

Kupffer Cell Activation and Inflammatory Progression in MASLD

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Abstract

Metabolic dysfunction-associated steatotic liver disease, or MASLD, is not only a disorder of hepatic fat accumulation, but also a disease shaped by metabolic stress and immune activation. Among the immune cells involved in this process, Kupffer cells play a central role because they are liver-resident macrophages located at the interface between hepatocytes, gut-derived signals, and systemic metabolic inflammation. Under normal conditions, Kupffer cells help maintain liver homeostasis by clearing pathogens, removing cellular debris, and regulating immune tolerance. In MASLD, however, persistent lipid overload, hepatocyte injury, oxidative stress, endotoxin exposure, and adipose tissue inflammation can shift Kupffer cells toward chronic inflammatory activation. Activated Kupffer cells release cytokines and chemokines such as TNF- α , IL-1 β , IL-6, and CCL2, which worsen hepatocyte stress, recruit additional immune cells, and support the transition from simple steatosis to metabolic dysfunction-associated steatohepatitis. Their interaction with hepatic stellate cells also connects inflammation with fibrosis development. This essay discusses Kupffer cell activation as a key mechanism in MASLD progression and argues that the disease should be understood as a dynamic process involving metabolic overload, immune response, failed inflammatory resolution, and fibrotic remodeling. Recognizing the dual role of Kupffer cells may help explain why MASLD progression cannot be reduced to fat accumulation alone.

Keywords: MASLD, Kupffer cells, liver inflammation, MASH, macrophages, lipotoxicity, fibrosis, gut-liver axis

1. Introduction

Metabolic dysfunction-associated steatotic liver disease, or MASLD, has become one of the most common chronic liver disorders in modern society. Its development is closely related to obesity, insulin resistance, type 2 diabetes, dyslipidemia, and other metabolic abnormalities. In the past, this condition was often discussed mainly as a problem of fat accumulation in the liver. Such an understanding is useful, but it is

not enough. In many patients, hepatic steatosis does not remain a simple storage problem. Excess lipid deposition can disturb hepatocyte function, increase cellular stress, and gradually trigger inflammatory responses inside the liver. Once inflammation becomes persistent, MASLD may progress toward metabolic dysfunction-associated steatohepatitis, fibrosis, cirrhosis, and even liver-related complications.

The progression of MASLD depends on several

connected mechanisms. Hepatocytes exposed to excessive fatty acids may develop mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, and lipotoxic injury. Injured hepatocytes then release danger signals that activate immune cells in the liver. At the same time, changes in gut microbiota and increased intestinal permeability may allow bacterial products to reach the liver through the portal circulation. These signals do not act separately. They meet in the hepatic microenvironment and form a continuous inflammatory stimulus. For this reason, MASLD should be understood not only as a metabolic disease, but also as an inflammatory disease shaped by interactions between liver cells, immune cells, gut-derived factors, and systemic metabolic stress.

Kupffer cells are especially important in this process. As the resident macrophages of the liver, they are located in the hepatic sinusoids and are among the first immune cells to respond to metabolic and microbial signals entering the liver. Under normal conditions, Kupffer cells help clear pathogens, remove cellular debris, and maintain immune balance. Their function is protective and necessary for liver homeostasis. In MASLD, however, the liver is repeatedly exposed to lipid overload, hepatocyte damage, endotoxins, and inflammatory mediators from adipose tissue. These persistent stimuli can shift Kupffer cells from a homeostatic state toward a more activated and pro-inflammatory phenotype.

Once activated, Kupffer cells produce cytokines and chemokines such as TNF- α , IL-1 β , IL-6, and CCL2. These mediators can worsen hepatocyte injury, recruit circulating monocytes and other inflammatory cells, and promote communication with hepatic stellate cells. Through these effects, Kupffer cells do not merely respond to liver injury. They also help amplify and maintain the inflammatory environment that drives disease progression. This makes them a key link between metabolic stress and inflammatory damage in MASLD.

2. MASLD as a Metabolic and Inflammatory Liver Disease

MASLD is often described as a liver disease caused by abnormal fat accumulation, but this description only shows the early surface of the disease. In many patients, fat deposition in the liver is connected with obesity, insulin resistance, type 2 diabetes, dyslipidemia, and other

metabolic disorders. These conditions change the way the liver receives, stores, and processes lipids. When the amount of fatty acids entering the liver is greater than the liver's ability to use or export them, triglycerides and other lipid products begin to accumulate in hepatocytes. At this stage, MASLD may appear mainly as hepatic steatosis. The liver contains too much fat, but severe inflammation may not yet be present.

The problem becomes more serious when lipid accumulation begins to disturb normal hepatocyte function. Not all lipid storage is equally harmful. Triglyceride storage can sometimes be seen as a protective way to reduce free fatty acid toxicity. The more damaging process comes from lipotoxicity, which refers to injury caused by toxic lipid species, saturated fatty acids, free cholesterol, and related metabolic stress. These substances can impair mitochondrial function, increase oxidative stress, and disturb endoplasmic reticulum activity. As hepatocytes struggle to manage this stress, their normal metabolic and synthetic functions become weakened. The liver then moves from simple fat storage toward a state of cellular injury.

Insulin resistance is central to this process. When insulin signaling becomes less effective, adipose tissue releases more free fatty acids into the circulation. The liver then receives more lipid substrate and is pushed to produce more triglycerides. Insulin resistance can also increase hepatic glucose production and worsen systemic metabolic imbalance. This means MASLD is not only a local liver condition. It is closely tied to whole-body metabolic dysfunction. The liver becomes both a target and a participant in this disturbed metabolic state.

Oxidative stress further links metabolism with inflammation. Excess lipid metabolism increases the burden on mitochondria. When mitochondrial function is impaired, reactive oxygen species may increase. These reactive molecules damage proteins, lipids, and DNA inside hepatocytes. Oxidative injury also promotes the release of danger signals from damaged cells. These signals are recognized by immune cells in the liver, especially Kupffer cells. In this way, hepatocyte stress does not remain a purely metabolic event. It becomes an immune signal that tells the liver there is tissue damage.

Inflammation is therefore not a secondary or accidental feature of MASLD. It is one of the main

processes that drives disease progression. When hepatocytes are injured, they release damage-associated molecular patterns and inflammatory mediators. These signals activate Kupffer cells and other immune cells. Activated immune cells then produce cytokines and chemokines that intensify local inflammation. This inflammatory environment can cause further hepatocyte injury, attract more immune cells, and create a cycle of damage and response. MASLD may then progress from simple steatosis to MASH, a stage marked by steatosis, inflammation, and hepatocyte injury.

The inflammatory nature of MASLD also explains why some patients develop fibrosis. Persistent inflammation stimulates hepatic stellate cells and changes the structure of liver tissue. Repeated injury and repair lead to extracellular matrix deposition. Over time, this process can produce fibrosis and increase the risk of cirrhosis and other liver-related complications. MASLD should therefore be understood as a disease shaped by both metabolic overload and immune activation. Fat accumulation begins the process, but inflammatory progression determines much of the later damage.

For this reason, Kupffer cells become especially important in the study of MASLD. They are located at the point where metabolic injury, gut-derived signals, and immune responses meet. In early steatosis, hepatocyte lipid accumulation may be the most visible feature. As the disease progresses, Kupffer cell activation helps turn metabolic stress into sustained inflammation. This shift from fat storage to inflammatory injury is central to understanding why MASLD can move from a relatively silent condition to a progressive liver disease.

3. The Biological Role of Kupffer Cells in the Liver

Kupffer cells are the resident macrophages of the liver. They are mainly located in the hepatic sinusoids, where they stay in close contact with blood flowing from the portal vein and hepatic artery. This position gives them a special role in liver immunity. Unlike many immune cells that enter tissues only after inflammation begins, Kupffer cells are already present in the liver under normal conditions. They act as a first line of immune surveillance and help the liver respond quickly to foreign substances, damaged cells, and metabolic changes.

The liver receives a large amount of blood from

the intestine through the portal circulation. This blood contains nutrients, bacterial products, food-derived molecules, and other substances absorbed from the gut. The liver must process these materials without producing excessive immune reactions all the time. Kupffer cells help maintain this balance. They can recognize and remove harmful pathogens, but they also help prevent unnecessary inflammation against harmless gut-derived molecules. This makes them important not only for immune defense, but also for immune tolerance.

One of the basic functions of Kupffer cells is phagocytosis. They clear bacteria, cell fragments, aged blood cells, and other particles from the circulation. This function protects the liver and the whole body from harmful materials entering through the gut. Kupffer cells also remove dead or damaged hepatocytes and help clean the local tissue environment. Without this clearance function, cellular debris would accumulate and become another source of inflammation. In this sense, Kupffer cells are not naturally harmful. Their normal work supports liver homeostasis.

Kupffer cells also communicate with other liver cells. They interact with hepatocytes, liver sinusoidal endothelial cells, hepatic stellate cells, and recruited immune cells. Through cytokines, chemokines, and direct cell contact, they help regulate the immune tone of the liver. Under healthy conditions, this communication is controlled and balanced. It allows the liver to defend itself when needed, while still preserving normal metabolic and synthetic functions.

Their role becomes more complex in MASLD. In the early stage, Kupffer cells may try to clear lipid debris, damaged cell components, and stress signals released by hepatocytes. This response can be protective at first. It helps limit damage and maintain tissue order. The problem appears when metabolic stress continues for a long time. Excess fatty acids, oxidative stress, gut-derived endotoxins, and inflammatory mediators repeatedly stimulate Kupffer cells. Their original protective response may then shift into a chronic inflammatory response.

This shift is important for understanding MASLD progression. Kupffer cells do not simply become harmful because they are activated once. Activation is a normal part of their immune function. The real issue is persistent activation under abnormal metabolic conditions. When stimulation does not stop, Kupffer cells may

continue to release inflammatory cytokines and chemokines. These mediators can damage hepatocytes, attract more immune cells, and strengthen local inflammation. The same cells that normally protect the liver can therefore become contributors to disease progression.

Kupffer cells should be understood as regulatory cells with a dual nature. They help preserve liver homeostasis in normal conditions, but they can also drive inflammation when the liver is exposed to long-term metabolic injury. This dual role is central to MASLD. It explains why Kupffer cells are not only passive responders to hepatocyte damage. They are active participants in deciding whether liver injury is resolved or whether it develops into persistent inflammation.

4. Triggers of Kupffer Cell Activation in MASLD

Kupffer cell activation in MASLD does not come from a single cause. It is usually the result of several forms of stress acting together in the liver. Lipid overload, hepatocyte injury, gut-derived bacterial products, insulin resistance, and adipose tissue inflammation all contribute to this process. These factors do not work in a simple order. They often appear at the same time and reinforce each other. This is why Kupffer cells in MASLD are exposed to continuous stimulation rather than a short and limited immune signal.

Lipotoxicity is one of the most important triggers. In MASLD, the liver receives an excessive amount of free fatty acids from the circulation. Some of these lipids can be stored as triglycerides, but this storage capacity is limited. When toxic lipid species, saturated fatty acids, and free cholesterol increase inside hepatocytes, they begin to disturb normal cell function. Hepatocytes may develop mitochondrial stress, oxidative injury, and endoplasmic reticulum stress. These changes weaken cellular metabolism and make hepatocytes more vulnerable to injury or death.

Damaged hepatocytes release danger signals into the surrounding liver tissue. These signals are often described as damage-associated molecular patterns. They include cellular fragments, mitochondrial components, nucleic acids, ATP, and other stress-related molecules. Kupffer cells can recognize these signals through pattern-recognition receptors. Once these receptors are activated, Kupffer cells begin to produce inflammatory mediators. In this way, hepatocyte lipotoxicity is translated into immune activation.

The original problem starts with abnormal lipid metabolism, but it soon becomes an inflammatory process.

Gut-derived endotoxins are another major source of Kupffer cell activation. The liver is directly connected to the intestine through the portal circulation. Under normal conditions, the intestinal barrier limits the movement of harmful bacterial products into the blood. In MASLD, gut microbiota changes and intestinal barrier dysfunction may increase the passage of bacterial products into the portal vein. Lipopolysaccharide is especially important in this process. When it reaches the liver, it can be detected by Kupffer cells through receptors such as Toll-like receptor 4.

This gut-liver connection helps explain why MASLD is not only a liver-localized disease. The liver constantly receives signals from the intestine, and Kupffer cells are among the first cells to respond to them. When endotoxin exposure is occasional and limited, Kupffer cell activation may help protect the body. When endotoxin exposure becomes repeated, the same response may turn into chronic inflammation. Toll-like receptor signaling can activate inflammatory pathways such as NF- κ B, leading to the production of cytokines including TNF- α , IL-1 β , and IL-6. These cytokines then worsen hepatocyte stress and help maintain the inflammatory environment.

Systemic metabolic inflammation also contributes to Kupffer cell activation. Many patients with MASLD also have obesity and insulin resistance. In obesity, adipose tissue is not only a site of fat storage. It can become an active inflammatory organ. Enlarged adipocytes and adipose tissue macrophages release inflammatory mediators into the circulation. At the same time, insulin resistance increases the release of free fatty acids from adipose tissue. The liver therefore receives both more lipid substrate and more inflammatory signals.

This continuous input keeps Kupffer cells under pressure. They are not responding to one isolated episode of injury. They are exposed to repeated signals from hepatocytes, the gut, and adipose tissue. These signals make it difficult for Kupffer cells to return to a resting or homeostatic state. As a result, Kupffer cell activation may become persistent. Persistent activation is especially damaging because it allows inflammatory cytokines and chemokines to be produced over a

long period.

The triggers of Kupffer cell activation in MASLD are therefore closely connected. Lipotoxicity injures hepatocytes and releases danger signals. Gut-derived endotoxins stimulate innate immune receptors. Systemic metabolic inflammation increases the flow of fatty acids and cytokines to the liver. Together, these factors create a liver environment in which Kupffer cells are repeatedly activated. This repeated activation becomes a key step in the movement from simple steatosis to inflammatory liver injury.

5. Inflammatory Signaling after Kupffer Cell Activation

After Kupffer cells are activated in MASLD, their role changes from quiet immune surveillance to active inflammatory signaling. They begin to release cytokines, chemokines, and other mediators that affect surrounding liver cells. This response may be useful when the liver faces a short-term threat, because it helps remove harmful substances and damaged cells. In MASLD, however, the stimulation is often continuous. Lipid overload, hepatocyte injury, and gut-derived endotoxins keep activating Kupffer cells. As a result, inflammatory signaling does not stop easily, and the liver remains in a state of repeated immune activation.

One important group of mediators released by activated Kupffer cells is inflammatory cytokines. TNF- α , IL-1 β , and IL-6 are especially relevant in MASLD. TNF- α can worsen insulin resistance, increase hepatocyte stress, and promote cell death. IL-1 β is closely related to inflammasome activation and can strengthen local inflammation. IL-6 may affect liver metabolism and immune responses, especially when it is produced for a long time. These cytokines do not act on only one target. They influence hepatocytes, endothelial cells, stellate cells, and other immune cells in the liver. Through these effects, Kupffer cells help turn metabolic injury into a broader inflammatory response.

Chemokines are also important after Kupffer cell activation. Activated Kupffer cells can release CCL2 and other chemokines that attract circulating monocytes into the liver. These monocytes can differentiate into macrophages and add to the inflammatory cell population. This means the inflammatory response is no longer limited to resident Kupffer cells. More immune cells enter the liver and participate in tissue injury. Some of these recruited cells

produce additional cytokines and reactive oxygen species, which increase hepatocyte damage. This process creates a cycle in which inflammation attracts more inflammatory cells, and these cells further strengthen inflammation.

NF- κ B signaling is one of the main pathways involved in this process. When Kupffer cells recognize lipopolysaccharide, danger signals, or toxic lipid-related molecules, NF- κ B can be activated. This pathway promotes the expression of inflammatory genes and increases the production of cytokines such as TNF- α and IL-6. NF- κ B signaling helps explain why Kupffer cell activation can become strong and persistent in MASLD. Once this pathway is repeatedly stimulated, the liver microenvironment becomes more inflammatory. Hepatocytes then face greater stress, and the possibility of progression from steatosis to steatohepatitis becomes higher.

The NLRP3 inflammasome is another important mechanism. Under metabolic stress, Kupffer cells can respond to danger signals and activate inflammasome pathways. NLRP3 inflammasome activation promotes the maturation and release of IL-1 β and IL-18. These cytokines can deepen inflammatory injury and affect surrounding liver cells. Inflammasome activation is especially important because it connects cellular stress with innate immune response. In MASLD, hepatocyte lipotoxicity and mitochondrial damage may provide signals that support this pathway. Kupffer cells then translate these stress signals into a stronger inflammatory reaction.

Kupffer cells also communicate with hepatocytes during inflammatory progression. Injured hepatocytes release danger signals that activate Kupffer cells. Activated Kupffer cells then release cytokines that further damage hepatocytes. This creates a feedback loop between hepatocyte injury and immune activation. The more hepatocytes are injured, the more signals they release. The more Kupffer cells are activated, the more inflammatory mediators they produce. This loop is one reason why MASLD may gradually move from simple fat accumulation to MASH.

Their communication with liver sinusoidal endothelial cells also matters. Endothelial cells help regulate immune cell movement into liver tissue. Under inflammatory conditions, signals from Kupffer cells may change endothelial cell behavior and make it easier for immune cells to enter the liver. This increases local immune cell infiltration. The liver then becomes a more active

inflammatory site, rather than a tissue only affected by lipid storage.

Kupffer cells also interact with hepatic stellate cells. This interaction is important because it links inflammation with fibrosis. Inflammatory cytokines, reactive oxygen species, and profibrotic mediators from Kupffer cells can stimulate hepatic stellate cells. Once stellate cells are activated, they begin to produce extracellular matrix. If this process continues, fibrosis can develop. This shows that inflammatory signaling after Kupffer cell activation does not only cause short-term immune injury. It can also contribute to long-term structural changes in the liver.

Kupffer cell activation produces a network of inflammatory signaling in MASLD. Cytokines damage hepatocytes and disturb metabolism. Chemokines recruit more immune cells into the liver. NF- κ B signaling maintains inflammatory gene expression. NLRP3 inflammasome activation increases IL-1 β and IL-18 release. Interactions with hepatocytes, endothelial cells, recruited monocytes, neutrophils, and hepatic stellate cells make the inflammatory response broader and more persistent. Through these pathways, Kupffer cells become a central driver of inflammatory progression in MASLD.

6. From Kupffer Cell Activation to MASH

The transition from simple steatosis to MASH is one of the most important points in MASLD progression. Simple steatosis mainly means that excess fat has accumulated in hepatocytes. At this stage, the liver may already be under metabolic pressure, but inflammation and hepatocyte injury may still be limited. MASH is different. It involves steatosis together with inflammatory cell infiltration, hepatocyte injury, and often early fibrotic changes. This shift does not happen only because more fat is stored in the liver. It happens when lipid accumulation begins to cause repeated cellular stress and immune activation. Kupffer cells are central to this process because they help convert metabolic injury into inflammatory damage.

In early MASLD, hepatocytes try to adapt to lipid overload. They store triglycerides, increase lipid oxidation, and adjust metabolic activity. These responses may protect the liver for a time. The problem appears when the amount and type of lipid stress exceed the adaptive capacity of hepatocytes. Toxic lipid species, oxidative stress, and mitochondrial dysfunction begin to damage hepatocytes. Injured hepatocytes release danger

signals into the liver microenvironment. Kupffer cells recognize these signals and become activated. This step is important because the disease begins to move beyond passive fat storage. The liver starts to show an active immune response to metabolic injury.

Activated Kupffer cells then amplify hepatocyte stress. They release inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. These mediators can weaken hepatocyte function, increase oxidative injury, and promote cell death. Once hepatocyte injury becomes more obvious, more danger signals are released. Kupffer cells respond again, producing more inflammatory mediators. This creates a feedback loop between hepatocyte damage and Kupffer cell activation. The liver is no longer dealing with a single episode of injury. It enters a repeated cycle of metabolic stress, immune activation, and further cell damage.

This process also changes the immune cell composition of the liver. Kupffer cells can release chemokines such as CCL2, which attract circulating monocytes into the liver. These monocytes may differentiate into macrophages and join the inflammatory response. As a result, the inflammatory process is no longer limited to resident Kupffer cells. Recruited macrophages, neutrophils, and other immune cells begin to participate in tissue injury. Some of these cells release additional cytokines and reactive oxygen species. This makes inflammation stronger and more difficult to resolve. The progression to MASH therefore reflects not only Kupffer cell activation, but also the expansion of a wider inflammatory network.

Kupffer cells also help explain why inflammation in MASH can become self-sustaining. In a short-term injury, macrophage activation may help clear damaged cells and restore tissue balance. In MASLD, the injurious signals often continue because insulin resistance, lipid overload, gut-derived endotoxins, and adipose tissue inflammation remain present. Kupffer cells are repeatedly stimulated by these signals. They may fail to return fully to a homeostatic state. When this happens, inflammation becomes persistent. The liver continues to receive inflammatory signals even when there is no acute infection or external injury.

The formation of hepatic crown-like structures also reflects this process. In areas where hepatocytes are injured or dying, macrophages may gather around lipid-laden or damaged

hepatocytes. These structures suggest that macrophages are actively responding to hepatocyte death and lipid debris. They may help clear damaged material, but they also mark a tissue environment where inflammation and metabolic stress are closely connected. This shows that MASH is not simply a more severe form of steatosis. It is a stage in which hepatocyte injury and macrophage-driven inflammation become linked in a visible and organized way.

Kupffer cell activation is therefore more than a sign that MASLD has become worse. It is one of the mechanisms that pushes the disease toward MASH. Kupffer cells receive signals from stressed hepatocytes, gut-derived products, and systemic metabolic inflammation. They then release cytokines and chemokines that damage hepatocytes, recruit more immune cells, and maintain local inflammation. Through this process, simple steatosis can gradually become steatohepatitis. The key change is the emergence of sustained inflammatory injury. Kupffer cells stand at the center of that change because they transform metabolic stress into an immune response that can no longer be easily resolved.

7. Kupffer Cells and Fibrosis Development

Fibrosis is one of the most important consequences of long-term inflammatory progression in MASLD. It shows that liver injury has moved beyond temporary cell stress and has begun to change the structure of the liver tissue. In the early stage of MASLD, fat accumulation and inflammation may still be partly reversible. When inflammation continues for a long time, the liver repeatedly tries to repair damaged tissue. This repair process may gradually become excessive. Extracellular matrix begins to accumulate, collagen deposition increases, and normal liver architecture is slowly disturbed. Kupffer cells are closely involved in this shift from inflammatory injury to fibrotic remodeling.

The main cellular target in fibrosis development is the hepatic stellate cell. Under normal conditions, hepatic stellate cells stay in a relatively quiet state and store vitamin A. When the liver is injured, these cells can become activated. Activated hepatic stellate cells change into myofibroblast-like cells and begin to produce collagen and other extracellular matrix components. This process is useful in short-term wound repair, but it becomes harmful when injury does not stop. In MASLD, persistent hepatocyte stress and Kupffer cell activation

create the conditions for continued stellate cell stimulation.

Activated Kupffer cells can promote hepatic stellate cell activation through several mediators. TGF- β is one of the most important profibrotic signals. It encourages stellate cells to produce extracellular matrix and supports the development of scar tissue. Kupffer cells can also release TNF- α , IL-1 β , IL-6, reactive oxygen species, and platelet-derived growth factors. These mediators do not act separately. They form a local signaling environment that pushes hepatic stellate cells toward activation and keeps them active. As a result, inflammation becomes linked with fibrogenesis.

This process shows that fibrosis is not separate from inflammation. In MASLD, fibrosis often develops because the liver is caught in a repeated cycle of injury and repair. Hepatocytes are damaged by lipotoxicity, oxidative stress, and inflammatory mediators. Kupffer cells respond to this damage and release cytokines and chemokines. These signals bring more immune cells into the liver and activate stellate cells. Stellate cells then deposit extracellular matrix. If the original metabolic stress continues, the repair response does not fully resolve. The liver keeps producing scar tissue instead of returning to normal structure.

Kupffer cells also influence fibrosis by shaping the wider immune environment of the liver. They recruit monocyte-derived macrophages and other inflammatory cells through chemokines such as CCL2. These recruited cells can produce more inflammatory and profibrotic mediators. In this way, Kupffer cells do not only act directly on stellate cells. They also help build a larger inflammatory network that supports fibrosis. The more this network expands, the harder it becomes for the liver to restore homeostasis.

The relationship between Kupffer cells and fibrosis is also connected to failed resolution. In a controlled repair process, macrophages help clear dead cells, remove debris, and support tissue recovery. In MASLD, however, the injurious signals often remain present. Lipid overload continues, gut-derived endotoxins continue to reach the liver, and insulin resistance continues to affect hepatic metabolism. Kupffer cells may remain activated instead of shifting toward a repair-resolving state. This prolonged activation keeps stellate cells exposed to profibrotic signals. Fibrosis then becomes a

structural result of chronic inflammation.

Kupffer cells therefore connect early metabolic injury with later fibrotic remodeling. At the beginning of MASLD, the main problem may appear to be fat accumulation in hepatocytes. As the disease progresses, Kupffer cells translate hepatocyte stress into inflammatory signaling. When this signaling persists, it activates hepatic stellate cells and supports extracellular matrix deposition. This is why Kupffer cell activation is important not only for understanding MASH, but also for explaining how MASLD can progress toward fibrosis. The fibrotic stage is not a separate event that appears after inflammation. It is the result of inflammation becoming repeated, unresolved, and structurally damaging.

8. Kupffer Cells and Fibrosis Development

Fibrosis represents a later and more structural consequence of inflammatory progression in MASLD. In the early stage of the disease, fat accumulation and inflammatory injury may still remain partly reversible. When injury continues, however, the liver begins to repair itself again and again. This repeated repair response can gradually become harmful. Instead of restoring normal tissue structure, the liver starts to accumulate extracellular matrix and collagen. Over time, this process changes the architecture of the liver and creates fibrotic tissue. Kupffer cells play an important role in this movement from inflammation to fibrosis.

The key cells directly responsible for fibrosis are hepatic stellate cells. Under normal conditions, hepatic stellate cells remain relatively inactive and help store vitamin A. When the liver is injured, these cells can become activated and change into myofibroblast-like cells. After activation, they begin to produce collagen and other extracellular matrix components. This response is part of wound healing, but in MASLD the injury is not short-lived. Lipid overload, oxidative stress, hepatocyte damage, and inflammation may continue for a long time. The repair process then becomes chronic, and fibrotic tissue gradually builds up.

Activated Kupffer cells can stimulate hepatic stellate cells through several signals. TGF- β is especially important because it directly promotes extracellular matrix production. Kupffer cells can also release TNF- α , IL-1 β , IL-6, reactive oxygen species, and other mediators that keep the liver in an inflammatory and profibrotic state. These signals do not only affect stellate cells in isolation.

They also influence hepatocytes, endothelial cells, and recruited immune cells. As a result, the liver microenvironment becomes more favorable to fibrosis.

This connection shows that fibrosis is not separate from inflammation. In MASLD, fibrotic progression often develops from repeated inflammatory injury. Damaged hepatocytes release danger signals. Kupffer cells respond to these signals and produce inflammatory mediators. These mediators worsen hepatocyte injury and stimulate hepatic stellate cells. Once stellate cells are activated, collagen deposition increases. If the original metabolic stress remains, this cycle continues. The liver is then caught between ongoing injury and excessive repair.

Kupffer cells also contribute to fibrosis by recruiting other immune cells into the liver. They can release chemokines such as CCL2, which attract circulating monocytes. These monocytes may become inflammatory macrophages after entering liver tissue. Some of them release additional cytokines and profibrotic mediators. This expands the inflammatory response and strengthens the signals that activate hepatic stellate cells. In this way, Kupffer cells do not act alone. They help organize a broader immune environment that supports fibrotic remodeling.

The role of Kupffer cells in fibrosis also reflects a failure of inflammatory resolution. In a normal healing process, macrophages help clear dead cells and then support tissue repair. In MASLD, the metabolic pressure usually remains. Excess fatty acids continue to enter the liver. Gut-derived endotoxins may continue to stimulate innate immune receptors. Hepatocytes continue to experience stress and injury. Under these conditions, Kupffer cells may remain activated for a long period. Their activity shifts from controlled defense to persistent inflammatory signaling.

Kupffer cells therefore connect early metabolic injury with later fibrotic remodeling. At first, MASLD may appear mainly as fat accumulation in hepatocytes. As the disease progresses, Kupffer cells translate hepatocyte stress into inflammatory signals. When these signals persist, hepatic stellate cells are repeatedly activated and extracellular matrix deposition increases. Fibrosis is not simply the final stage after inflammation. It is the structural result of inflammation that has become chronic, repeated, and poorly resolved.

Kupffer cells have a dual role in MASLD. They are not simply inflammatory cells that damage the liver. Under normal conditions, they are necessary for liver protection and tissue balance. They remove bacteria, clear dead cells, process cellular debris, and help maintain immune tolerance in the liver. Even in the early stage of MASLD, their activation may have a protective meaning. When hepatocytes are injured by lipid overload, Kupffer cells help remove damaged material and limit further tissue disturbance. This response is part of the liver's normal defense system.

The problem begins when this response lasts too long. In MASLD, the source of injury is usually not temporary. Excess fatty acids continue to enter the liver. Hepatocytes continue to experience oxidative stress and lipotoxic injury. Gut-derived endotoxins may repeatedly stimulate innate immune receptors. Adipose tissue inflammation may also keep sending inflammatory mediators into the circulation. Under these conditions, Kupffer cells are not given enough opportunity to return to a resting or regulatory state. Their protective activation gradually becomes chronic activation.

Chronic Kupffer cell activation changes the effect of these cells on the liver. Instead of only clearing harmful material, they begin to produce inflammatory cytokines and chemokines over a long period. TNF- α , IL-1 β , IL-6, and CCL2 can worsen hepatocyte stress, attract more immune cells, and support the development of a persistent inflammatory environment. This means the same cells that help protect the liver can also become a source of continuing injury. The key issue is not Kupffer cell activation itself. Activation is a normal and necessary part of immune defense. The real problem is prolonged activation that cannot be properly resolved.

This dual role also shows why the old M1/M2 macrophage model is not enough to explain MASLD. The M1/M2 model describes macrophages as either pro-inflammatory or anti-inflammatory, but liver macrophages in MASLD are more complex than this. Kupffer cells and recruited macrophages may show mixed features. Some macrophages promote inflammation and fibrosis. Some help remove dead cells and support tissue repair. Some may change their function as the disease moves from steatosis to MASH and then to fibrosis. A simple division between harmful and protective macrophages cannot fully explain these changes.

In MASLD, macrophage populations also change with disease stage. Resident Kupffer cells respond early to hepatocyte stress and gut-derived signals. As inflammation develops, circulating monocytes enter the liver and become monocyte-derived macrophages. These recruited macrophages may strengthen inflammation and interact with hepatic stellate cells. In fibrotic areas, some macrophage subsets may be closely associated with scar formation. At the same time, other macrophages may participate in debris clearance and tissue repair. This shows that the macrophage response in MASLD is dynamic rather than fixed.

The dual role of Kupffer cells is important for understanding inflammatory progression. If Kupffer cells clear damaged cells effectively and then shift toward resolution, liver injury may be limited. If metabolic stress continues and inflammatory signaling remains active, Kupffer cells may help sustain MASH and fibrosis. Disease progression therefore depends partly on whether the macrophage response moves toward resolution or remains trapped in chronic activation. MASLD becomes more severe when the balance shifts away from repair and toward persistent inflammation.

This point is also important for treatment thinking. It would be too simple to see Kupffer cells only as therapeutic targets that should be suppressed. Removing or blocking their function too broadly could weaken host defense, debris clearance, and tissue repair. A better approach would be to reduce harmful inflammatory activation while preserving their protective functions. In this sense, Kupffer cells should be understood as regulatory cells whose effects depend on context, duration of stimulation, and disease stage. Their dual role helps explain why MASLD progression is not a straight path from fat accumulation to injury, but a changing process shaped by both damage and repair.

9. Therapeutic Implications

The role of Kupffer cells in MASLD has important implications for treatment thinking. If MASLD is viewed only as a disease of fat accumulation, treatment will mainly focus on reducing hepatic lipid content. This is necessary, but it is not enough to explain or control disease progression. In many patients, the more serious damage comes from the inflammatory response that follows metabolic stress. Kupffer cell activation shows that MASLD management

should also consider immune regulation, gut-liver signaling, inflammatory pathways, and fibrosis development. The goal should not only be to reduce fat in the liver, but also to prevent metabolic stress from becoming chronic inflammatory injury.

Improving metabolic health remains the most basic intervention direction. Weight loss, better insulin sensitivity, healthier lipid metabolism, and improved glucose control can all reduce the pressure placed on the liver. When fewer free fatty acids enter the liver, hepatocytes experience less lipotoxic stress. Reduced hepatocyte injury means fewer danger signals are released into the hepatic microenvironment. Kupffer cells then receive less stimulation. In this sense, metabolic improvement can indirectly reduce Kupffer cell activation by lowering the upstream causes of inflammation.

Reducing lipotoxicity is also important. MASLD progression is closely related to toxic lipid species, oxidative stress, mitochondrial dysfunction, and hepatocyte injury. If hepatocytes can better handle lipid overload, the release of damage-associated signals may decrease. This would weaken one of the main triggers of Kupffer cell activation. From this point of view, treatments that improve mitochondrial function, reduce oxidative stress, or limit harmful lipid accumulation may help interrupt the connection between metabolic overload and immune activation.

The gut-liver axis is another possible direction. Kupffer cells are exposed to gut-derived products through the portal circulation. When intestinal barrier function is impaired, bacterial products such as lipopolysaccharide may reach the liver more easily and activate innate immune receptors. Restoring gut barrier function and improving gut microbiota balance may reduce this source of stimulation. This does not mean that MASLD can be treated only through the intestine, but it shows that liver inflammation is affected by signals outside the liver. Reducing endotoxin exposure may help decrease repeated Kupffer cell activation.

Direct regulation of inflammatory pathways is also theoretically important. Kupffer cell activation involves signaling pathways such as NF- κ B and NLRP3 inflammasome activation. These pathways promote the release of inflammatory cytokines, including TNF- α , IL-1 β , and IL-6. If excessive activation of these pathways

can be controlled, liver inflammation may be reduced. However, this approach needs caution. Inflammatory signaling is not always harmful. It also helps the liver defend against pathogens and clear damaged cells. Treatment should avoid completely blocking normal immune responses.

Another important direction is the interaction between Kupffer cells and hepatic stellate cells. Fibrosis develops when hepatic stellate cells are repeatedly activated and begin producing extracellular matrix. Kupffer cells contribute to this process by releasing profibrotic and inflammatory mediators. If abnormal communication between Kupffer cells and stellate cells can be reduced, it may help slow fibrotic progression. This is especially important because fibrosis is closely related to long-term outcomes in MASLD. Controlling inflammation without addressing fibrosis would leave a major part of disease progression unresolved.

The dual role of Kupffer cells must be considered in any therapeutic strategy. Kupffer cells are not simply harmful targets that should be eliminated. They clear pathogens, remove dead cells, regulate immune balance, and support tissue repair. If their activity is suppressed too broadly, the liver may lose important protective functions. A more reasonable approach would be to reduce persistent pro-inflammatory activation while preserving their homeostatic and repair functions. In other words, the aim should be immune regulation rather than immune removal.

These therapeutic implications show that MASLD treatment should be understood in a broader way. Metabolic control remains the foundation, but inflammatory progression must also be addressed. Kupffer cells provide a useful entry point because they connect lipid overload, hepatocyte injury, gut-derived endotoxins, immune cell recruitment, and fibrotic remodeling. Targeting these connections may help prevent MASLD from progressing toward MASH and fibrosis. The practical challenge is to control harmful chronic inflammation without damaging the normal protective role of liver macrophages.

10. Conclusion

Kupffer cell activation is a key mechanism for understanding inflammatory progression in MASLD. MASLD does not progress only because fat accumulates in hepatocytes. Fat accumulation creates metabolic pressure, but the more serious change begins when this pressure leads to

hepatocyte injury, immune activation, and persistent inflammation. Kupffer cells are central in this process because they stand at the point where several disease signals meet. They respond to lipotoxic stress, damaged hepatocytes, gut-derived endotoxins, and systemic metabolic inflammation. Through these responses, they help convert metabolic dysfunction into liver inflammation.

The role of Kupffer cells is especially important in the shift from simple steatosis to MASH. In early steatosis, the main feature may be excess lipid storage. When hepatocytes become stressed or injured, they release danger signals that activate Kupffer cells. Activated Kupffer cells then produce cytokines and chemokines that worsen hepatocyte injury and recruit additional immune cells into the liver. This creates a cycle in which metabolic damage and immune response reinforce each other. The liver is no longer only storing excess fat; it becomes an inflammatory tissue environment.

Kupffer cells also help connect inflammation with fibrosis. Persistent activation can stimulate hepatic stellate cells through inflammatory and profibrotic mediators. Once stellate cells are activated, extracellular matrix deposition increases and fibrotic remodeling begins. This shows that fibrosis is not separate from inflammation. It develops when inflammatory injury becomes repeated and poorly resolved. Kupffer cells therefore link early metabolic stress with later structural damage in the liver.

At the same time, Kupffer cells should not be understood as purely harmful. Their normal functions include immune surveillance, pathogen clearance, removal of dead cells, and maintenance of liver homeostasis. The problem in MASLD is not activation itself, but long-term activation under continuous metabolic stress. When Kupffer cells cannot shift from inflammatory response to resolution, they become part of a chronic injury process. This dual role is important for both disease interpretation and treatment thinking.

MASLD progression is a dynamic process involving metabolic overload, hepatocyte stress, gut-liver signaling, immune cell recruitment, inflammatory persistence, and fibrotic remodeling. Kupffer cell activation connects these processes into a continuous disease pathway. Understanding this mechanism helps move the discussion of MASLD beyond simple

fat accumulation. It shows why controlling inflammation and restoring immune balance are important for preventing the progression from steatosis to MASH and fibrosis.

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