



## The Role of Different Macrophage Phenotypes in the Pathogenesis of Liver Diseases and the Possibility of Their Use in Regenerative Medicine

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### Abstract

According to modern literature, macrophage liver representation has two populations: tissue macrophages or Kupffer cells, and infiltrating monocytes/macrophages. They differ in their origin, functions, mechanisms of maintaining their own numbers and play a significant role in the pathogenesis of liver pathologies. Kupffer cells are self-renewing, resident, and predominantly non-migrating phagocytes. Liver damage causes their activation, which leads to the secretion of the inflammatory cytokines and chemokines. This promotes the recruitment of monocytes to the liver and the emergence of a large number of inflammatory infiltrating macrophages. Kupffer cells and macrophages possess properties of plasticity and adapt their phenotype in accordance with the signals of the microenvironment. It is about their diverse and anti-inflammatory function in liver diseases. It is believed that they control inflammation, fibrosis, angiogenesis, tumor growth, tissue repair organ, and monitor the occurrence of the tumor. Data obtained in animal models and early clinical trials, patients with steatohepatitis and fibrosis demonstrate that the sight on the macrophages of the liver may be a promising therapeutic approach in acute and chronic liver diseases. Of particular interest this marks a controlled reprogramming of macrophages. This makes them a promising goal in the development of new therapeutic strategies for the treatment of liver pathologies.

**Keywords:** Liver; Kupffer Cells; Macrophages; Inflammation; Fibrosis; Hepatitis; Ocellular Carcinoma

### Introduction

The first successful liver transplant was performed in 1967. Since then, liver transplantation has become the most successful method of treating acute liver failure and end-stage disease of an organ, but the lack of donors is a problem to be solved. Regenerative medicine offers new approaches to the treatment of liver diseases, based on the significant success of basic and biomedical research over the last 20-30 years. Obviously, the scientific basis of cell therapy of liver diseases and tissue and organ engineering

should be provided by studying cellular and molecular mechanisms of organ regeneration under physiological conditions (homeostatic regeneration), during an enhanced functional load (adaptive regeneration) or after injury (turnip activation regeneration) [1-3].

The liver consists of several cell types: hepatocytes, cholangiocytes, perisinusoidal cells (Ito cells), stellate macrophages (Kupffer cells), endothelial cells, hepatic NK cells, oval cells, and hepatic stem cells [1,3]. Recent studies have shown that liver macrophages are

represented by two populations: tissue or resident macrophages and infiltrating monocytes/macrophages. They differ in origin, functions, mechanisms to maintain the number and play so important a role in the pathogenesis of liver pathologies. Of particular interest is the controlled reprogramming of macrophages. This makes them a promising goal in the development of new therapeutic strategies for the treatment of liver pathologies [4,5]. This article proposes a distinction between resident macrophages, called Kupffer cells, and infiltrating monocytes, called macrophages.

The goal is to compile modern scientific data in the study of liver macrophages, identify problems and prospects for their further study and use in regenerative medicine.

### Resident macrophages or Kupffer cells

Stellar macrophages were first described by a German anatomist and histologist KW Kupffer in 1876. After 22 years, they were reopened by the Polish pathologist T. Browicz, who identified them as phagocytic cells of the liver capillaries. In 1974, E. Wisse, using electron microscopy, identified resident sinusoidal macrophages of the liver and called them Kupffer cells [1,6,7].

Modern methods of ontogenesis research refute the fact that the pool of Kupffer cells is constantly replenished by monocytes of bone marrow origin. Kupffer cells are believed to originate from the yolk sac erythromyeloid precursors, acquire tissue-specific characteristics, and maintain their numbers by proliferating *in situ*. There is evidence in the literature that Kupffer cells originate in the liver from local precursor [8,9]. Ability to self-renew cells are strictly controlled by transcription factors MAFB. Until now, the embryonic precursors of these cells have not been established, and the mechanisms supporting the Kupffer cell population in adult organisms have not been determined. This problem has practical implications in clinical situations such as liver and bone marrow transplantation. Determining the source and pathways of differentiation of tissue macrophages will clarify the role of these cells in liver pathologies and will allow the development of new treatments focused on macrophages.

K cells upfera localized in sinusoidal capillaries and are able to migrate along the endothelial cells, which allows them to effectively remove foreign pathogens entering the liver. They serve as the first line of defense against immunoreactive material coming from the gastrointestinal tract, and can be considered as the final

component that complements the barrier function of the intestine [3,9,10]. Their amount in the liver is strictly maintained. However, the mechanisms of this control and the fate of the cell are not fully understood. In the liver of intact mice claim Rothe many analysis revealed tsirkad hydrochloric regulation of not only Kupffer cells but also path components of the immune response (Tlr4, Myd88, Irak4 and Tak1), which are reaching a maximum during the daytime. There are contradictions elations in a lifetime Kupffer cells. Studies in animals deprived of Kupffer cells (in the experiment used a substance disodium clodronate) showed that their change in the liver occurs within 14-21 days. Other studies indicate a longer period (from one month to three or more). It is assumed that cell turnover is associated with a programmed death. cells (apoptosis), and/or migration to other destinations, such as lymph nodes [8,11,12]. Kupffer mouse cells express markers CD 11 b +, CD 68 +, F 4/80 ++, CLEC 4 f +, TIM 4 +, TLR 4 +, TLR 9 +, CR1g +. The phenotype of human Kupffer cells less oharakter izovan than animals, as most researchers in their work do not distinguish between Kupffer cells and infiltrating monocytes/macrophages. In humans, they can be identified by the expression of CD68 +, CD14 +, TLR4 +. It was revealed that Kupffer's cells of humans and rodents do not express CX<sub>3</sub> CR1 [3].

According to modern literature, Kupffer's cells have the property of plasticity, changing their phenotype and function in response to signals from the microenvironment. The cc change phenotype is called reprogramming, polarization, activation, or an alternative phenotype [13-15]. Plasticity allows Kupffer cells to acquire a wide range of functions from pro-inflammatory (M1, or classically activated macrophages) to anti-inflammatory (M2, or alternatively activated macrophages). Despite the widespread use of the M1/M2 classification, there are currently no standards for describing cell activation.

M 1 phenotype cell Kupfera characterizing tsya elevated expression pro-inflammatory cytokines (IL -1, IL- 6, IL- 12, IL -15, IL- 18, IL- 23, IL -1 β), factor necrosis tumors alpha (TNF - α), interferon gamma (INF - γ), inducible NO - synthetase (iNOS), active forms oxygen. These substances trigger the processes of inflammation and damage to the liver. IL-6 induces the proliferation of hepatocytes and cholangiocytes and can lead to carcinogenesis through the activation of PI3K, Ja k-STAT and MAPK signaling pathways. Active oxygen species cause damage to the endoplasmic reticulum

of hepatocytes apoptosis, liver steatosis, inflammation. M1 macrophages express a number of chemokines CXCL9, CXCL10, CXCL11, CCL2, CCL3 and CCL5 [16-18].

The M2 phenotype of Kupffer cells demonstrates low expression of pro-inflammatory cytokines, but increased expression of anti-inflammatory mediators (IL4, IL10, IL13), transforming growth factor- $\beta$  (TGF -  $\beta$ ), matrix metalloproteinases-9, -12, -13 (MMPs), vascular endothelial growth factor (VEGF), arginase-1 and a number of chemokines (CCL 13, CCL 14, CCL22, CCL23, CCL24). Depending on the functions performed and the synthesizing substances, M2 is divided into subtypes: M2a, M2b and M2c [19-21].

Experimental data show that the balance between M1/M2 cell types may be key in the pathogenesis pathologies of the liver. In BALB/c mice that have dominant macrophages of type M2, steatosis and liver inflammation are weakened compared with C57BL/6 mice (dominant M1 type) [8,22]. Another study using BALB/c and C57BL/6 mice showed that M2 cells induce M1 cell apoptosis through IL-10 secretion and regulate the M1/M2 balance, which leads to protective effects. This suggests that activation of M2 cells and regulation of the M1/M2 balance can be a potential target for treating liver pathologies. Understanding the exact mechanisms of regulation of the ratio of these cells requires careful study. Over the past decade, the method of *in vitro* several key macrophage balance regulators were identified: a family of signal transducers and transcription activators STAT; nuclear receptor PPAR $\gamma$ , activated by peroxisome proliferators and functioning as a transcription factor; family of CCAAT/enhancer-binding proteins (C/E BP). Recent studies have shown that miRNA (miRNA) and for other non-coding RNA (lncRNA) affect the polarization of macrophages. MiR-124 deactivates Kupfer cells, miR-155 inhibits the polarization of the M2 phenotype, and miR-223 inhibits the polarization of the M1 phenotype [23-25]. It was revealed that Kruppel - like factor 4 (KLF4) contributes to the polarization of Kupffer cells in the M1 phenotype, thereby increasing the severity of alcohol- induced liver damage [12].

Recently, evidence has accumulated indicating the existence of intermediate phenotypes of Kupffer cells, which do not correspond to either M1 or M2 type. SAMs macrophages associated with spontaneous resolution of liver fibrosis were detected in experimental

animals. This type of cell expresses high levels of anti- fibrotic cytokines, TGF- $\beta$  and platelet-derived growth factor: (PDGF) [23,26-28]. Another identified Kupffer cell phenotype is associated with hepatocarcinoma. Tumor- associated macrophages preferentially express the M2 phenotype and are characterized. increased expression of VEGF, MMPs and growth factors (FGF, HGF, PDGF). An experimental study demonstrated that, under certain conditions, Kupffer cells of the M1 type can stimulate inflammatory reaction secreting IL10 and VEGF. Based on these data, the M3 phenotype was proposed, combining the M1 and M2 types [28,29].

Initially M1/M2 classification was based on experiments showing that macrophages derived from monocytes can differentiate towards M1 cells with interferons  $\gamma$  or M2 direction via IL -4. This leads to typical cytokine response profiles [30]. Recently, *in vitro* method n When exposed to macrophages diverse signals [cytokines, fatty acids, etc. prostaglandins, lipopolysaccharide, heat shock proteins (HSP), the protein band high mobility box 1 (HMGB1, amphoterine) etc.] identified by Okiyo range of activation conditions that do not meet t polarization M1/M2 [31,32]. Data on the regulation of Kupffer cells by phenotype *in vivo* practically absent.

Obviously, the binary classification is untenable and requires revision. It does not take into account the complex *in vivo* heterogeneity, where Kupffer cells take on different phenotypes in response to the many stimuli to which they are subjected. These phenotypes cannot be accurately reproduced in tissue culture models, and this indicates the need for research *in vivo*. Protocols should be developed to describe the activation of macrophages, to which matured will include reproducible experimental standards (description of experimental conditions, genetic background animal model of the particular disease, cell separation techniques, the isolation and analysis methods), ontogeny macrophages minimum reporting standards, activators and activation markers.

### Monocytes bone marrow origin

When n p resulting damage liver irkuliruyuschie bone marrow-derived monocytes were actively recruited into the liver. It is known that the rate of inflow of peripheral monocytes to the liver is higher than in other organs [4,7,27]. In animals, the expression of Ly6c is used to characterize populations of circulating monocytes and macrophages. Two subtypes of circulating monocytes were revealed: classical Ly6c<sup>hi</sup> (Ly-6c<sup>high</sup>) and nonclassical

Ly6c<sup>lo</sup> (Ly-6c<sup>low</sup>). Ly6c<sup>hi</sup> characterized as CD11b + CCR2 ++ CX3CR1 + iNOS + TNF + CD4 - cells and have pro-inflammatory M1 similar phenotype. Ly6c<sup>lo</sup> defined as CD11b + CCR2 + CX3CR1 ++ CD206 + MMP9 + MMP12 + cells and can play an anti-inflammatory role (M2-like phenotype) [33,34].

The origin of non-classical monocytes Ly6c<sup>lo</sup> is a subject of controversy among researchers. I suppose that the more mature phenotype Ly6c<sup>lo</sup> can develop from Ly6c<sup>hi</sup> monocytes, and their conversion, probably occurs in the bone marrow. This process is regulated by CCAAT/enhancer-binding protein  $\beta$ . However, there are experimental data showing that Ly6c monocytes are<sup>lo</sup> occur in the bone marrow from other progenitors, regardless of Ly6c<sup>hi</sup>. Lifespan Ly6c<sup>lo</sup> monocytes controlled Ly6c<sup>hi</sup> monocytes peripheral blood [35,36].

Monocytes people not express Ly6c. They are classified comfort of CD14 and CD16 expression. Monocytes CD14 ++ CD16 - make up 95% and express CCR2, CD62L (L-selectin), Fc $\gamma$ RI (CD64), CLEC5A +, S100A9. CD14 - CD16 + monocytes express MHC-II, Fc $\gamma$ RII (CD32), CD163 +, CCR2 +, CX<sub>3</sub>CR1 ++, Stabilin-1 + and they account for about 15%. Monocytes of mouse Ly6c<sup>hi</sup> are assumed to be analogous to CD14 ++ CD16 - human monocytes, and Ly6c<sup>lo</sup> - analogues of CD14 - CD16 + [37]. Transcriptome analysis of human monocytes cultured with various stimuli (cytokines, fatty acids, lipopolysaccharides, etc.), Revealed a range of states of activation of macrophages, which do not correspond to either M1 or M2 type (intermediate phenotype CD14 + CD16 +) [28]. Probably, the signals received by macrophages in their local microenvironment are diverse and dynamic in time and space. Macrophages not only correspond to different phenotypes, but can reversibly switch from one type to another.

#### By notch and Kupfer and macrophages for liver damage

Each large number of receptors allows Kupffer cells to respond to a wide range of molecular fragments of substances associated with damage (DAMPs). The DAMPs family of proteins include HSP, HMGB1, S100-calcium binding protein-A8/A9 (S100A8/9), extracellular matrix proteins. Activated Kupffer cells and pathogens associated molecular patterns (PAMPs), such as lipopolysaccharide and flagellin. PAMPs mainly come from the intestines and are important inducers of inflammatory processes [38,39].

The injury of hepatocytes and monocytes leads to the release of DAMPs. They are perceived by Kupffer cells through toll-like receptors (TLR1, TLR2, TLR3 and TLR4), purinergic receptors (P2X), receptors of the final glycation products (RAGE) and are activated in the M1 phenotype. At the onset of damage, the number of Kupffer cells decreases. This is probably due to the influx of a large number of infiltrating monocytes Ly6c<sup>hi</sup>. Monocytes are believed to be recruited through the interactions CCR2/CCL2, CXCR3/CXCL10, CCR1/CCL5 and CCR8/CCL1 [40]. One of the main sources of CCL2 is Ito cells, which are activated by the TLR4 ligand and direct the recruitment of monocytes [14]. People migrating monocytes probably associated with the activation of the receptor and Kupffer cells CX3CR1 endothelial ligand CX3CL1 [13].

The interaction of a CCR2/CCL2 and/or CCR8/CCL1 affects the ratio of Ly6c<sup>hi</sup> and Ly6c<sup>lo</sup>. By the immunohistochemical method, it was revealed that Ly6c<sup>hi</sup> monocytes form a ring around the damaged tissue site to determine the extent of the damage. Then they differentiate into monocytes Ly6c<sup>lo</sup>, which contribute to tissue repair. At an early stage of liver damage in animals, monocyte migration from the peritoneum through the mesothelium was observed. The contribution of these cells to the pathogenesis of the disease is currently unknown [41,42]. Thus, the local polarization and recruitment of macrophages from other places, probably, is so important a receptacle in the pathogenesis of the disease.

A large number of macrophages of the intermediate phenotype CD14 + CD16 + was detected in the damaged liver of patients. Perhaps this is due to the increased ability of these cells to migrate through with sinusoidal endothelial cells (LSEC). CD14 + CD16 + cells show high phagocytic activity, secrete proinflammatory and fibrogenic mediators. Identified in uncontrolled migration of macrophages, which affects the local balance of inflammatory and anti-inflammatory cells. Phenotype CD14 - CD16 + undergoes a reverse migration from the liver to the bloodstream through the LSEC and may contribute to systemic inflammatory reactions, while CD14 ++ CD16 - cells remain in the liver [43,44].

Upon the termination of the effect of the damaging substance Ly6c<sup>hi</sup>, macrophages transform into the anti-inflammatory phenotype Ly6c<sup>lo</sup>. Possibly, a warning light and inflammation in tissue repair associated with a polarization dependent macrophages

and T from the colony stimulating factor 1 (CSF1), an inhibitor of leukocyte proteases (SLPI) in necrotic areas. The phenotype of CCR2<sup>lo</sup> CX3CR1<sup>hi</sup> cells secretes VEGF-A, which helps to restore vascular architecture and increases the phagocytic ability of cells [13,35,45].

On the model of acute liver damage, it has been shown that macrophages form phenotypically and functionally different subsets that are not dependent on Kupffer cells. Other studies have found that when Kupffer cells are depleted during liver damage, macrophages populate a free niche and acquire the Kupffer cell phenotype [12,16]. Consequently, regardless of the cell origin, the liver microenvironment provides decisive factors determining the functional phenotype of the cells. It is necessary to take into account the fact that these observations were made on models with experimental depletion of Kupffer cells.

A long cycle of recurring outbreaks of tissue damage and inflammation underlies chronic liver disease leading to fibrosis, cirrhosis and, in some patients, hepatocellular carcinoma. Liver fibrogenesis was previously considered as a unidirectional process. At present, there is evidence that even progressive fibrosis and in some cases cirrhosis of the liver are partially reversible. This concept has been demonstrated both in experimental models of chronic liver damage, and in human liver diseases. In humans, the successful treatment of chronic viral hepatitis can lead to a marked improvement in the structure of the liver, which indicates that the liver has the potential to regenerate and remodeling scar tissue [16,22,27].

During chronic damage, the macrophages of Ly6c<sup>hi</sup> activate Ito cells, which are transformed into collagen-producing myofibroblasts [14]. An experimental study of fibrosis revealed the opposite functions of macrophages. Selective depletion of macrophages in transgenic mice not only prevented the development of fibrosis in chronic damage, but also delayed recovery processes after the cessation of damage [37]. Analysis of RNA sequencing data showed that Ly6c<sup>hi</sup> enhance fibrosis, while Kupffer cells activate pathways associated with the initiation of inflammation and lipid metabolism. Fibrogenic macrophages can switch their phenotype towards the reducing macrophage Ly-6c<sup>lo</sup> which are characterized by high expression of anti-inflammatory IL and MMPs -9, MMPs -12, MMPs -13 [8,22].

Recently, research has demonstrated the importance of the chemokine receptor CCR2 and its monocytic ligand - chemoattractant protein 1 (MCP-1/CCL2) in experimental liver fibrosis [41]. The experiment showed that pharmacological inhibition of CCR2 or MCP-1 (via mNOX-E36) reduces the migration of Ly6c<sup>hi</sup> monocytes *in vitro* and *in vivo* [44]. In CCR8-deficient mice, a significant decrease in liver fibrosis was shown in two independent experimental models. Interestingly, in mice, the profibrogenic effect of infiltrating monocytes depends on the genetic background. BALB/c mice, which by their nature are dominated by Th2 immune responses, are more protected against liver damage and subsequent fibrosis due to impaired monocyte infiltration than C57BL/6 mice with a predominant Th1 immune response. This indicates that polarization of M1 and M2 can directly affect the outcome of the disease in chronic liver damage [46]. Functional switching mechanisms require further research aimed at study of the dynamics of recruitment and the role of these macrophages in liver damage to develop therapeutic strategies directed towards these cell phenotypes.

In an experimental study of chronic liver damage, it was found that uptake of hepatocyte residues by macrophages induces the expression of Wnt3a (canonical protein of the Wnt signaling pathway). This contributes to the differentiation of progenitor cells of the liver towards functional hepatocytes [36]. Introduction of bone marrow occurrence to intact animals stimulates the proliferation of liver progenitor cells, the so-called ductal response, releasing the cytokine TWEAK (TNF-like weak inducer of apoptosis). In experimental models of hepatotoxicity with acetaminophen, it was shown that inhibition of TLR2, TLR3, TLR4, HMGB-1 and the purinergic receptor P2X7 reduces liver damage [39].

Transferring experimental results to patients is not an easy task. The gene profiles show an overlap between Ly6c<sup>hi</sup>/Ly6c<sup>lo</sup> mouse macrophages and CD14<sup>++</sup>CD16<sup>-</sup>/CD14<sup>-</sup>CD16<sup>+</sup> human macrophages. At the same time, clear functional differences were revealed. It is difficult to integrate intermediate CD14<sup>+</sup>CD16<sup>+</sup> phenotype into the nomenclature of animals. It should be noted that human CD16<sup>+</sup> monocytes can directly activate Ito cells. In rodent models not revealed fibers of connective tissue, surrounding almost all hepatocytes observed in patients with advanced fibrosis. This is probably due to the rapid resolution of fibrosis in rodents compared with humans. Despite these differences, there are paral-

lels between animals and humans. CCL2/CCR2 plays a similar role in fibrosis and filtration of macrophages in the livers of patients and animals [46-50].

The role of macrophages in cholestatic liver diseases has not been fully studied. H arushenie regulation of secretion and excretion of bile acids affects the function and differentiation of macrophages. In experimental animal models, bile acids have been shown to contribute to the activation of proinflammatory macrophages [48]. In mice lacking bile acid transporter *MDR2 (Abcb4)*, I develop tsya hepatobiliary inflammation and fibrosis with some, but not all, features of n ervichnogo biliary cholangitis and. The process involves the accumulation of peribiliary proinflammatory macrophages recruited in response to secretion by cholangiocytes IL-8 and CCL2. Pharmacological treatment of mice with the antagonist CCR2/CCR5 cenicriviroc reduced macrophage infiltration and liver damage. By Kupfer's yearlings, the bile acid receptor associated with G-protein Gpbar1 (TGR5) is expressed. Effects of bile acids on TGR5 improves kro in snab voltage liver and increases its regenerative potential [38,40,48,51]. Pharmacological activation of the pathway may have therapeutic potential for the treatment of cholestatic liver disease.

Studies of recent years have shown the role and ssotsiirovannyh tumor macrophages (TAMs) in the development of hepatocellular carcinoma. In the context of liver carcinogenesis, macrophages exhibit dualistic functions. Monocytes of the phenotype CCR2 + CCL2 - monitor the occurrence of a tumor by eliminating aging precancerous hepatocytes in a healthy liver. AT tumors monocytes are reprogrammed into a type that inhibits the function of NK cells, which leads to tumor growth [49-56]. TAMs are the dominant cellular component of the human tumor stroma. The increased density of TAMs along the edge of the tumor correlates with a poor prognosis for patient survival. Expressed by macrophages retse ptor TREM-1 regulates secretion iju proinflammatory mediators and starts carcinogenesis. In the experiment in mice with deficiency TREM - 1 hepatocellular malar carcinoma did not develop. Kupffer secretion was attenuated by pro-inflammatory cytokines and inhibition of signaling pathways (p38, ERK1/2, JNK, MAPK and NF-κB) that regulate inflammation [57,58]. TAMs for chemokine and cytokine secretion are similar to alternatively activated M2 type macrophages. Consequently, substances secreted by macrophages, Kupffer cells and TAMs overlap. It is believed that Kupffer cells, in

response to signals from the start- bath tumor, contribute to its development in the early stages, whereas monocytes/macrophages - in the later stages, including the formation of metastases [59]. The recruitment of monocytes during hepatocellular carcinoma is likely to depend on tumor-associated neutrophils, Kupffer cells and aging hepatocytes. And the nfilter monocytes enhance the expression of S100A8 and S100A9 tumor cells. This is associated with an increase in the formation of tumor metastases. In addition, the bond Tumor macrophages can reconstruct the extracellular matrix, which contributes to the formation of a tumor in the niches of the collagen matrix. The flight and molecular mechanisms of progression of hepatocellular carcinoma in patients have yet to be discovered [50,59].

### Conclusions and Perspectives

Kupffer cells and macrophages are an attractive target when developing new therapeutic strategies for the treatment of liver diseases. However, p azrabotka Face the macrophage therapy is a C specific difficulties.

Most of the knowledge about the plasticity of macrophages obtained by *in vitro*. They have been analyzed in detail only by the use of etry cytoocyte. Role of roll stands approx Coop Fehr often study using liposomes loaded clodronate m (a substance that temporarily depletes T cells by Kupffer), gadolinium chloride (a substance which reduces the number of Kupffer cells). An *in vivo* immunohistochemical study of macrophages provides unique and additional information on b their localization in natural conditions. It is possible that current definitions of various subtypes of liver macrophages include populations of functionally different cells. The distribution of various phenotypes in the diseased liver with various pathologies still before the end has not been studied. M ap Kery and gene expression profiles are yet to be decoded.

The functional differences between macrophage subtypes are not fully understood. It is not known how macrophages affect the outcome of liver disease. In recent years, research has mainly focused on the activation and polarization of macrophages derived from monocytes. At the same time, etc. of still unclear whether the stage of polarization are stable or transient activation state, explain whether they are functional and phenotypic heterogeneity of macrophages *in vivo* in a state of normal and pathological conditions, and as such there is a polarized state. Complex and thorough re-

search is needed, before new therapeutic agents aimed at infiltration or polarization of macrophages are included in clinical trials.

There are problems that must be overcome in relation to experimental studies. Experimental models often reflect only certain aspects of pathogenesis (inflammation and fibrosis) and rarely include the full range of etiological mechanisms. Moreover, they develop faster than human diseases. This affects the adaptation of macrophages to damage. It must be remembered that patients are more heterogeneous, than inbred lines of mice, with respect to internal (genetics, gender, age, comorbidities) and external (diet, infections) factors that may influence the activation of macrophages.

One obstacle in the development of new treatments is a significant lack of data on liver macrophages in humans. This is due to the limited access to the tissue of human at different stages. Zabol Evan and, as a consequence, difficult analysis of subtypes of macrophages *in vivo*. Heterogeneous and partially overlapping functional subtypes of human macrophages and animals require further exploration.

Despite the difficulties, it is safe to say that Kupffer cells and macrophages in perspective can be used in the development of new therapeutic strategies for the treatment of liver pathologies. These will include: weakening the activation of Kupffer cells; inhibiting the recruitment of macrophage progenitor cells (i.e., monocytes) to the damaged liver; manipulation of polarization and differentiation of Kupffer cells and macrophages for the transition to a restorative reparative phenotype; infusion of pro-inflammatory macrophages.

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