipid synthesis and disposal leads to hepatic steatosis, the main characteristic of NAFLD. Mitochondrial dysfunction also contributes to the generation of reactive Oxygen Species (ROS). In response to oxidative stress, Kupffer cells and recruited immune cells release pro-inflammatory cytokines, which perpetuate hepatic inflammation. This inflammatory environment leads to the activation of HSC, which is responsible for the deposition of extracellular matrix proteins and contributing to the development of fibrosis. The oxidative stress damages cellular components, including lipids, proteins, and DNA, which triggers hepatocellular injury and inflammation.[31-34]

It is observed that imbalanced gut bacteria also play a role in NAFLD by affecting the integrity of the intestinal barrier. Research has indicated that high-fat diets can reduce the expression of tight junction proteins like occludin, which are crucial for maintaining the integrity of the gut barrier. This disruption allows harmful substances such as lipopolysaccharides (LPS) to enter the bloodstream, leading to inflammation in the liver. The gut-liver axis is responsible for the transfer of microbial by-products, such as short-chain fatty acids, which can benefit liver metabolism. However, an imbalance in gut bacteria can impact the production of these beneficial by-products.[35-38]

The pathological changes result in macrophages remaining chronically activated, a state known as polarization, where they adopt specific functional states or phenotypes. Macrophages can polarize into two primary phenotypes: classically activated macrophages (M1), which are pro-inflammatory, and alternatively activated macrophages (M2), which are anti-inflammatory and promote tissue repair. M1 macrophages, induced by LPS and interferon-γ (IFN-γ), are renowned for their pro-inflammatory roles. They release significant amounts of pro-inflammatory cytokines, such as IL-1β, inducible nitric oxide synthase (iNOS), and Tumor Necrosis Factor-α (TNF-α). On the other hand, M2 macrophages, activated by interleukin (IL)-4 and IL-13, are recognized for their anti-inflammatory functions. These macrophages secrete anti-inflammatory factors, including IL-10, transforming growth factor-β (TGF-β), and arginase 1. Research has demonstrated

that saturated fatty acids polarize Kupffer cells/macrophages towards an M1-predominant phenotype, while Ω-3 polyunsaturated fatty acids (Ω-3 PUFA) polarize them towards an M2 phenotype. The polarization process consists of the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) signaling pathways; these pathways are favored by excessive consumption of high-energy diets, which contributes to fat accumulation in adipose tissue, which releases Free Fatty Acids (FFAs) and adipokines into the bloodstream. This results in elevated levels of circulating triglycerides and free fatty acids. High-energy diets can also cause gut leakage, leading to the translocation of bacterial products such as lipopolysaccharides (LPS) into the bloodstream. LPS are detected by pattern recognition receptors (PRRs) such as TLR4/NF-κB. This Activating of TLR4/NF-κB or specifically their adapter protein Myeloid Differentiation Primary Response Protein 88 (MyD88) signaling pathway by M1-polarized macrophages significantly diminishes expression of arginase 1, induces the production of pro-inflammatory cytokines and promotes lipid synthesis, and accumulation in hepatocytes, favoring hepatic steatosis. Furthermore, the pro-inflammatory signals (e.g., TNF-α, IL-1β, IL-6, TGF-β) from Kupffer cells activate hepatic stellate cells, which differentiate into myofibroblasts. Myofibroblasts are responsible for producing extracellular matrix components, leading to fibrosis in the liver. Persistent activation of these cells contributes to the progression of liver disease, ultimately leading to cirrhosis *(Figure 1)*. Additionally, the inhibition of

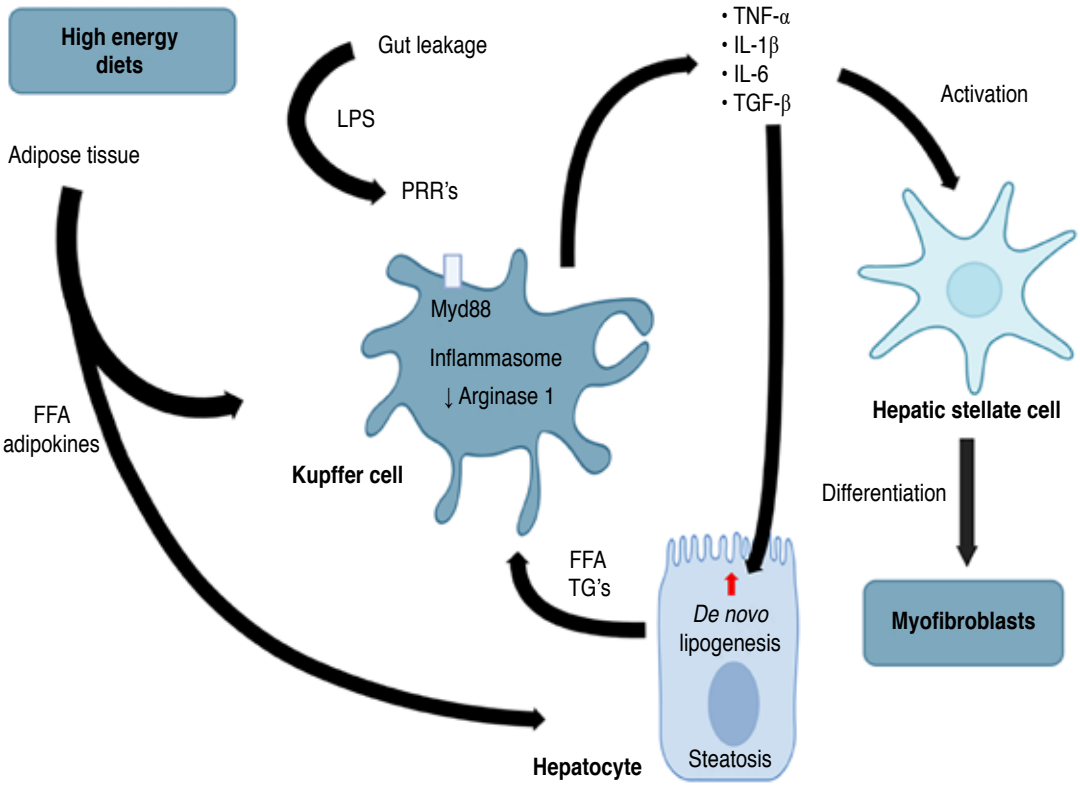

Figure 1: Altered macrophage dysfunction. Different stimuli, including Lipopolysaccharides and *de novo* lipogenesis, can classically activate macrophages (M1). Myd88 receptors, an adapter protein for the TLR/NF-κB-mediated inflammation in macrophages, finally generate pro-inflammatory cytokines, eventually favoring the activation of hepatic stellate cells and fibrosis, contributing to the progression of Nonalcoholic Fatty Liver Disease (NAFLD).
FFA = Free Fatty Acids. LPS = Lipopolysaccharides. PRR = Pattern Recognition Receptors. TG = Triglyceride.

hepatic macrophage apoptosis by Chitinase 3-like 1 can lead to macrophage accumulation and activation, exacerbating liver fibrosis. Interestingly, PPAR-γ upregulation can reverse M1 macrophage polarization and reduce the activity of TLR4/NF-κB, having anti-inflammatory and anti-fibrotic effects in NAFLD.[39-41]

The NLRP3 inflammasome is one of the most extensively studied inflammasomes, which are multiprotein complexes found within cells of the immune system. Under normal circumstances, inflammasomes detect harmful stimuli, such as Pathogen-Associated Molecular Patterns (PAMPs) from infections or Danger-Associated Molecular Patterns (DAMPs) from cell damage. Their activation facilitates the activation of the enzyme caspase-1 processes and activates pro-inflammatory cytokines like IL-1β and IL-18, which are then released to induce inflammation and help fight the infection or repair damaged tissue. However, chronic activation of NLRP3 in hepatic macrophages can lead to innate inflammatory responses and pyroptosis-regulated signaling pathways, which is required for the development of fibrosis in NAFLD.[42] Pharmacological inhibition of the NLRP3 inflammasome has emerged as a promising therapeutic strategy for various inflammatory diseases. Compounds such as MCC950 and CP-456,773 have demonstrated efficacy in suppressing NLRP3 activation, thereby reducing the production of pro-inflammatory cytokines like IL-1β and alleviating associated pathologies in animal models.[43] In another example, sulforaphane, a known NLRP3 inhibitor, has demonstrated protective effects against NAFLD in high-fat diet-induced mouse models by reducing hepatic inflammation and lipid accumulation.[44]

Additionally, the dysregulation of macrophage-hepatic stellate cell interactions targeting macrophage PPAR-γ can exacerbate NAFLD progression.[45,46]

CURRENT THERAPIES

Non-pharmacological therapies

Research has shown that exercise can significantly change the behavior of liver macrophages. It promotes a shift from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages in the liver. This shift enhances the M2 macrophage phenotype and inhibits M1 macrophages, thereby reducing chronic inflammation.[47] This is corroborated by findings from O-Gorman et al., who reported that aerobic exercise led to significant reductions in hepatic TNF-α levels and resident macrophage infiltration in a controlled trial.[48] Similarly, it was demonstrated that voluntary distance running in mice resulted in decreased levels of pro-inflammatory cytokines and changes in the intrahepatic immune environment, which are critical for mitigating liver injury.[49]

Resistance exercise has been demonstrated to reduce liver fat and its mediators independently of weight loss, indicating that the benefits of exercise go beyond mere caloric expenditure.[50] The underlying mechanisms through which exercise exerts its beneficial effects on liver macrophages include the enhancement of autophagy and the reduction of oxidative stress, thereby preventing the overactivation of the innate immune response in NAFLD.[51]

Extensive research has been conducted on the effects of caloric restriction on liver macrophages and their functions. One-way caloric restriction influences liver macrophages is by activating SIRT1, which is a protein deacetylase that regulates metabolic pathways. The activation of SIRT1 has been associated with inhibiting inflammatory pathways in macrophages, improving insulin sensitivity, and reducing the production of pro-inflammatory cytokines. Caloric restriction also triggers autophagy through SIRT1 and AMPK mediation, which are vital for maintaining macrophage function and longevity. For aged macrophages, the decline in autophagic activity is linked to dysfunctional lysosomes and increased inflammatory responses.[52-55]

Novel pharmacological therapies

As of the most recent updates, there are no FDA-approved drugs specifically targeting macrophage dysfunction. However, several therapeutic approaches are under investigation

that may indirectly influence macrophage function as part of broader strategies to treat NAFLD and NASH. One approach involves modifying macrophage polarization by restraining M1 activation or promoting M2 activation. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) engage the GLP-1 receptor, leading to a reduction in the population of pro-inflammatory monocytes in the liver. This modulation of macrophage polarization can help suppress inflammation and prevent the advancement of NAFLD.[56]

Peroxisome proliferator-activated receptor delta (PPAR-δ) can also be helpful in regulating the polarization of Kupffer cells towards the anti-inflammatory M2 phenotype by inhibiting the pro-inflammatory transcription factor NF-κB, which is crucial for M1 macrophage activation and promotes a shift towards M2-like phenotype. These agents also enhance liver histology in NASH.[57-59]

Cenicriviroc (CVC) or TAK-652 is a medication that works by targeting the C-C chemokine receptors CCR2 and CCR5. Its primary mechanism of action involves reducing inflammation and fibrosis in the liver by inhibiting the infiltration of monocytes and macrophages. CVC effectively blocks the migration of CCR2+ monocytes to the liver by disrupting the CCL2-CCR2 pathway.[16,60]

In addition, CVC has been shown to encourage a transition in macrophage polarization from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype. This modulation not only helps decrease inflammation but also assists in improving liver fibrosis, as indicated by enhancements in fibrosis scores in clinical trials.[61,62]

Obeticholic acid (OCA) is also a potential drug option. It is a semi-synthetic bile acid that acts as a potent agonist of the farnesoid X receptor, which is mainly found in the liver, intestine, and kidney. This receptor regulates bile acid homeostasis, lipid metabolism, and immune responses within the liver.[63-65] OCA treatment has been linked to a decrease in inflammatory cell infiltration in the liver, as evidenced by reduced levels of monocyte chemoattractant protein-1 (MCP-1) mRNA, which is essential for macrophage recruitment.[63,66] Furthermore, OCA has been reported to enhance gut barrier function and reduce bacterial translocation improving gut integrity and decreasing systemic exposure to bacterial products that can activate liver macrophages and exacerbate inflammation.[67]

Targeting specific signaling pathways has shown promise in regulating macrophage activation in NAFLD. For instance, the Rictor/Akt/FoxO1 signaling pathway has been identified as a critical player in activating proinflammatory macrophages and disease progression in NAFLD.[56] The heme oxygenase system has been suggested as a potential therapeutic target to modulate macrophage polarization towards the anti-inflammatory M2 phenotype.[68]

Recently, the chemokine CXCL16 has emerged as a significant player in the pathogenesis of NAFLD, particularly in its progression to NASH and liver fibrosis. CXCL16 is primarily known for its role in recruiting immune cells, particularly natural killer T cells, to the liver, where it contributes to inflammatory processes and liver injury.[69,70] Elevated CXCL16 levels in NAFLD patients suggest its role in disease progression and potential as a biomarker for liver inflammation. The upregulation of the CXCL16/CXCR6 axis in response to liver injury has been linked to increased macrophage infiltration and activation of hepatic stellate cells.[71-74]

The mechanism by which CXCL16 influences NAFLD involves its interaction with the CXCR6 receptor, which is expressed on various immune cells, including NKT cells. This interaction promotes the accumulation of these cells in the liver. Pharmacological inhibition of CXCL16 has been shown to reduce liver macrophage infiltration and ameliorate steatohepatitis in experimental models.[69,70]

In conclusion, modulating hepatic macrophage activation in NAFLD is a promising area of research. Various therapeutic avenues are being explored to target macrophage polarization, signaling pathways, and specific molecules to mitigate inflammation and disease progression in NAFLD.

Authors' point of view

We emphasize the critical role that macrophages, especially Kupffer cells, play in the development

and progression of NAFLD. We believe it is essential to understand how macrophages contribute to hepatic inflammation, fibrosis, and metabolic dysregulation. The connection between steatosis, insulin resistance, and the polarization of macrophages towards pro-inflammatory phenotypes (M1) is a key factor in the worsening of this disease. We also explore the potential of targeting macrophage polarization and signaling pathways as therapeutic strategies for NAFLD. Our analysis highlights how interventions like exercise, caloric restriction, and new pharmacological agents hold promise in modulating macrophage activity and improving liver histology. Through this discussion, we advocate for continued research into the modulation of hepatic macrophages to alleviate the impact of NAFLD, particularly in populations with high prevalence rates and significant risk factors.

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Correspondence:
Luis José Pinto-García
E-mail: luisjosepinto@outlook.com