Japanese Journal of Gastroenterology and Hepatology

Review Article

ISSN: 2435-1210 | Volume 10

# Advances in the Study of the Role of Efferocytosis in Liver Disease

**Wang T[1], Yao M[1], Zhao Q[1], Liu H[2], Shen H[3] and Sun Q[1,3,4*]**

[1]Integrated Chinese and Western Medicine School, Southwest Medical University, Luzhou Sichuan, China

[2]School of Pharmacy, Southwest Medical University, Luzhou, Sichuan, China

[3]The affiliated Traditional Chinese Medicine Hospital of Southwest Medical University, Luzhou, Sichuan, China

[4]Drug Research Center of Integrated Traditional Chinese and Western Medicine, Affiliated Traditional Chinese Medicine Hospital, Southwest Medical University, Luzhou, Sichuan, China

***Corresponding author:**

Qin Sun,
Integrated Chinese and Western Medicine School, Drug Research Center of Integrated Traditional Chinese and Western Medicine, Affiliated Traditional Chinese Medicine Hospital, Southwest Medical University, Luzhou, Sichuan, China

Received: 16 Feb 2024
Accepted: 25 Mar 2024
Published: 30 Mar 2024
J Short Name: JJGH



**Keywords:**

Macrophage; Efferocytosis; Phagocyte; Apoptosis; Liver Diseases

**Citation:**

Sun Q. Advances in the Study of the Role of Efferocytosis in Liver Disease. J Gastro Hepato. 2024; V10(9): 1-10

## 1. Abstract

Efferocytosis is the process by which phagocytes remove programmed dead cells, a process understood as the burial of apoptotic cells, hence the term "efferocytosis". A growing number of studies have demonstrated that impairment of macrophage efferocytosis function is inextricably and closely related to the pathological process of liver diseases, and that intrahepatic macrophage recruitment and polarization play a crucial role in the progression of liver inflammation and fibrosis. Nowadays, there are articles reviewing the mechanism of macrophage efferocytosis in atherosclerosis, respiratory diseases, and immune system diseases, etc., but there is no comprehensive analysis of the role of macrophage efferocytosis in liver diseases. This review firstly describes the process of efferocytosis and the functions of the different phases of efferocytosis, and then discusses the mechanism of efferocytosis in the liver. In conclusion, a correct understanding of the mechanism of efferocytosis can provide a new way of thinking about the treatment and use of medication in the treatment of liver diseases.

## 2. Introduction

Macrophages are essential immune cells that play a critical role in eliminating inflammation and promoting tissue repair. They are capable of engulfing and removing apoptotic cells from the body, a process known as "efferocytosis". Defects in efferocytosis as a major cause of inflammatory diseases [1], Intact and effective efferocytosis is essential for maintaining homeostasis in the body's internal environment. Apoptotic cells are cells that die due to various reasons, and their removal is an important part of maintaining the order of life. Macrophages remove these apoptotic cells through efferocytosis, preventing them from releasing further harmful substances and ensuring the stability of the cellular environment and the health of the body. Impaired clearance of apoptotic cells has been shown to be associated with abnormal immune system responses, atherosclerosis, and the development of various diseases [2]. After phagocytosis of apoptotic cells by macrophages, their cellular contents (e.g., lipids, sugars, proteins, etc.) are dramatically increased to cope with the enormous metabolic capacity by altering and/or enhancing the original metabolic pattern and to maintain their intrinsic function in preparation for the next round of efferocytosis [3]. Enhancing macrophage efferocytosis is important for inhibiting the development of chronic inflammatory diseases. Elucidating the physiological mechanism of efferocytosis process and finding effective interventions, and searching for effective prevention and treatment targets at the molecular level is an important direction of exploration in the clinical treatment of chronic diseases.

## 3. The Regulatory Role of Macrophages and Neutrophils in the Body's Internal Environment

Elie Metchnikoff discovered the body's first immune mechanism in the late 19th century: a mobile process capable of phagocytosing microorganisms and stromal debris, a process he named "phagocytosis" and cells he called "phagocytes" [4]. Phagocytes include macrophagocytes, which are mononuclear macrophages in blood and various organ tissues, and microphagocytes, which are neutrophils in peripheral blood [5].

Macrophages are specialized phagocytes that readily engulf a wide variety of particles. Neutrophils are primarily derived from bone marrow hematopoietic stem cells and circulate in the blood. Neutrophils have limited phagocytosis capacity, although they have a more diverse set of skills. The phagocytosis of a macrophage is dependent on the nature of the target with which it interacts. When targets enter the macrophage periphery, they may interact with the macrophage via chemical signals that trigger receptors on the cell surface to bind to ligands, and these binding triggers macrophage activation and the formation of macrophage phagocytic vesicles, which completely encapsulate the target. Subsequently, lysosomes within the macrophage release digestive enzymes that degrade the phagocytosed target into small molecules, thus completing the phagocytosis process.

Neutrophils are a type of polymorphonuclear leukocyte and are an important component of the body's non-specific immunity. Neutrophils are in the front line of the body's defense against microbial pathogens, especially in the invasion of septic bacteria. When inflammation occurs, they are attracted to the site of inflammation by chemotactic substances, producing and releasing potent cytotoxic substances that participate in the host's defense against bacterial and fungal infections. When apoptosis occurs in neutrophils induced by aging or in a particular situation, they will be phagocytosed and removed by macrophages. Phagocytosis of apoptotic neutrophils by macrophages promotes anti-inflammatory signaling by macrophages to resolve inflammation, prevents neutrophil lysis and suppresses immune response [6].

## 4. Macrophage Clearance of Apoptotic Cells and Modulation of Inflammation

### 4.1. Apoptosis

Cell death and the removal of dead cells are essential for the maintenance of homeostasis in the organism's internal environment. Most cell death in the organism is programmed death, known as apoptosis. Molecular signals released by apoptotic cells have an impact on monocyte-macrophage function. Macrophage differentiation and activation are determined by specific growth and differentiation factors, receptor signaling pathways, and transcription factors [7]. Macrophages migrate to specific injury and infection sites, thereby causing acute and chronic inflammation, both locally and systemically.

### 4.2. Mechanisms of Efferocytosis

Efferocytosis is the process by which phagocytes (including specialized phagocytes such as macrophages and dendritic cells, or non-specialized phagocytes such as epithelial cells and smooth muscle cells) are removed from programmed dead cells. Efferocytosis, a term later coined by deCathelineau and Henson, is resulting from the Latin efferre, meaning "to take to the grave" [8]. The intensity of efferocytosis is influenced by multiple factors, such as the ratio of phagocytes to apoptotic cells, the nature of the phagocytes, the size of the dead cells, and the secretion of relevant signaling molecules. Efferocytosis plays an important physiological role in maintaining tissue homeostasis, promoting tissue repair and maintaining the health of the organism by organizing secondary necrosis of dying cells to avoid the release of harmful cellular contents that may cause inflammation [9].

During efferocytosis, phagocytes take up apoptotic cells and form a large vesicle containing dead cells, which is called the "efferosome". Macrophage efferocytosis remains a highly conserved principle in the evolution of biology, recognizing and removing apoptotic cells. The steps involved in cell clearance include phagocytosis to the vicinity of the dead cells, specific recognition and internalization of the dead cells, and degradation of the cadaver. These are specified as follows:

**4.2.1. Find me:** In order to ensure that apoptotic cells can be found in a timely and accurate manner, during the process of apoptosis, the dead cells due for release soluble chemokines to the surrounding environment, i.e., "find me" signaling molecules to actively attract the resident macrophages in order to stimulate their clearance ability, and the receptor on the surface of the macrophage receives the signal, and will come to the vicinity of the apoptotic cells and get ready for "battle" through the interaction between the two to sense and recognize. Receptors on the surface of the macrophage receive the signal and quickly come to the vicinity of the apoptotic cell and get ready for "battle", and the two sense and recognize each other through interaction. The main "find me" signals that have been discovered so far are Lysophosphatidylcholine (LPC) [10], sphingosine-1phosphate(S1P) [11], Nucleotides, adenosine triphosphate (ATP) and uridine triphosphate (UTP) [12], CX3CL1,also known as fractalkine [13], RP S19 [14]. During apoptosis, apoptotic cells are encapsulated into apoptotic vesicles by activated cysteine asparaginase as well as its substrate, poly ADP ribose polymerase (PARP), and is subsequently processed and recirculated by surrounding phagocytes, thereby effectively preventing pro-inflammatory cells from releasing their internal substances and triggering inflammation [15].

**4.2.2. Eat me:** Upon completion of macrophage recruitment, the next process is initiated, whereby receptors on the surface of the recruited macrophage receive the "eat me" signal from the apoptotic cell and rapidly bind to their ligands on the surface of the recruited macrophage to trigger the initiation of the efferocytosis process. A number of eat me signaling molecules have been proposed in a number of studies, including Phosphatidylserine (PtdSer), Calcium reticulin, Low Density Lipoprotein (LDL) [16], Carbohydrate (aminosugar or mannose), Intercellular Adhesion Molecule 3 (ICAM3) [17] et al.

Among them, an important role is played by PtdSer. PS is the most

abundant negatively charged glycerophospholipid in eukaryotic cell membranes, which is usually found in the inner leaflet of the cell membrane and is rapidly exposed to the cell surface during apoptosis to promote the specific recognition of dead cells by macrophages [18]. It has been extensively shown to mediate PS binding to and recognition of macrophage receptors thereby mediating the occurrence of phagocytosis, which will not be relevantly expressed here, whereas existing research has uncovered new areas of relevance suggesting that PtdSer can directly bind to and be recognized by different phosphatidylserine receptors on the surface of phagocytes, where the lipids are flipped via a variety of proteins known as scramblases between the flipped between the inside and outside of the cell membrane, Scramblases disrupt membrane asymmetry, thereby randomizing all phospholipid species between leaflets, effectively increasing the accumulation of PS on the outside of the membrane in the context of PS biology. Upon loss of membrane asymmetry, PS crosses the bilayer and interacts with a new set of extracellular serum proteins to trigger a range of biochemical and immune responses to PS receptors, PS externalization is one of the hallmark signals that mark cells for cytosolic burial, and phagocytes differentiate between PS exposed by living as well as by apoptotic cells, thereby inducing phagocytosis to occur [19].

Another signal, the "don't eat me" signal, appears on the surface of healthy cells at this stage, including CD47 [20], CD24 [21], CD31 [22], Programmed death ligand-1 (PD-L1) [23], β2-microglobulin (β2M) [24], These "don't eat me" signals in turn bind to "anti-phagocytic receptors" on phagocytes, such as the macrophage surface receptor signaling protein (SIRPα) and the salivary acid-binding immunoglobulin lectin 10 (Siglec-10), thereby aiding evasion [25]. Interaction between CD47 and SIRPα on living cells leads to tyrosine phosphorylation of the cytoplasmic structural domain of SIRPα, which results in recruitment and activation of the phosphatase SHP1/2. Subsequently, SHP1/2 inhibits phagocytosis by inhibiting nonmuscle myosin IIA [26].

**4.2.3. Engulfment:** During the phagocytosis phase, the PS receptor of macrophages can directly or indirectly recognize PS exposed on the surface and prepare apoptotic cells for internalization by inducing Rac1-mediated actin cytoskeletal rearrangement, and the two form phagocytic vesicles. Macrophages integrate various signals from apoptotic cells and then pool them through two phagocytic signaling pathways, ELMO1/Dock180 and GULP1, and this integrated processing activates Rac1, an evolutionarily highly conserved GTPase, which leads to the phagocytic stage of efferocytosis [27]. Activated Rac1 forms a phagocytosis loop that promotes actin polymerization and cytoskeletal rearrangement through the Scar/WAVE complex to complete the phagocytosis of apoptotic cells [28]. Apoptotic neutrophils, T cells, and human lineage cells release the potential phagocyte molecule annexin-I, which promotes effective phagocytosis of apoptotic cells through the mechanism of the FPR2/ALX receptor and its internalization [29,30].

**4.2.4 Digest me:** Phagocytes face a great metabolic burden after ingesting a large number of apoptotic cells, which requires that phagocytes must rapidly remove the contents. Under the control of the Rab GTPase family of proteins, phagosomes containing dead cell corpses will mature to target lysosomes through a multistep process [31], After maturation, the phagosome will fuse directly with lysosomes through the formation of Ca2+ dependent SNARE complexes, such as VAMP7 and Syntaxin 7, and the lysosomes can derive a variety of digestive enzymes, and the phagosome will combine with the lysosome to form a new phagolysosome, and the apoptotic cells can be digested by a variety of digestive enzymes when they enter into the new phagolysosome, and the high-acid environment of pH 4.5-5.0 can activate the hydrolytic enzymes in lysosomes to promote the internalization and degradation of the lysosomal enzymes [15]. NADPH oxidase, which is inactive in healthy macrophages and neutrophils, is activated by exposure to microorganisms or inflammatory mediators, and thus recruited to produce reactive oxygen species (ROS) products. The production of ROS leads to the rapid lipolysis of LC3 with phagosomal membranes to form the single-membrane phagolysosomes containing apoptotic cells called LAPosome. The attachment of LC3 facilitates the fusion of the LAPosome with lysosomes to degrade pathogens, effectively increasing the clearance rate of apoptotic cells and maintaining immune silencing, a process known as LC3-associated phagocytosis (LAP) [32-34].

Each process of cell burial is essential and is connected and cooperative with each other, and only in perfect coordination can macrophages efficiently recognize, phagocytose, digest and remove apoptotic cells. Any defect in one of the above steps will lead to the aggregation of apoptotic cells, and the lesions will continue to expand and progress, thus destroying the internal environmental homeostasis of the organism.

## 5. Role of Macrophage Efferocytosis in Liver Disease

### 5.1. Macrophage Polarization

Macrophages (Mø) possess three core functions: immunomodulation, phagocytosis and antigen presentation. These functions are essential for the maintenance of a normal immune response under various pathophysiological conditions [35]. Diversity and plasticity are among the important characteristics of macrophages, and macrophage polarization refers to different activation states at specific times and places [36], Macrophages respond to environmental signals by differentiating into different phenotypes, and their remarkable plasticity enables them to assist in the removal of foreign bodies, promote tissue regeneration, and regulate tissue homeostasis. Macrophages are capable of responding differently to surrounding stimuli (e.g. microbial products, damaged cells, activated lymphocytes) under different physiopathological conditions, integrating different signals from different damaged tissues, microbes, and normal tissue environments, and reprogramming both classically activated (M1 macrophages) and alternatively activated (M2 macrophages) to

acquire different functional phenotypes [37,38], Macrophage characterization and regulation are complex and interrelated, which are closely related to the dynamics of their microenvironment [39], M1 is generally activated by interferon-γ and lipopolysaccharide (LPS), M1 mainly secretes pro-inflammatory factors and plays an important role in the early stage of inflammation, phagocytosis of pathogens and apoptotic cells through activation of the NADPH oxidase system and the subsequent production of ROS; M2 is activated by Th2 cytokines, such as IL-4, IL-13, and immune complexes, M2 expresses inhibitory inflammatory factors and mainly plays a role in the late stage of inflammation, inhibits the inflammatory response, and acts as a reparative and remodeling factor of the tissue [40,41]. The M1/M2 phenotypic imbalance is a central mechanism controlling the pathogenesis of chronic inflammatory diseases. This suggests that strategies that inhibit M1 macrophage polarization and/or favor the M2 macrophage phenotype can prevent further inflammation and thus limit tissue damage.

### 5.2. Macrophages in the Liver

The liver is the base of the strike pole, the residence of the soul. Strike pole, that is, the distribution, the meaning of banishment, expressed in Chinese medicine terminology, that is, excretion, the liver in the human body is mainly able to dredge, regulate the function of gas, so as to regulate the gas lifting in and out of the movement, so that the internal organs and tissues play a normal physiological function. In the human body, the liver is a complex and unique immune organs, liver storage macrophages accounted for 80% to 90% of the body's macrophages [42]. There are approximately 20-40 macrophages per 100 hepatocytes in healthy rodent livers [43]. Thus, hepatic macrophages have a key role in maintaining homeostasis in the liver tissue itself and in the organism as a whole. The number of hepatic macrophages increases dramatically when the liver undergoes various inflammatory injuries [44]. Hepatic macrophages consist of two main groups: tissue-resident Kupffer cells (KCs) and monocyte-derived macrophages (MDMs).

Kupffer cells remain in liver tissue for long periods of time, rather than traveling around the body as other immune cells do. This residency allows Kupffer cells to perform specific functions in the liver; in addition, Kupffer cells are self-maintaining in that they are able to maintain their numbers in the liver by self-proliferation; and localized proliferative properties further illustrate the specific proliferative capacity of Kupffer cells in the liver; another important property is tolerogenicity, which means that Another important property is tolerogenicity, which means that Kupffer cells are able to suppress the immune response under certain circumstances, preventing excessive immune responses from damaging liver tissue [45]. Kupffer are specialized phagocytes capable of removing microorganisms and metabolites from hepatic sinusoids to maintain immune tolerance, detecting liver tissue damage, and subsequently activating pro-inflammatory cascade responses. They have the ability to produce large amounts of cytokines, chemokines and other bioactive molecules in response to stimuli [46].

In contrast, MDM cells are differentiated from monocytes in the peripheral blood. Monocytes are a type of white blood cell in the blood that are able to travel to different parts of the body and differentiate into various immune cells. In their natural environment, MDM cells are immunogenic and capable of triggering an immune response. In addition, MDM cells readily receive signals from the local microenvironment that promote their functional differentiation and infiltration. This functional differentiation allows MDM cells to perform specific immune functions in different microenvironments [45].

As important regulators of innate immune homeostasis TAM receptor tyrosine kinases, including AXL, Mertk, and TYRO-3, are expressed on monocytes and macrophages and act by inhibiting the phagocytic clearance of apoptotic cells through containment of the Toll-like receptor (TLR) signaling pathway and facilitation of apoptosis [47-49]. Mer tyrosine kinase (Mertk) and Axl have been found to be predominantly expressed on KCs and endothelial cells and are key receptors for maintaining liver homeostasis and tolerance [50], play different roles in the homeostatic and ablative phases of tissue inflammation, and their respective roles depend on the type of cell expressed and the varying degree of manifestation at the disease stage [51], Specifically mediates phagocytosis of apoptotic cells in the maintenance of homeostasis and inflammatory environments, respectively, and Mertk functions as a tolerogenic receptor in resting macrophages and immunosuppressive environments, in contrast to AXL, which is a receptor for inflammatory responses induced by inflammatory factor stimulation [49].

### 5.3. Efferocytosis and Liver Diseases

**5.3.1. Alcoholic Liver Disease:** Alcoholic Liver Disease(ALD),is the result of the interaction between toxic reactive metabolites from alcohol metabolism, oxidative stress occurring in the liver, and the secretion of multiple inflammatory mediators by activated immune cells [52,53]. Numerous studies have demonstrated that, Increased neutrophils in the liver of ALD patients correlate with disease severity [54]. A particular type of programmed cell death of neutrophils, called NETosis, exerts this immune effect by releasing a reticular substance capable of trapping and killing pathogens, called the Neutrophilextracellular traps,NETs [55]. Bukong et al. from the University of Massachusetts Medical School found that acute alcohol abuse induces spontaneous formation of NETs in neutrophils, however, in alcohol-exposed neutrophils, which receive stimulation or antigenic attack, further NETs formation is inhibited, and efferocytosis is also disrupted, leading to long-term liver inflammation and injury. In order to prevent further inflammation after NETosis, macrophage cytoconjugation removes the NETs [56]. This process is mediated by extracellular preconditioning of NETs by DNase I and by serum complement C1q, which promotes the conditioning of NETs, and by DNA fractions of NETs, which can potentially induce a type I IFN response, and suggests that macrophages, which do not produce proinflammatory cytokines after uptake of NETs alone, are able to

process them in an immunosilent manner when they are entered via the endocytosis-phagocytosis pathway [9]. It has been further shown that alcohol impairs efferocytosis by inhibiting macrophage milk fat globule-EGF factor 8 (MFGE8) gene expression, leading to hepatocyte necrosis, which explains why alcohol leads to liver injury, which leads to hepatocellular necrosis, which explains why alcohol causes liver injury from another perspective [57].

**5.3.2. Non-alcoholic Steatohepatitis:** Non-alcoholic fatty liver disease (NAFLD) is a continuous spectrum of liver disease, and a proportion of patients with NAFLD develop a more inflammatory disease called non-alcoholic steatohepatitis (NASH) [58]. If treatment is ineffective, this may further progress to severe liver fibrosis, cirrhosis, or hepatocellular carcinoma.KC plays a central role in the etiology of NASH. KC produces endogenous miR-690 through exosomal secretion, which directly inhibits fibrogenesis in HSC, inflammation in recruited hepatic macrophages (RHMs), and de novo lipogenesis in hepatocytes [59]. These studies suggest that miR-690 in exosomes may be a therapeutic approach for NASH. Animal studies have confirmed that macrophages with inflammatory manifestations exacerbate the severity of NAFLD. Activation of these macrophages induces the production of inflammatory cytokines and contributes to oxidative stress, which ultimately triggers the development of liver fibrosis and other related complications. Thus, these macrophages play an important role in the development of NAFLD. More specifically, their activation is a key factor in the development of inflammatory cytokine production, increased oxidative stress, and associated complications such as liver fibrosis [60,61]. Myeloid cell-expressed receptor 2 (TREM2) on hepatic macrophages has emerged as an immunoglobulin superfamily receptor located in a single transmembrane site on cell membranes, and has become an important cell surface molecule with a protective role against NASH development [62]. Decreased TREM2 protein expression at the onset of NASH leads to the accumulation of dead hepatocyte debris, which promotes inflammation and leads to the accelerated development of NASH. The experimental team of Xiaochen Wang from the University of Texas Southwestern Medical Center demonstrated that the TREM2 gene is a key factor in maintaining hepatic immune homeostasis to prevent the development of NASH. The study further revealed that TREM2 expression is induced by sphingosine 1 phosphate (S1P) released from apoptotic hepatocytes, and that high TREM2 expression enhances efferocytosis and ensures that macrophages are able to remove apoptotic hepatocytes in a timely and efficient manner, thus revealing an important mechanism of chronic liver inflammation and NASH lesions caused by obesity in the body [63].

**4.3.3 Liver fibrosis:** Fibrotic organization of the liver is a trauma healing response in which the damaged area is encapsulated by extracellular matrix (ECM) or scarring. Activated hepatic stellate cells are the main source of ECM production, and macrophages play a key role in the activation of hepatic stellate cells.

The stromal cell protein cell communication network factor 1 (CCN 1) is a 40-kDa secreted stromal cell protein, and CCN 1 triggers macrophage efferocytosis by binding to PS on apoptotic cells and bridging them to macrophages to be engulfed by binding of integrin αvβ3, a phagocytic receptor in macrophages [64]. However, CCN1 has a bidirectional regulatory effect on the promotion and repair of hepatic fibrosis in different factors and environments, and CCN 1 can also contribute to the development of fibrosis through the mediated efferocytosis of apoptotic neutrophils by hepatic macrophages leading to an increase in the production of the activated transforming growth factor TGF-β1, which in turn induces myofibroblast differentiation of HSC.

Ping An's team [65] demonstrated that fibrosis susceptibility leads to impaired efferocytosis by performing an in vivo phagocytosis test of fluorescently labeled apoptotic thymocytes in FVB and BALB mouse strains using the hepatotoxic drug thioacetamide (TAA) and a healthy mouse control, and used microarrays to identify 5 phagocytic genes including genes encoding phagocytic receptors (Cd14, Marco); recognition and phagocytosis molecules (Csf1); and phagosome maturation (Serpine1, Tgm2). Also, this experimental study verified by depleting in vivo macrophage and myeloid cell subpopulations in comparison to the fibrotic response in control and late injury time points that in vivo resident F4/80(+) Kupffer cells and infiltrating Gr-1(+) myeloid cell subpopulations were effective at efferocytosis, removing dead hepatocytes and preventing liver-damaged cellular mitochondria (predominantly mtDNA as the active component)-derived damage-associated molecular patterns (mito-DAMPs) from liver-damaged cells are released and may serve as key determinants of resistance to liver fibrosis. Prolonged exposure to mito-DAMPs after injury is sufficient to trigger fibrotic activation of HSC in vivo and in vitro due to inefficient efferocytosis of dead hepatocytes or exogenous mitoDAMPs administration.

It has been previously reported that hepatic stellate cells and many other cells are able to phagocytose apoptotic vesicles of hepatocytes that slowly engulf nearby injured or dead cells [66-68], However, when considering the ability of phagocytes to actively sense and detect dead cells, the efferocytosis aspect is slightly more effective than any other stromal cell. Therefore, therapeutic targeting and modulation of macrophage efferocytosis released by mitoDAMPs may be important in the existence of a diagnostic and therapeutic pathway for liver fibrosis.

**5.3.4. Cirrhosis:** Cirrhosis not only manifests as excessive deposition of fibrous tissue, but also the basic architecture of the liver has been destroyed. The immune response in cirrhosis is regulated by the expression of AXL and Mertk in peripheral blood mononuclear cells, which are differentially expressed and inversely regulated in different stages of cirrhosis and inflammation49, Immune responses in patients with cirrhosis and acute non-chronic liver failure can be modulated by AXL expressed on circulating monocytes. Axl monocytes accumulate in the inflammatory milieu of cirrhosis and have increased expression when undergoing efferocytosis, preserving patho-

gen phagocytosis and enhancing efferocytosis [69]. Mertk expression was further induced by uptake products from apoptotic cells, and cholesterol metabolites from cell membrane debris activated liver X receptor (LXR), LXR binds and activates the Mertk promoter and promotes the release of anti-inflammatory factors during tissue injury [70]. In the presence of portal hypertension in cirrhosis, pathologic translocation occurs, i.e., there is an increased load of intestinal translocated bacteria and bacterial products from the gut to the body circulation [71], Intestinal macrophages in cirrhosis are activated as a result of bacterial translocation. AXL-expressing monocytes may expand in response to the uptake of pathogens and bacterial products under conditions of pathologic bacterial translocation and clear chronic inflammation of accumulated apoptotic cellular debris in response, while the excessive systemic inflammatory response is suppressed [69]. GAS-6 and Protein S can be recognized and driven to produce dependent phagocytosis by Mertk on macrophages, but for Axl, only GAS-6 drives Axl-dependent phagocytosis [49,72], GAS-6, which accumulates in cirrhotic livers, is secreted by activated hepatic stellate cells and downregulates AXL in vitro [49]. The activation of hepatic stellate cells in mice exposed to a carbon tetrachloride model is dependent on Gas6-mediated activation of Axl, which in turn upregulates signaling protein kinase B (PKB) and NF-κB [73]. This provides new insights into the clinical management of cirrhosis and liver fibrosis.

**5.3.5. Cholestatic liver disease:** Cholestatic liver disease(CLD),is characterized by the accumulation of bile acids in the liver, leading to progressive destruction of bile duct cells and hepatocytes and persistent liver inflammation. Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), which are cholestatic liver diseases targeting the biliary epithelium, are the two most common types of CLD, and macrophages play an important role in the pathogenesis of cholestatic liver disease. In cholestatic liver disease, the perichollic area recruits pro-inflammatory M1 and alternative M2 monocyte-derived macrophages, and inhibition of macrophage recruitment reduces perichollic fibrous inflammation and improves disease outcome [74]. Arid3a belongs to the ARID protein family of chromatin regulators and transcription factors. Upregulation of Arid3a in hepatic macrophages triggers the expression of a pro-inflammatory phenotype, which in turn further exacerbates the development of cholestatic liver injury by interfering with the Mertk-mediated efferocytosis of apoptotic bile duct cells in cholestasis, which has been shown to act as a scavenger receptor and a mediator of efferocytosis expressed on macrophages previously [75]. The phenotype of Arid3a-deficient macrophages can be repaired by the efferocytosis receptor Mertk, thus the Arid3a-MerTK axis is expected to be a new target for the treatment of cholestatic liver disease [76]. This suggests that macrophage efferocytosis of apoptotic bile duct cells is essential for repair and recovery of cholestatic liver disease. However, whether inflammatory biomolecules located highly expressed in bile duct epithelial cells promote macrophage recruitment in CLD remains to be demonstrated in more studies.

**5.3.6. Hepatocellular carcinoma (HCC):** There is also a bidirectional regulation of efferocytosis expressed by tumor cells. In the early stages of tumor development, efferocytosis promotes tumor progression by decreasing immune system attack. At the same time, certain malignant cells may express receptors and ligands associated with efferocytosis, enabling them to engulf surrounding apoptotic cells. They escape detection by the immune system by interfering with the activation of M1 macrophages and increasing the number of M2 macrophages, thus furthering tumor progression [77,78]. Conversely, In advanced stages of tumor development, the efferocytosis turns to help the immune system attack the tumor, which in turn curtails the growth of the tumor [79]. M1 polarization of Kupffer cells contributes to the prevention of Hepatocellular carcinoma (HCC) by promoting the recruitment of CD8+ T cells, whereas M2 polarization becomes important in driving the development of HCC [80]. Oncogene astrocyte elevation gene 1 (AEG-1) stimulates hepatocellular carcinogenesis by activating NF-κB in Kupffer cells [81]. AEG-1 expression was significantly higher in macrophages than in hepatocytes [82], and can resist macrophage differentiation into M1 or M2, causing efferocytosis to be diminished or even lost81. Ke Xu's team [83] screened six risk models for efferocytosis-associated genes (6-ERGs) (ADAM9, GAPDH, SIRT6, LGALS3, CD5L, and IL33) and identified two ERG-associated subtypes (high-risk and low-risk subgroups), highlights the critical role of efferocytosis in the progression of HCC and provides an important predictive basis for clinical decision-making to guide strategy development for immunotherapy and chemotherapy. This highlights the importance of efferocytosis in the progression of HCC and provides important clinical decision-making implications for the prediction of both immunotherapy and chemotherapy [6]. Individuals with high levels of ERGs exhibited elevated macrophage M2 infiltration and reduced expression of M2-related markers (PD-L1 and PDL2), reinforcing the argument that diminished macrophage immunity is tightly correlated with the elimination of efferocytosis [83]. This shows that in the treatment of HCC, efferocytosis can provide clinical decisions as an important target for therapy.

**5.3.7. Abnormalities of Liver Metabolism and Type II Diabetes Mellitus**

Liver metabolism is not only closely related to macrophage efferocytosis but also has a complex relationship with glucose homeostasis [84]. The liver is the control center of glucose metabolism in the human body and is also the organ that directly regulates blood glucose. The liver has a unique way of handling insulin, and it has two chances to degrade insulin: the first one is through the portal vein of the liver, where insulin can start to be degraded after entering the liver; and the second one is through the circulation, where the undegraded insulin can continue to be degraded in the liver, and about 75% of insulin can be degraded in the liver through these two ways [85]. Abnormalities in liver metabolism will inevitably lead to disturbances in insulin

metabolism, and there is no way to avoid decreased insulin clearance due to liver damage, decreased hepatic sensitivity to insulin, and an abnormal rate of insulin degradation.

Insulin is produced by pancreatic β-cells, and apoptotic β-cells are one of the major sources of diabetic autoantigens; in the pre-diabetic phase, high β-cell mortality or defective clearance of apoptotic cells promotes autoimmune 86, Type II diabetes mellitus (T2D), is a chronic metabolic disease whose pathogenesis is based on relative insulin deficiency due to pancreatic β-cell defects and insulin resistance. When pancreatic β-cell destruction occurs, extrahepatic IGF-1-producing pancreatic macrophages exert a cytosolic role to attenuate pancreatic islet inflammation and reduce insulin resistance (IR) [87]. Chenxi Zheng 's study [86] found that calreticulin (CRT) is a key "eat me" signal that mediates apoptotic vesicle (apoV) efferocytosis and macrophage regulation, and that CRT-mediated MSC-derived apoV can be phagocytosed by macrophages. CRT-mediated MSC-derived apoV can be phagocytosed by macrophages, and its efferocytosis contributes to the treatment of T2D, attenuates the T2D phenotype, and regulates hepatic macrophage function to maintain the homeostasis of the environment, which ameliorates hepatic steatosis and improves insulin sensitivity. This demonstrates that efferocytosis has a broad research perspective for the study of T2D and its complications.

## 6. Conclusions

In recent years, macrophage efferocytosis has gradually become a research hotspot, and researchers and scholars have deepened their understanding of its importance in disease development and tissue repair. efferocytosis is a complex process that involves the interactions of multiple molecules and signaling pathways, and plays a crucial role in maintaining homeostasis in vivo. A growing number of studies have shown that defective or abnormal mechanisms of efferocytosis are closely related to the onset and progression of many human diseases. For example, diseases such as atherosclerosis, systemic lupus erythematosus, obesity, rheumatoid arthritis, aging, cancer and diabetes mellitus have been found to be associated with abnormal efferocytosis. Therefore, the study of efferocytosis not only contributes to a deeper understanding of the pathogenesis of these diseases, but also has the potential to provide new ideas and methods for their treatment.

This review has shown in detail that in liver-related diseases, efferocytosis by macrophages phagocytosing apoptotic cells plays an indispensable role in maintaining the dynamic homeostasis of tissues in both alcoholic and non-alcoholic liver diseases. Moreover, a large number of studies have further confirmed the bidirectional regulation of efferocytosis in liver-related diseases, which is reflected in the fact that, on the one hand, activated macrophages maintain the homeostasis of the intracellular environment of the hepatocyte by removing apoptotic cells, which plays a protective and tissue repairing role; on the other hand, under certain conditions, macrophages may also release various inflammatory factors or chemokines, which are biologically active, and which can be used for the treatment of liver diseases. chemokines, and these bioactive substances may have a destructive effect on the surrounding tissues, such as liver fibrosis and hepatocellular carcinoma in which this bidirectional regulatory property exists.

Currently, the efforts of researchers have identified a large number of macrophage surface receptors that have tight binding relationships with specific growth and differentiation factors, receptor signaling pathways, and transcription factors that work together to regulate efferocytosis. This discovery provides new potential therapeutic strategies for liver inflammation-related diseases. However, despite this progress, it remains a major challenge to clarify how efferocytosis precisely targets specific tissue cell receptors in liver diseases and what complex transport systems are involved, which requires more scholars to devote themselves to the study of the dynamics of efferocytosis in the liver, aiming to provide more theoretical basis and design of clinical drugs. design, aiming to provide more theoretical basis and possibilities for clinical drug development and design. It is hoped that through in-depth research, more precise and effective therapeutic programs can be provided for patients with inflammatory diseases of the liver in the future.

## 7. Funding

This research was funded by Sichuan Provincial Science and Technology Departm, grant number No. 2021YFH0150; funded by Luzhou Science and Technology Bureau grant number No. 2021LZXNYD-Z09; funded by Sichuan Provincial Science and Technology Departm grant number No. 2022YFS0635.

## 8. Acknowledgments

We would like to thank Menglin Yao for searching the relevant literature and summarizing some of it, Hao Liu for his care and companionship during the writing process, Qixin Zhao for providing some ideas and suggestions, Ting Wang for compiling and summarizing the whole review, Hongping Shen and Dr. Sun for their revision suggestions after reading the article.

### References

1. Abdolmaleki F, Farahani N, Gheibi Hayat SM, Pirro M, Bianconi V, Barreto GE, et al. The Role of Efferocytosis in Autoimmune Diseases. Front Immunol. 2018; 9: 1645.
2. Morioka S, Maueröder C, Ravichandran KS. Living on the Edge: Efferocytosis at the Interface of Homeostasis and Pathology. Immunity. 2019; 50(5): 1149-62.
3. Mueller PA, Kojima Y, Huynh KT, Maldonado RA, Ye J, Tavori H, et al. Macrophage LRP1 (Low-Density Lipoprotein Receptor-Related Protein 1) Is Required for the Effect of CD47 Blockade on Efferocytosis and Atherogenesis-Brief Report. Arterioscler Thromb Vasc Biol. 2022; 42(1): e1-e9.
4. Weavers H, Martin P. The cell biology of inflammation: From common traits to remarkable immunological adaptations. J Cell Biol. 2020; 219(7).

5. Tao X. Research on biological immunity based intrusion detection method. Master. University of Electronic Science and Technology. 2013.
6. Poon IK, Lucas CD, Rossi AG, Ravichandran KS. Apoptotic cell clearance: basic biology and therapeutic potential. Nat Rev Immunol. 2014; 14(3): 166-80.
7. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. Immunity. 2010; 32(5): 593-604.
8. deCathelineau AM, Henson PM. The final step in programmed cell death: phagocytes carry apoptotic cells to the grave. Essays Biochem. 2003; 39: 105-17.
9. Farrera C, Fadeel B. Macrophage clearance of neutrophil extracellular traps is a silent process. J Immunol. 2013; 191(5): 2647-56.
10. Lauber K, Bohn E, Kröber SM, Xiao YJ, Blumenthal SG, Lindemann RK, et al. Apoptotic cells induce migration of phagocytes via caspase-3-mediated release of a lipid attraction signal. Cell. 2003; 113(6): 717-30.
11. Gude DR, Alvarez SE, Paugh SW, Mitra P, Yu J, Griffiths R, et al. Apoptosis induces expression of sphingosine kinase 1 to release sphingosine-1-phosphate as a "come-and-get-me" signal. Faseb j. 2008; 22(8): 2629-38.
12. Elliott MR, Chekeni FB, Trampont PC, Lazarowski ER, Kadl A, Walk SF, et al. Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance. Nature. 2009; 461(7261): 282-6.
13. Truman LA, Ford CA, Pasikowska M, Pound JD, Wilkinson SJ, Dumitriu IE, et al. CX3CL1/fractalkine is released from apoptotic lymphocytes to stimulate macrophage chemotaxis. Blood. 2008; 112(13): 5026-36.
14. Nishimura T, Horino K, Nishiura H, Shibuya Y, Hiraoka T, Tanase S, et al. Apoptotic cells of an epithelial cell line, AsPC-1, release monocyte chemotactic S19 ribosomal protein dimer. J Biochem. 2001; 129(3): 445-54.
15. Boada-Romero E, Martinez J, Heckmann BL, Green DR. The clearance of dead cells by efferocytosis. Nat Rev Mol Cell Biol. 2020; 21(7): 398-414.
16. Feng M, Chen JY, Weissman-Tsukamoto R, Volkmer JP, Ho PY, McKenna KM, et al. Macrophages eat cancer cells using their own calreticulin as a guide: roles of TLR and Btk. Proc Natl Acad Sci U S A. 2015; 112(7): 2145-50.
17. Naeini MB, Bianconi V, Pirro M, Sahebkar A. The role of phosphatidylserine recognition receptors in multiple biological functions. Cell Mol Biol Lett. 2020; 25: 23.
18. Fadok VA, Voelker DR, Campbell PA, Cohen JJ, Bratton DL, Henson PM. Exposure of phosphatidylserine on the surface of apoptotic lymphocytes triggers specific recognition and removal by macrophages. J Immunol. 1992; 148(7): 2207-16.
19. Birge RB, Boeltz S, Kumar S, Carlson J, Wanderley J, Calianese D, et al. Phosphatidylserine is a global immunosuppressive signal in efferocytosis, infectious disease, and cancer. Cell Death Differ. 2016; 23(6): 962-78.
20. Majeti R, Chao MP, Alizadeh AA, Pang WW, Jaiswal S, Gibbs Jr. KD, et al. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell. 2009; 138(2): 286-99.
21. Barkal AA, Brewer RE, Markovic M, Kowarsky M, Barkal SA, Zaro BW, et al. CD24 signalling through macrophage Siglec-10 is a target for cancer immunotherapy. Nature. 2019; 572(7769): 392-6.
22. Azuma Y, Nakagawa H, Dote K, Higai K, Matsumoto K. Decreases in CD31 and CD47 levels on the cell surface during etoposide-induced Jurkat cell apoptosis. Biol Pharm Bull. 2011; 34(12): 1828-34.
23. Gordon SR, Maute RL, Dulken BW, Hutter G, George BM, McCracken MN, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. Nature. 2017; 545(7655): 495-9.
24. Barkal AA, Weiskopf K, Kao KS, Gordon SR, Rosental B, Yiu YY, et al. Engagement of MHC class I by the inhibitory receptor LILRB1 suppresses macrophages and is a target of cancer immunotherapy. Nat Immunol. 2018; 19(1): 76-84.
25. Segawa K, Suzuki J, Nagata S. Constitutive exposure of phosphatidylserine on viable cells. Proc Natl Acad Sci U S A. 2011; 108(48): 19246-51.
26. Tsai RK, Discher DE. Inhibition of "self" engulfment through deactivation of myosin-II at the phagocytic synapse between human cells. J Cell Biol. 2008; 180(5): 989-1003.
27. Park SY, Kim IS. Engulfment signals and the phagocytic machinery for apoptotic cell clearance. Exp Mol Med. 2017; 49(5): e331.
28. Le AH, Yelland T, Paul NR, Fort L, Nikolaou S, Ismail S, et al. CYRI-A limits invasive migration through macropinosome formation and integrin uptake regulation. J Cell Biol. 2021; 220(9).
29. Szondy Z, Sarang Z, Kiss B, Garabuczi É, Köröskényi K. Anti-inflammatory Mechanisms Triggered by Apoptotic Cells during Their Clearance. Front Immunol. 2017; 8: 909.
30. Scannell M, Flanagan MB, deStefani A, Wynne KJ, Cagney G, Godson C, et al. Annexin-1 and peptide derivatives are released by apoptotic cells and stimulate phagocytosis of apoptotic neutrophils by macrophages. J Immunol. 2007; 178(7): 4595-605.
31. Rink J, Ghigo E, Kalaidzidis Y, Zerial M. Rab conversion as a mechanism of progression from early to late endosomes. Cell. 2005; 122(5): 735-49.
32. Asare PF, Roscioli E, Hurtado PR, Tran HB, Mah CY, Hodge S. LC3-Associated Phagocytosis (LAP): A Potentially Influential Mediator of Efferocytosis-Related Tumor Progression and Aggressiveness. Front Oncol. 2020; 10: 1298.
33. Yang CS, Lee JS, Rodgers M, Min CK, Lee JY, Kim HJ, et al. Autophagy protein Rubicon mediates phagocytic NADPH oxidase activation in response to microbial infection or TLR stimulation. Cell Host Microbe. 2012; 11(3): 264-76.
34. Shi J, Wu X, Wang Z, Li F, Meng Y, Moore RM, et al. A genome-wide CRISPR screen identifies WDFY3 as a regulator of macrophage efferocytosis. Nat Commun. 2022; 13(1): 7929.

35. Pidwill GR, Gibson JF, Cole J, Renshaw SA, Foster SJ. The Role of Macrophages in Staphylococcus aureus Infection. Front Immunol. 2020; 11: 620339.

36. Zhang W, Lang R. Macrophage metabolism in nonalcoholic fatty liver disease. Front Immunol. 2023; 14: 1257596.

37. Tan HY, Wang N, Li S, Hong M, Wang X, Feng Y. The Reactive Oxygen Species in Macrophage Polarization: Reflecting Its Dual Role in Progression and Treatment of Human Diseases. Oxid Med Cell Longev. 2016; 2016: 2795090.

38. O'Shea JJ, Paul WE. Mechanisms underlying lineage commitment and plasticity of helper CD4+ T cells. Science. 2010; 327(5969): 1098-102.

39. Schwabe RF, Tabas I, Pajvani UB. Mechanisms of Fibrosis Development in Nonalcoholic Steatohepatitis. Gastroenterology. 2020; 158(7): 1913-28.

40. Horwood NJ. Macrophage Polarization and Bone Formation: A review. Clin Rev Allergy Immunol. 2016; 51(1): 79-86.

41. Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, et al. Macrophage plasticity, polarization, and function in health and disease. J Cell Physiol. 2018; 233(9): 6425-40.

42. LI Ting, LIU Huabao, HU Wenyan, RAO Chunyan. The role of inflammation in liver fibrosis. - Journal of Clinical Hepatobiliary Disease. 2022; 38(10): 2368.

43. Lopez BG, Tsai MS, Baratta JL, Longmuir KJ, Robertson RT. Characterization of Kupffer cells in livers of developing mice. Comp Hepatol. 2011; 10(1): 2.

44. Karlmark KR, Weiskirchen R, Zimmermann HW, Gassler N, Ginhoux F, Weber C, et al. Hepatic recruitment of the inflammatory Gr1+ monocyte subset upon liver injury promotes hepatic fibrosis. Hepatology. 2009; 50(1): 261-74.

45. Mengqi L, Yi Z, Jia L. Exploration of the function of hepatic macrophages in tissue homeostasis and liver diseases. Advances in Pharmacology. 2018; 42(10): 723-36.

46. Heymann F, Tacke F. Immunology in the liver--from homeostasis to disease. Nat Rev Gastroenterol Hepatol. 2016; 13(2): 88-110.

47. Rothlin CV, Ghosh S, Zuniga EI, Oldstone MB, Lemke G. TAM receptors are pleiotropic inhibitors of the innate immune response. Cell. 2007; 131(6): 1124-36.

48. Lemke G, Rothlin CV. Immunobiology of the TAM receptors. Nat Rev Immunol. 2008; 8(5): 327-36.

49. Zagórska A, Través PG, Lew ED, Dransfield I, Lemke G. Diversification of TAM receptor tyrosine kinase function. Nat Immunol. 2014; 15(10): 920-8.

50. Zagórska A, Través PG, Jiménez-García L, Strickland JD, Oh J, Tapia FJ, et al. Differential regulation of hepatic physiology and injury by the TAM receptors Axl and Mer. Life Sci Alliance. 2020; 3(8).

51. Pop OT, Geng A, Flint E, Singanayagam A, Ercan C, Possamai L, et al. AXL Expression on Homeostatic Resident Liver Macrophages Is Reduced in Cirrhosis Following GAS6 Production by Hepatic Stellate Cells. Cell Mol Gastroenterol Hepatol. 2023; 16(1): 17-37.

52. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 2011; 141(5): 1572-85.

53. Wang M, You Q, Lor K, Chen F, Gao B, Ju C. Chronic alcohol ingestion modulates hepatic macrophage populations and functions in mice. J Leukoc Biol. 2014; 96(4): 657-65.

54. Das S, Maras JS, Hussain MS, Sharma S, David P, Sukriti S, et al. Hyperoxidized albumin modulates neutrophils to induce oxidative stress and inflammation in severe alcoholic hepatitis. Hepatology. 2017; 65(2): 631-46.

55. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, et al. Neutrophil extracellular traps kill bacteria. Science. 2004; 303(5663): 1532-5.

56. Bukong TN, Cho Y, Iracheta-Vellve A, Saha B, Lowe P, Adejumo A, et al. Abnormal neutrophil traps and impaired efferocytosis contribute to liver injury and sepsis severity after binge alcohol use. J Hepatol. 2018; 69(5): 1145-54.

57. Wang X, Bu HF, Zhong W, Asai A, Zhou Z, Tan XD. MFG-E8 and HMGB1 are involved in the mechanism underlying alcohol-induced impairment of macrophage efferocytosis. Mol Med. 2013; 19(1): 170-82.

58. Han Bing, Tu Chuantao. The role of hepatic macrophages in hepatic fibrosis formation in NASH patients and its progress in clinical translational research. Journal of Practical Liver Disease. 2022; 25(03): 309-313.

59. Gao H, Jin Z, Bandyopadhyay G, Rocha KCE, Liu X, Zhao H, et al. MiR-690 treatment causes decreased fibrosis and steatosis and restores specific Kupffer cell functions in NASH. Cell Metab. 2022; 34(7): 978-990.e4.

60. Hammerich L, Tacke F. Hepatic inflammatory responses in liver fibrosis. Nat Rev Gastroenterol Hepatol. 2023; 20(10): 633-646.

61. Wang T, Ma C. The hepatic macrophage pool in NASH. Cell Mol Immunol. 2021; 18(8): 2059-60.

62. Seidman JS, Troutman TD, Sakai M, Gola A, Spann NJ, Bennett H, et al. Niche-Specific Reprogramming of Epigenetic Landscapes Drives Myeloid Cell Diversity in Nonalcoholic Steatohepatitis. Immunity. 2020; 52(6): 1057-74.e7.

63. Wang X, He Q, Zhou C, Xu Y, Liu D, Fujiwara N, et al. Prolonged hypernutrition impairs TREM2-dependent efferocytosis to license chronic liver inflammation and NASH development. Immunity. 2023; 56(1): 58-77.e11.

64. Kim KH, Cheng N, Lau LF. Cellular communication network factor 1-stimulated liver macrophage efferocytosis drives hepatic stellate cell activation and liver fibrosis. Hepatol Commun. 2022; 6(10): 2798-811.

65. An P, Wei LL, Zhao S, Sverdlov DY, Vaid KA, Miyamoto M, et al. Hepatocyte mitochondria-derived danger signals directly activate hepatic stellate cells and drive progression of liver fibrosis. Nat Commun. 2020; 11(1): 2362.

66. Zhan SS, Jiang JX, Wu J, Halsted C, Friedman SL, Zern MA, et al. Phagocytosis of apoptotic bodies by hepatic stellate cells induces NADPH oxidase and is associated with liver fibrosis in vivo. Hepatology. 2006; 43(3): 435-43.

67. Canbay A, Taimr P, Torok N, Higuchi H, Friedman S, Gores GJ. Apoptotic body engulfment by a human stellate cell line is profibrogenic. Lab Invest. 2003; 83(5): 655-63.

68. Arandjelovic S, Ravichandran KS. Phagocytosis of apoptotic cells in homeostasis. Nat Immunol. 2015; 16(9): 907-17.
69. Brenig R, Pop OT, Triantafyllou E, Geng A, Singanayagam A, Perez-Shibayama C, et al. Expression of AXL receptor tyrosine kinase relates to monocyte dysfunction and severity of cirrhosis. Life Sci Alliance. 2020; 3(1).
70. N AG, Bensinger SJ, Hong C, Beceiro S, Bradley MN, Zelcer N, et al. Apoptotic cells promote their own clearance and immune tolerance through activation of the nuclear receptor LXR. Immunity. 2009; 31(2): 245-58.
71. Zapater P, Francés R, González-Navajas JM, de la Hoz MA, Moreu R, Pascual S, et al. Serum and ascitic fluid bacterial DNA: a new independent prognostic factor in noninfected patients with cirrhosis. Hepatology. 2008; 48(6): 1924-31.
72. Seitz HM, Camenisch TD, Lemke G, Earp HS, Matsushima GK. Macrophages and dendritic cells use different Axl/Mertk/Tyro3 receptors in clearance of apoptotic cells. J Immunol. 2007; 178(9): 5635-42.
73. Fourcot A, Couchie D, Chobert MN, Zafrani ES, Mavier P, Laperche Y, et al. Gas6 deficiency prevents liver inflammation, steatohepatitis, and fibrosis in mice. Am J Physiol Gastrointest Liver Physiol. 2011; 300(6): G1043-53.
74. Guicciardi ME, Trussoni CE, Krishnan A, Bronk SF, Pisarello MJL, O'Hara SP, et al. Macrophages contribute to the pathogenesis of sclerosing cholangitis in mice. J Hepatol. 2018; 69(3): 676-86.
75. Scott RS, McMahon EJ, Pop SM, Reap EA, Caricchio R, Cohen PL, et al. Phagocytosis and clearance of apoptotic cells is mediated by MER. Nature. 2001; 411(6834): 207-11.
76. Chen R, Huang B, Lian M, Wei Y, Miao Q, Liang J, et al. A+T rich interaction domain protein 3a (Arid3a) impairs Mertk-mediated efferocytosis in cholestasis. J Hepatol. 2023.
77. Brightwell RM, Grzankowski KS, Lele S, Eng K, Arshad M, Chen H, et al. The CD47 "don't eat me signal" is highly expressed in human ovarian cancer. Gynecol Oncol. 2016; 143(2): 393-397.
78. Zhao Y, Wei K, Chi H, Xia Z, Li X. IL-7: A promising adjuvant ensuring effective T cell responses and memory in combination with cancer vaccines? Front Immunol. 2022; 13: 1022808.
79. Zhou Y, Yao Y, Deng Y, Shao A. Regulation of efferocytosis as a novel cancer therapy. Cell Commun Signal. 2020; 18(1): 71.
80. Liu N, Wang X, Steer CJ, Song G. MicroRNA-206 promotes the recruitment of CD8(+) T cells by driving M1 polarisation of Kupffer cells. Gut. 2022; 71(8): 1642-1655.
81. Robertson CL, Mendoza RG, Jariwala N, Dozmorov M, Mukhopadhyay ND, Subler MA, et al. Astrocyte Elevated Gene-1 Regulates Macrophage Activation in Hepatocellular Carcinogenesis. Cancer Res. 2018; 78(22): 6436-6446.
82. Robertson CL, Srivastava J, Siddiq A, Gredler R, Emdad L, Rajasekaran D, et al. Genetic deletion of AEG-1 prevents hepatocarcinogenesis. Cancer Res. 2014; 74(21): 6184-93.
83. Xu K, Liu Y, Luo H, Wang T. Efferocytosis signatures as prognostic markers for revealing immune landscape and predicting immunotherapy response in hepatocellular carcinoma. Front Pharmacol. 2023; 14: 1218244.
84. Zheng C, Sui B, Zhang X, Hu J, Chen J, Liu J, et al. Apoptotic vesicles restore liver macrophage homeostasis to counteract type 2 diabetes. J Extracell Vesicles. 2021; 10(7): e12109.
85. Meier JJ, Veldhuis JD, Butler PC. Pulsatile insulin secretion dictates systemic insulin delivery by regulating hepatic insulin extraction in humans. Diabetes. 2005; 54(6): 1649-56.
86. Mathis D, Vence L, Benoist C. Beta-Cell death during progression to diabetes. Nature. 2001; 414(6865): 792-8.
87. Nackiewicz D, Dan M, Speck M, Chow SZ, Chen YC, Pospisilik JA, et al. Islet Macrophages Shift to a Reparative State following Pancreatic Beta-Cell Death and Are a Major Source of Islet Insulin-like Growth Factor-1. iScience. 2020; 23(1): 100775.