DOI: https://doi.org/10.17816/gc610252

Баланс иммунных клеток как потенциальный биомаркёр прогрессирования неалкогольной жировой болезни печени

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АННОТАЦИЯ

Неалкогольная жировая болезнь печени (НАЖБП) — широко распространённое хроническое, медленно прогрессирующее метаболическое многофакторное заболевание, представленное рядом клинико-морфологических форм: стеатозом, неалкогольным стеатогепатитом (НАСГ) (с фиброзом или без него) и циррозом печени. Поиск малоинвазивных и экономически эффективных биомаркёров НАЖБП является ключевой задачей в диагностике, стадировании прогрессирования и долгосрочном мониторинге НАЖБП. Обсуждается возможность использования баланса иммунных клеток в качестве потенциальных малоинвазивных периферических маркёров прогрессирования НАЖБП. В прогрессировании НАСГ (от стеатоза к фиброзу и циррозу) важную роль играет воспаление, реализующееся за счёт активации клеток Купфера и повышенной миграции моноцитов, дендритных клеток, нейтрофилов, активированных Т-лимфоцитов в ткани органа. Макрофаги, происходящие из моноцитов, по мере прогрессирования НАСГ постепенно начинают преобладать над пулом резидентных макрофагов. Риск развития НАСГ и фиброза у пациентов с НАЖБП повышается с увеличением соотношения нейтрофилов/лимфоцитов в печени. Увеличение количества Th17 и снижение — Treg-клеток могут способствовать усилению стеатоза печени и развитию воспаления при НАЖБП, а также ускорять переход от простого стеатоза к стеатогепатиту и фиброзу. Представлены сведения об участии некодирующих РНК в регуляции баланса иммунных клеток при НАЖБП, что позволяет также рассматривать их как дополнительные, наряду с клеточными, маркёры прогрессирования данного заболевания.

Ключевые слова: неалкогольная жировая болезнь печени; биомаркёры НАЖБП; фиброз печени; иммунные клетки.

Как цитировать:
Топчиева Л.В., Курбатова И.В., Дуданова О.П., Васильева А.В., Жулай Г.А. Баланс иммунных клеток как потенциальный биомаркёр прогрессирования неалкогольной жировой болезни печени // Гены и клетки. 2024. Т. 19, № 1. С. 105–125. DOI: https://doi.org/10.17816/gc610252

Рукопись получена: 17.10.2023 **Рукопись одобрена:** 08.02.2024 **Опубликована online:** 05.03.2024

DOI: https://doi.org/10.17816/gc610252

Immune cell balance as potential biomarker of progressing non-alcoholic fatty liver disease

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is a widespread chronic, slowly progressive metabolic multifactorial disease. It is represented by several clinical and morphological forms: steatosis, nonalcoholic steatohepatitis (NASH) (with or without fibrosis), and liver cirrhosis. The search for minimally invasive and cost-effective biomarkers of NAFLD is a key task in the diagnosis, staging of progression, and long-term monitoring of NAFLD. This article discusses the possibility of using immune cell balance as potential minimally invasive peripheral markers of NAFLD progression. In the progression of NASH from steatosis to fibrosis and cirrhosis, inflammation plays an important role because of the activation of Kupffer cells and increased migration of monocytes, dendritic cells, neutrophils, and activated T lymphocytes into the tissues. Macrophages originating from monocytes, with NASH progression, gradually begin to prevail over the pool of resident macrophages. The risk of NASH and fibrosis development in patients with NAFLD increases with the ratio of neutrophils/lymphocytes in the liver. An increase in the Th17 cell count and a decrease in T-regulatory cell count can contribute to increased hepatic steatosis and inflammation development in NAFLD and accelerate the transition from simple steatosis to steatohepatitis and fibrosis. Information on the participation of noncoding RNAs in the regulation of the balance of immune cells in NAFLD is presented, which also allows us to consider them as additional, along with cellular, markers of disease progression.

Keywords: non-alcoholic fatty liver disease; biomarkers of NAFLD; liver fibrosis; immune cells.

To cite this article:
Topchieva LV, Kurbatova IV, Dudanova OP, Vasileva AV, Zhulai GA. Immune cell balance as potential biomarker of progressing non-alcoholic fatty liver disease. *Genes & cells.* 2024;19(1):105–125. DOI: https://doi.org/10.17816/gc610252

Received: 17.10.2023 **Accepted:** 08.02.2024 **Published online:** 05.03.2024

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a widespread, slowly progressing, multifactor metabolic disease. According to different authors, 20%–40% of the planet's population is affected by NAFLD. By 2030, liver cirrhosis (LC) as an outcome of NAFLD is predicted to top the list of indications for liver transplantation. NAFLD is already a major cause of liver-associated morbidity and mortality in developed countries. In Russia, NAFLD now holds a leading position among internal organ diseases [1].

Of particular interest at present is the problem of detailed NAFLD pathogenetic mechanisms that underlie its progression. NAFLD involves lipid overaccumulation (>5%) in the liver with the development of insulin resistance, inflammation, and fibrosis and proceeds in stages from steatosis to steatohepatitis and LC. The sequence of NAFLD clinical morphologies is distinguished according to the following stages: steatosis, nonalcoholic steatohepatitis (NASH) (with or without fibrosis), and LC [1, 2].

Nonalcoholic fatty liver disease pathogenesis involves complex mechanisms, including lipotoxicity, induction of insulin resistance, inflammation and death of hepatocytes (necrosis and apoptosis), activation of stellate cells, fibrogenesis, and fibrosis, which cause NASH and its subsequent transformation into LC. Nonalcoholic steatohepatitis (NASH) manifests as inflammatory infiltration of the liver parenchyma and stroma with ballooning of hepatocytes and focal necrosis. NASH is an intermediate and central stage in the succession of a single pathological process (nonalcoholic steatosis and nonalcoholic steatofibrosis). Hepatic steatosis is an early form of NAFLD with a benign clinical course, whereas NASH develops with potential progression to LC and hepatocellular carcinoma. The mortality rate in patients with NAFLD is higher than that in the general population because not only of hepatic causes but also cardiovascular catastrophes and otopathology.

The key problems in diagnosing NAFLD are differentiating NASH from simple steatosis and identifying liver fibrosis. The gold standard for handling these problems is liver biopsy; however, it has some major drawbacks such as invasiveness, risk of life-threatening complications, poor tolerability, sampling variability, and high cost. There is also a financial perspective to this technique because it requires hospital confinement and a certified specialist to perform the procedure. Furthermore, the amount of tissue taken for liver biopsy is only approximately 1/50 000 of the organ's total volume and cannot faithfully represent damage, inflammation, and fibrosis [3].

Finding minimally invasive and cost-effective biomarkers of NAFLD is a key challenge for its diagnosis, staging, and long-term monitoring.

APPROACHES FOR ASSESSING NAFLD PROGRESSION

Two different approaches to minimally invasive techniques are employed: the "biological" approach based on the quantification of biomarkers in blood samples and the "physical approach based on the measurement of liver stiffness by ultrasonic or magnetic resonance elastography." As to the "physical" approach, the most popular today are imaging techniques, such as ultrasonography (USG), magnetic resonance imaging (MRI), computed topography, and elastography; however, these methods have certain limitations. USG, the most readily available method, can detect fat accumulation in the liver but cannot identify the degree of inflammation or fibrosis [4]. USG detects a diffuse increase in liver echogenicity versus kidney echogenicity and US attenuation with poorer visualization of the intrahepatic vessels and diaphragm. The diagnostic value of USG is notably lower in patients with obesity because of signal attenuation within the subcutaneous adipose tissue. The sensitivity of this method ranges from 60 to 95% and its specificity is 84–100%; however, the levels in patients who are obese dropped to 49 and 75%, respectively [5].

The nonabsolute efficacy of imaging methods in diagnosing NAFLD urges researchers to look for new variations of these methods and combine them with blood biochemical parameters to improve diagnostic accuracy [6].

Fibrosis grading is a decisive tool for NAFLD diagnosis and prognosis. Transformed into myofibroblasts under the effect of multiple stimuli (apoptotic bodies, cytokines, endotoxins, free radicals, and adipokines), stellate cells synthesize connective tissue proteins. Several informative biomarkers of fibrosis in patients with NAFLD have been identified, such as the levels of hyaluronic acid [7], cytokeratin 18 [8], fibroblast growth factor 21 [9], type III procollagen peptide [10], and type IV collagen 7s [11]. For accurate grading of fibrosis, researchers have designed composite laboratory tests encompassing several indices that reflect the different perspectives of the complex fibrosis process, such as the liver fibrosis index-4 (FIB4) [12], NAFLD fibrosis score (NFS) [13], and aspartate aminotransferase [AST]/platelet ratio index (APRI) [14].

Some studies have attempted to use serum biomarker levels as the basis for designing predictive models for diagnosing or grading steatosis (such as the fatty liver index) or for staging fibrosis (e.g., NFS). In particular, the level of circulating keratin 18 fragments can be used to differentiate patients with NASH from those with simple steatosis, procollagen III N-Terminal propeptide (PIIINP), or Pro-C3 content to identify patients with advanced fibrosis [15, 16]. Some of them are specific to NAFLD (e.g., BARD scores and NFS), whereas others were originally designed for hepatitis C (AST/alanine transaminase [ALT] ratio, APRI, and

DOI: https://doi.org/10.17816/gc610252

FIB-4 fibrosis score). Some of these are patented formulas (FibroTest, Fibrometer, Hepascore, and the Enhanced Liver Fibrosis test). Researchers note the practical advantages of applying serum biomarker levels, such as good interlaboratory reproducibility and potential widespread availability; however, none of them are liver-specific, and their results can be influenced by comorbid conditions [17]. No highly sensitive and specific blood tests are available thus far to differentiate NASH from simple steatosis. None of the imaging methods can reliably differentiate NASH from simple steatosis, although the performance of MRI-based methods is promising. In advanced fibrosis, the most accurate and confirmed identification methods include magnetic resonance elastography, transient elastography, FIB-4, and NFS. Finally, accumulating evidence shows that the quantification of serum markers and assessment of liver stiffness by transient shear wave elastography accurately identify the subgroup of patients with NAFLD who have a higher risk of liver-related complications or liver transplantation [13, 17, 18].

Thus, a topical issue on the agenda is the search for new biomarkers of NAFLD progression. A suggestion regarding biochemical markers, e.g., using the content of some proteins in plasma, namely, PNPLA3 and PPP1R3B as biomarkers of steatosis and COL1A1 as a potential marker of fibrosis in NAFLD [19], is useful. Studies have argued that single biomarkers are hardly diagnostic or predictive of disease stages because of their heterogeneity [20].

Disease risk and severity can be evaluated using a combination of biomarkers. Thus, Watt et al. [20] suggested using the level of cytokines (interleukin [IL]-6, IL-8, and tumor necrosis factor [TNF]-α) and two markers of fibrosis (PIIINP and ST2/IL-33R) as diagnostic differentiators between simple steatosis and nonalcoholic steatohepatitis. Considering the complex pathogenetic mechanisms behind NAFLD, markers of disease progression may also be diverse. The key is to identify markers that are clearly related to specific NAFLD forms and degrees of fibrosis and can be estimated by minimally invasive techniques, e.g., using peripheral blood.

IMMUNE CELL BALANCE AS A POSSIBLE MARKER OF NAFLD PROGRESSION

The mechanisms underlying NAFLD pathogenesis include inflammation, cytotoxic effect of excessive nonesterified fatty acids and their metabolites, and development of insulin resistance. An important factor in the progression of nonalcoholic steatohepatitis (from steatosis to fibrosis and LC) is inflammation, which is affected by the activation of resident hepatic immune cells, namely, Kupffer cells (KCs), and intensified migration of dendritic cells (DCs), neutrophils, and activated T cells to the organ tissues. Macrophages in adipose tissue synthesize proinflammatory cytokines, generating chronic mild inflammation in the organism. Structural alterations of hepatic cell membranes by lipid peroxidation and the transport of intestinal bacterial products to the liver by the portal bloodstream trigger the activation of hepatic macrophages, which begin to secrete inflammatory cytokines, chemokines, and adhesion molecules, inducing the recruitment of inflammatory cells to the liver. Levels of genes encoding markers of immune cell differentiation are epigenetically regulated by noncoding RNAs [21], which are differentially expressed under inflammation and at different stages of NAFLD progression [22, 23]. MicroRNAs regulate gene expression at the transcriptional and posttranscriptional levels. Generally, microRNAs bind complementarily to the 3′-untranslated region of mRNA (3'UTR) of the target genes. This leads to mRNA degradation or translational repression [24]. However, some microRNAs can stabilize mRNA or promote translation by binding to the 5′ UTR of mRNAs. Long noncoding RNAs (LncRNAs) include a diverse class of RNAs, including long intergenic RNAs, enhancer RNAs, and sense or antisense transcripts [23]. They perform various functions, including the regulation of transcription, formation/organization of the nuclear domain, and regulation of protein function and stability and microRNA levels through their binding or, in other words, "sponging" (competitive RNAs). They can encode small proteins or peptides. Epigenetic factors are directly involved in regulating the balance of immune cells. Several microRNAs and LncRNAs associated with the Th17/regulatory T cell (Tregs) ratio and differentiation of M1 and M2 macrophages have been identified [25–27]. The profile and quantity of these noncoding RNAs are likely to be associated with changes in the pool of immune cells and can be used as additional markers of NAFLD progression, particularly in cases where liver biopsies are needed to assess immune cell balance.

T cells

In addition to the activation of innate immunity, the response incites adaptive immune cells, namely, Th1 and Th17 helper cells. Th17 cells recruit leucocytes (mainly neutrophils) to the inflammation site by secreting various cytokines. Chronic mild local and systemic inflammation is maintained. Proinflammatory cytokines initiate the transformation of stellate cells into myofibroblasts and induce fibrosis. Thus, immunocompetent cells mainly affect the inflammation process in the liver. Hepatic stellate cells (HSCs) are potential key actors in the inflammation process and regulate fibrosis development because of their ability to transdifferentiate into myofibroblast-like cells [28]. In another study, the authors [29] isolated mouse HSCs, and these cells were activated by treatment with interferon gamma (IFNγ) solution or by coculture with T lymphocytes. On the surface of activated HSCs, increased expression levels of major histocompatibility complex class I molecules, costimulatory molecules, and death protein ligand 1 (PD-L1)

were observed. The decrease in the proliferation index and cytotoxic activity of $CD8^+$ T cells when cocultured with HSCs is likely associated with an increased interaction between PD-L1 on the surface of HSCs and PD-1 expressed by $CD8^+$ T cells [29].

Data revealed that liver-infiltrating $CD4^+$ cells play a decisive role in the development of inflammation and fibrosis in chronic liver diseases, including NAFLD [30, 31]. $CD4^+$ cells are heterogeneous cells with varying functional characteristics. Tregs mediate immune tolerance, inhibit the proliferation and activation of effector cells, and prevent excessive immune responses. Th17 cells mediate inflammation. Tregs and Th17 cells differentiate from naïve $CD4^+$ T cells. The balance between Tregs and Th17 cells maintains immune homeostasis. However, in pathological conditions, this balance is impaired [32]. Most studies on the role of these cells in NAFLD pathogenesis were performed with mice with steatosis or steatohepatitis induced experimentally by feeding them a high-fat diet (HFD-induced steatosis). The development of HFD-induced steatosis was accompanied by depleting hepatic Treg pool. Adoptive transfer of Tregs notably reduced liver inflammation in mice fed a HFD [33]. A rise in the quantity of Th17 cells, which produce the proinflammatory cytokine IL-17 (a key chemoattractant for neutrophils) may promote hepatic steatosis and inflammation in NAFLD and accelerate the progression from simple steatosis to steatohepatitis [34]. The transcription factor RORγt is one of the key factors of Th differentiation toward Th17. In mice with HFD-induced NASH, compared with animals receiving a normal diet, the level of proinflammatory $CD4^+RORγt^{++}$ cells was the highest in visceral fat, whereas their subcutaneous fat contained high amounts of anti-inflammatory Tregs. The authors suggested that Treg increase in the SAT attempts to restore the proinflammatory-prone Th17/Treg balance [35]. In addition, the study revealed that the $CD4^+RORγt^{++}$ and $CD4^+CD25^+FOXP3^+$ cell populations correlated with disease severity graded by glucose and cytokine levels and by histological parameters, particularly lobular inflammation.

Some information on the T cell profile in humans with NAFLD is available. In particular, patients with steatosis and nonalcoholic steatohepatitis were found to have lower frequencies of resting Tregs ($CD4^+CD45RA^+CD25^{++}$) and higher frequencies of $IFNγ^+$ and/or $IL\text{-}4^+$ cells in the peripheral blood than healthy people [36]. IFNγ is a proinflammatory Th1-associated cytokine. An increased frequency of Th1 cells and Th1-related genes in NAFLD was reported in both humans and experimental mouse models [37]. Steatosis progression toward NASH is accompanied by an increase in the number of IL-17-producing cells in the hepatic tissue [36]. The authors sought immunological parameters in the peripheral blood to differentiate between steatosis and NASH. The Th17/rTreg and Th2/rTreg ratios in the peripheral blood were significantly higher in patients with NASH than in those with steatosis. Seike et al. revealed the differences between the T cell profiles of the blood mononuclear fraction in healthy individuals and patients with NAFLD [38]. The $CD25^+CD45^+CD4^+$ cell count was higher in patients with advanced-stage NAFLD and progressing liver fibrosis, indicating immune activation. Wang et al. [39] examined correlations between the subpopulations of T cells, Tregs, and liver fibrosis grade in patients with NAFLD. They found that the Th17 cell count and the Th17/Treg ratio were higher in the affected group than in the control group and correlated positively with ALT and AST activities, malonic dialdehyde levels, and contents of type III procollagen and inflammation factors. Patients with NAFLD were divided into groups A (Th17/Treg ratio <1.15) and B (Th17/Treg ratio ≥1.15). Liver damage indices, hepatic fibrosis grade, and levels of inflammation markers were higher in patients with a Th17/Treg ratio ≥1.15 [38].

Thus, alterations in T cell balance in the peripheral blood and liver may be a marker of NAFLD progression. The Th17/Treg balance is regulated by miR-195 [25]. Overexpression of miR-195 in rats with experimentally induced NAFLD reduced the Th17/Treg ratio by inhibiting CD40 expression (CD40 or TNFRSF5 is a costimulatory protein of antigen-presenting cells, a receptor in the TNF receptor suprafamily). lncRNA MEG3 is another regulator of the Treg/Th17 ratio [26]. LncRNAJPX shatters the Treg/Th17 balance in allergic rhinitis by targeting the miR-378g/CCL5 axis [21]. The regulation of Treg/Th17 balance is influenced by lncRNA KCNQ1OT1 [40]. Moreover, lncRNA HOTAIR is an actor in the activation of stellate cells and development of fibrosis. It inhibits miR-17-5p, promoting RORγt-mediated differentiation of Th17 cells, intensified IL-17A secretion, and HSC activation [41].

An important player in Treg homeostasis and survival is miR-155 [42–44]. MiR-155 is involved in the differentiation and survival of $CD4^+$ Th cells [45]. The expression of miR-155 in activated $CD4^+$ T cells may promote Th17 differentiation [46], and the knockout of the *BIC* gene, which encodes this microRNA, disrupts the Th1/Th2 balance in $CD4^+$ T cells *in vitro* [47]. *In vitro* experiments demonstrated that miR-155-deficient T cells overproduced IL-4 and underproduced IFNγ compared with cells derived from wild-type mice [47].

Natural killer T (NKT) cells

Natural killer T cells (NKT cells) are a heterogeneous group of unconventional T cells that express markers characteristic of both natural killer and T lymphocytes [48]. They are characterized by the T cell receptor (TCR)–CD3 complex and the molecules CD56 and CD16 typical of NKT cells on the surface. NKT cells are classified as innate immune cells. In addition to their cytotoxic function, they produce Th1 and Th2 cytokines (primarily IFNγ and IL-4). NKT cells have a regulatory function, limiting the intensity of the immune response and autoaggression [49, 50]. These cells also express adhesion molecules (LFA-1, LFA-2, and LFA-3; αMβ2, αXβ2, L-selectin, VLA-4, and VLA-5; PECAM-1; and CEACAM-1), cytokines, and chemokine receptors

(IL-1R, IL-2ra, IL-2Rb/IL-2Rc, IL-6Rα, IL-7Ra, IL-8R, IL-10R, IL-12Rβ1, IL-15ra, IL-18R, IL-21ra, IFNGR2, TGFBR, c-Kit, CXCR1, CXCR3, CXCR4, CCR4, CCR5, CCR6, CCR7, IChemR23, and CX3CR1) [51, 52]. NKT cells can be activated by both self-antigens and foreign antigens, which are represented by lipids and glycolipids [53]. Most NKT cells recognize antigens through the transmembrane protein molecule CD1d, which is a nonclassical MHC molecule that can present lipids. After the binding of CD3 and CD1d, NKT cells are activated and quickly begin to produce Th1 and Th2 cytokines. CD1d is expressed on KCs, HSCs, hepatocytes, circulating DCs, and hepatic sinus endothelial cells [54].

In mouse liver, NKT cells constitute 20%–30% of the total population of hepatic lymphocytes; however, this percentage is much lower in humans (<1% of hepatic lymphocytes) [55].

Based on their TCR subunit composition, these cells can be divided into two subpopulations: classical NKT, also known as type I or invariant (iNKT), which express a semi-invariant TCR [56], and nonclassical NKT or type II, whose TCR has a wider repertoire [57]. Mature NKT cells are characterized by the presence of CD56- and MHC-binding receptors on their surface, such as CD94/NKG2A and immunoglobulin-like receptors (KIR). To examine the role of NKT cells in the pathogenesis of liver diseases, mice with experimentally induced steatosis or steatohepatitis were used. These cells are conserved in humans and mice. The highly conserved TCR in humans consists of the Va24–Ja18 subunits paired with the Vb11 subunit, which is specific for glycolipid antigens. Mouse iNKT cells express the TCRαVα14/Jα18 chain paired with the more diverse TCRβVβ8.2, Vβ7, and Vβ2 chains. Type II NKT cells express a relatively more diverse TCR repertoire and appear to have regulatory functions [58]. Type II NKT cell TCR contacts its ligand primarily through its βchain rather than the αchain, suggesting that the TCR Vβ chain significantly contributes to the fine specificity of type II Ag NKT cells. Thus, type II NKT cells use TCR binding features common to both iNKT and conventional T cells. Therefore, both subsets of NKT cells exhibit different modes of antigen recognition [59, 60].

Invariant NKT cells develop in the thymus and spread to the periphery. Although they are most commonly found in the liver, they are also found in the thymus, spleen, peripheral blood, bone marrow, and adipose tissue. Compared with mice, humans have fewer iNKT cells and have large differences in the number of circulating iNKT cells [55, 59].

Similar to what occurs with other innate immune cells (such as macrophages, NKT cells, or neutrophils), NKT cells rapidly respond to stimulation capable of activating them by secreting large quantities of various effector cytokines and chemokines [61]. Because of the wide repertoire of cytokines that NKT cells can secrete, these cells participate in various immune responses, including responses against infectious agents [62, 63] and tumors [60], regulating different autoimmune and inflammatory diseases [64].

The mechanism of involvement of NKT cells in the regulation of inflammatory reactions in the liver is associated with their interaction with KCs, which can enhance or, conversely, reduce liver damage [65]. CD1d molecules on the surface of KCs present TCR glycolipid antigens to iNKT cells, which activates iNKT cells [66]. IL-12, IL-1β, and IL-15, which are produced by KCs, recruit iNKT cells, promote their activation, and maintain their population [67, 68]. In the early stages of NAFLD, iNKT cells are recruited to participate in the repair of liver damage by secreting IL-4 [69]. In methionine–choline-deficiency (MCD) animals, iNKT cells are recruited, aggregated into small clusters, and dynamically interact with KCs in the early stage of steatohepatitis. Most importantly, iNKT cells can phagocytose free lipids released by necrotic hepatocytes while being in a nonclassical activation state with a high IFN-γ expression [70]. Given the key roles of KC and iNKT cells in the early stages of NAFLD, their interaction represent a significant driving force in NASH progression. However, their precise role and interaction in mediating NAFLD progression caused by the toxic effects of excess free and oxidized lipids in the liver remains largely unknown.

Invariant NKT and type II NKT cells may play opposite roles in the development of liver diseases. Moreover, literature data indicate both the protective and pathogenetic roles of these cells in liver damage [71–75]. Evidence shows that in liver injury, type I NKT cells predominantly play a proinflammatory role, whereas type II NKT cells suppress inflammatory responses. The functions of type I NKT cells in NAFLD were assumed to be similar to those of $CD8^+$ T cells, which play a significant role in NASH progression. In contrast, type II NKT cells are mainly involved in immunoregulatory functions because of their ability to suppress inflammation. However, the role of type II NKT cells in liver protection is still poorly understood [74]. Further research is required to identify their possible roles.

Several studies on mouse models have been devoted to the role of both types of NKT cells in the development of liver damage [75–82]. Using mouse models, the development and progression of NAFLD were found to be associated with a decrease in the iNKT cell count [83]. Adoptive transfer of iNKT cells results in decreased hepatic steatosis and improved glucose tolerance [84]. In mice fed a choline-deficient diet, which promotes steatosis, the hepatic iNKT pool decreased [85]. HFD-fed mice showed increased iNKT apoptosis, which contributed to the development of insulin resistance and hepatic steatosis [86]. The literature data regarding the pro- and anti-inflammatory properties of these cells in the liver in NAFLD are contradictory because of the clinical form and severity of the disease. The early phase of steatohepatitis is thought to be associated with a lower frequency of iNKT cells [86], whereas the progression of steatohepatitis is accompanied by an increased iNKT cell count and increased secretion of IL-15 [79, 85]. In mice fed an MCD diet, NASH progression was associated with

increased levels of the chemokine CXCL16 (an iNKT cell chemoattractant) [87] and the recruitment and accumulation of iNKT cells in the liver [82, 88]. The absence of invariant NKT cells contributed to increased liver inflammation and fibrosis in mice fed a HFD [89]. These findings indicate that iNKT cells play a protective role against liver inflammation progressing to fibrosis but not against steatosis, enhanced by dietary excess fat, suggesting a key role of these cells in NASH pathogenesis. In diet-induced steatosis, mild-to-moderate NASH, and early fibrosis, liver NKT cells are relatively depleted, resulting in a proinflammatory state [90]. In severe NASH and advanced liver fibrosis, NKT cells inhibit the fibrogenic response associated with NASH [90].

In addition, sex differences must be considered when studying the role of these cells in the pathogenesis of NAFLD [91]. Thus, Cuño-Gómiz et al. showed that female Balb/c mice with a Th2-dominant immune response and CD1d-deficient mice on the HF-CD diet showed less liver damage, inflammation, and fibrosis compared with males after 6 weeks [91].

Significantly fewer studies have focused on the role of NKT cells in the progression of NAFLD and liver damage in humans. Patients with NAFLD have an accumulation of iNKT cells in the liver [87] and decreased number in the peripheral blood [82, 92]. Other authors also showed that the iNKT cell count was higher in patients with NASH than in healthy people [80, 81]. The frequency of hepatic iNKT cells correlates positively with steatosis severity [93]. Increased expression of CD69 on the surface of iNKT cells in the liver of patients with NAFLD suggests that they are in an activated state [88]. Stimulation of a-GalCer iNKT isolated from the liver of patients with NAFLD increased the production of IFNγ by these cells [88, 93]. Expression levels of CD1d in the liver were increased in patients with NAFLD, indicating that the presentation of lipid antigens to iNKT cells may be enhanced, resulting in increased iNKT cell activation [82, 88]. Another study also showed that patients with NAFLD had higher numbers of iNKT cells than those with drug-induced liver disease or a group of healthy individuals [94]. Interestingly, the pool of $CD69^+$iNKT cells was greater in patients with NAFLD and liver fibrosis ($F \geq 2$) than in patients with less fibrosis ($F \leq 1$) and controls. The number of these cells positively correlated with insulin resistance, AST levels, FIB4, and APRI. The authors conclude that $CD69^+$iNKT cell count may be a biomarker of liver fibrosis progression in NAFLD [95].

Diedrich et al. [92] performed immunophenotyping of peripheral blood mononuclear cells of patients with NAFLD and healthy people. In the peripheral blood mononuclear cell fraction of patients with NAFLD, decreased expression of the NKG2D activator receptor was observed among iNKT cells compared with healthy controls. The value of indicators characterizing the development of hepatic steatosis (histological data and ultrasound data) negatively correlated with the quantity of circulating $NKG2D^+$iNKT cells. These data indicate a potential role for NK and iNKT cells in the regulation of liver fibrosis and steatosis in NAFLD. Thus, literature data indicate that iNKT cells contribute to the initiation and progression of liver fibrosis in patients with NAFLD.

Literature shows a relationship between NKT cells and liver damage. iNKT and NKT type II cells play opposing roles in the development of liver diseases. iNKT cells contribute to the development of liver injury, whereas type II NKT cells are associated with the activation of anti-inflammatory responses. Many challenges are associated with studying the role of NKT cells in mouse models. The results of the study may depend on the experimental model of NAFLD and on the sex of the experimental animals. As mentioned above, in mouse liver, NKT constitute 20–30% of the total population of hepatic lymphocytes. In humans, this percentage is much lower (<1% of hepatic lymphocytes) [55]; however, significantly fewer human studies exist. The authors of some studies have suggested that iNKT cells are involved in the regulation of liver fibrosis and steatosis in NAFLD and that $CD69^+$iNKT may be a biomarker for liver fibrosis progression in NAFLD.

$CD8^+$ cytotoxic T cells

$CD8^+$ T lymphocytes are a population of lymphocytes with high cytotoxic activity. Perforin and granzymes are the main factors involved in the cytotoxic effect of $CD8^+$ T lymphocytes [95]. However, the population of $CD8^+$ T lymphocytes is heterogeneous. Subpopulations of naïve cells, memory cells, and cells with regulatory functions are described. They differ in surface and intracellular markers and produce various mediators, which indicate their roles in the regulation of inflammatory processes in NAFLD.

NAFLD progression is accompanied by an increase in the pool of activated cytotoxic $CD8^+$ T cells in the liver [79, 80, 96]. Thus, in mice fed an methionine–choline-deficient diet (MCD) for 8 weeks, the development of signs of liver damage was accompanied by the recruitment of $CD8^+$ T lymphocytes [79]. Wolf et al. [80] obtained similar data and showed that long-term use of a high-fat, choline-deficient (HF-CD) diet in mice resulted in the activation of intrahepatic $CD8^+$ T and NKT cells and an increase in inflammatory cytokines. The CD62L-$CD44^+CD8^+$ and CD62L-$CD44^+CD8^+$ cell count increased in the liver of mice. This study also showed an increase in the pool of $CD3^+CD57^+$NKT and $CD8^+$ T cells in the liver of patients with NASH. These results suggest a cooperative effect of NKT cells and cytotoxic $CD8^+$ T cells in NASH and hepatocellular carcinoma through interaction with hepatocytes. NKT cells and cytotoxic $CD8^+$ T cells are the main producers of the LIGHT (TNFSF14) molecule, which is significantly increased in patients with NAFLD [80].

Ghazarian et al. [96] showed that in patients with NAFLD, $CD8^+$ T cells represent the dominant population of intrahepatic immune cells, which is associated with impaired glucose regulation. Compared with animals on a normal diet,

mice on a HFD had an increased CD62L-CD44$^+$CD8$^+$ and CD62L-CD44$^+$CD8$^+$ cell count in the liver [96]. In patients with NAFLD, the frequency of intrahepatic CD8$^+$ T cells is positively correlated with glycated hemoglobin (HbA1c) levels. The liver CD8$^+$ T cell count is closely related to NAFLD activity [96]. These results allow us to consider these indicators as markers of NAFLD progression.

According to Haas et al. [97], circulating and hepatic cytotoxic CD8$^+$ T lymphocytes are significantly associated with the histological features of NASH, such as lobular inflammation and balloon dystrophy, in patients with NAFLD. The number of CD8$^+$ T cells producing granzymes A and B is significantly higher in patients with NASH. The CD8 T lymphocyte count correlates with hepatic markers of inflammation and antigen presentation in NASH [97]. The CD8$^+$ T cell count in the liver increases as NAFLD progresses from steatosis to steatohepatitis. The CD8$^+$ T cell pool in the liver of obese mice with NASH increased 3.5-fold compared with that in mice with obesity and hepatic steatosis [98]. Isolated hepatic CD8$^+$ T cells from these mice expressed a cytotoxic phenotype expressing IL-10, and the depletion of CD8$^+$ T cells resulted in a significant reduction in liver inflammation, HSC activation, and macrophage accumulation. IL-10 is an anti-inflammatory cytokine that suppresses the synthesis of collagen I, inhibits Kupffer cell activation, limits IL-17 production, and reduces HSC activation [99]. In another study, tissue-resident CD8$^+$ T cells with a memory phenotype were shown in mice to promote liver fibrosis resolution by inducing apoptosis of activated HSCs [100]. Here, the depletion of CD8$^+$ T cells impaired fibrosis resolution, whereas the adoptive transfer of these cells prevented fibrosis progression. Thus, information about the role of CD8$^+$ T cells in the progression of inflammation and fibrosis is contradictory and requires further study.

Obesity is associated with NAFLD occurrence and progression. In overweight individuals, the blood plasma content of leptin, a peptide hormone that regulates energy metabolism, increased. The relationship between the CD8$^+$ T lymphocyte count and the level of leptin in the blood has been shown. Thus, in a rat model with experimentally induced NASH, the infiltration of CD8$^+$ T lymphocytes into the liver was positively correlated with the levels of leptin in the blood and the levels of the proinflammatory cytokines IL-18 and IL-1β and was associated with the recruitment and differentiation of macrophages in the liver. Leptin activates caspase-1 and caspase-3 in hepatocytes and causes hepatocyte pyroptosis. Leptin likely regulates the pyroptosis of macrophages and hepatocytes through CD8$^+$ T lymphocytes during NAFLD progression [101].

Using histochemical methods, the CD8$^+$ cell count increased in the liver of people with obesity, NASH, and cirrhosis, which positively correlated with α-smooth muscle actin, a marker of HSC activation [98]. CD8$^+$ T cells isolated from nonobese mice could not activate HSC compared with cells isolated from obese mice. Thus, Breuer et al. demonstrated for the first time that hepatic CD8$^+$ T cells play a key role in the progression of obesity-related NASH through HSC activation [98].

Several studies supported the pathogenetic role of CD8$^+$ T cells in NAFLD progression [96]. Thus, β2m –/– mice lacking CD8$^+$ T and NKT cells were shown to be protected from both steatosis and NASH induced by a CF-HFD. This is likely due to the decreased production of LIGHT by CD8$^+$ T and NKT cells [80]. Selective ablation of CD8$^+$ T cells is also effective in reducing steatohepatitis in wild-type mice fed a high-fat, high-carbohydrate (HF-HC) diet [102]. Other data also indicate the pathogenic role of CD8$^+$ T cells. Thus, Bhattacharjee et al. showed that C57Bl6/J mice deficient in CD1d (CD1dKO) and CD8$^+$ T cells (mice with injected antibodies to CD8) fed an HF-HC diet had lower triglyceride levels in the liver and a lower count of activated resident cells [103]. Biochemical indicators of NASH activity (ALT activity, expression of smooth muscle actin gene, *Acta2*, collagen type 1 alpha and type 1 alpha 2 *Col1a1*, and Col1a2 genes) in these animals were also significantly lower than those in C57Bl6/J mice fed an HF-CD diet [103].

Thus, the literature indicates the inclusion of CD8$^+$ cytotoxic T cells in the pathogenesis of NAFLD. Moreover, the progression of this disease from steatosis to steatohepatitis is accompanied by increased CD8$^+$ T cell count in the liver. However, this indicator is difficult to use as a minimally invasive marker of NAFLD progression. Thus, more studies are needed to assess how the CD8$^+$ T cell count in the liver is related to their number in the peripheral blood, as well as to changes in biochemical parameters. Such attempts are already being made. In particular, information on the correlation of the CD8$^+$ T cell count in the liver with the HbA1c level, obtained in the study by Ghazarian et al. [96], can be used in the future as biochemical markers of NAFLD progression, reflecting the pool of these cells in patients.

Macrophages

Adipose tissue dysfunction and excessive accumulation of lipids arguably lead to lipotoxicity, thereby initiating NASH, which progresses through the intensification of inflammatory responses [104, 105]. Inflammatory responses and subsequent fibrogenesis are initiated by hepatic macrophages [106]. Hepatic macrophages are a heterogeneous population of immune cells that have diverse functions in homeostasis and pathogenesis. Hepatic macrophages can either arise from circulating monocytes, which are recruited to the injured liver via chemokine signaling, or from self-renewing embryo-derived local macrophages, termed KCs. KCs appear essential for sensing hepatic tissue injury and initiating inflammatory responses, whereas infiltrating monocyte-derived macrophages are linked to chronic inflammation and fibrogenesis [106–108].

Macrophage heterogeneity is expressed by a high diversity of cytokines released, cell surface markers,

and transcriptional profiles. These cells were classified into "proinflammatory" M1 and "immunoregulatory" M2 macrophages. M1 macrophages are intimately linked to $CD4^+$ cells primed by type 1 helper T cells (Th1), whereas M2 macrophages reciprocally engage with Th2 cells. M1 macrophages are typically induced by IL-12, IFN-c, or bacterial lipopolysaccharide, whereas M2 macrophages are controlled by IL-4 and IL-13 [107]. Liver macrophages appear to express markers of M1 and M2 differentiation simultaneously [107].

The functions of hepatic macrophages appear to be largely determined by their origin. The progression of chronic liver diseases from hepatitis to fibrosis and, ultimately, to cirrhosis is closely related to enrichment in nonclassical macrophages derived from $CD14^+CD16^+$ monocytes in the liver of patients with different diseases [109]. In NASH, liver injury caused by an excess of lipids and damage/death of hepatocytes triggers the activation of resident KCs with subsequent secretion of proinflammatory cytokines and chemokines and intensified recruitment of monocytes from the bloodstream [110]. Tran et al. [111] demonstrated that as NASH progresses, the monocyte-derived part of macrophages gradually begins to prevail over the macrophage pool of embryonic origin. Macrophages of monocytic origin have a higher proinflammatory potential than resident KCs of embryonic origin. Thus, the homeostasis of KCs is impaired in NASH.

Activation of hepatic macrophages can be modulated by metabolic signals, as evidenced by the overload of lipids and some cholesterol derivatives in KCs in models of fatty liver disease and steatohepatitis [112]. The central location of KCs in the sinusoids also allows intimate interactions with other nonparenchymal hepatic cell populations. Hepatic macrophages interact with other immune cells; for instance, they secrete the chemokine CXCL16, which attracts NKT cells and activates proinflammatory signals in macrophages [106, 107]. Han et al. [71] used single-cell RNA sequencing, KCs derived from mouse embryos were characterized, and two populations of KCs were identified: KC-1 and KC-2. KC-1 expressed CD170, exhibiting immunoreactivity and immunoregulatory abilities, whereas KC-2 expressed genes associated with lipid metabolism. In a cell coculture system, primary liver iNKT cells stimulated IL-10 expression in the macrophage cell line RAW264.7 and primary KC-1. Blocking the CD206 signal in KC-1 or knocking down CD206 in RAW264.7 cells significantly reduced IL-10 expression. Thus, iNKT cells promote IL-10 production in KC-1, exhibiting anti-inflammatory properties [71]. On the contrary, evidence shows that KCs can activate HSCs to transdifferentiate into myofibroblasts, the major collagen-producing cell type in hepatic fibrosis [107]. KCs activate stellate cells, likely involving the profibrotic and mitogenic cytokines transforming growth factor-β and platelet-derived growth factor [106, 107]. Liver-infiltrating monocytes appear to exert major profibrotic functions during fibrosis progression [107]. Although macrophages participate in shaping the proinflammatory phenotype in the early stage of NASH, they may switch to a reparative phenotype in the chronic phases of liver disease resolution to restrain hepatic fibrosis [106, 108]. Terminally differentiated monocyte-derived hepatic macrophages can express several matrix metalloproteinases (MMPs), including MMP-9, MMP-12, and MMP-13, which are involved in matrix degradation and thereby favor the resolution of liver injury and fibrosis [107].

Most studies evaluating the role of macrophages in NAFLD pathogenesis were conducted using animals with experimentally induced steatosis or steatohepatitis. Performing these studies in patients with NAFLD requires invasive intervention. Moreover, patients are rarely prescribed a biopsy and only if the development of LC is suspected. Therefore, assessing the pool of M1/M2 macrophages in the liver of individuals with different disease forms and severities of liver fibrosis is extremely difficult. Literature data show the use of cytokine ratios to assess the M1/M2 balance of macrophages of monocytic origin and activated KCs in patients with NAFLD. Thus, the balance of Th1/Th2 cells and M1/M2 macrophages in healthy people and patients with NASH was assessed by the ratio of the concentration of cytokines (INFγ/IL-4, $TNFα^+$IL-6^+IL-23/IL-10, respectively for T helper cells and macrophages) in the peripheral blood and blood from the renal vein [113]. Compared with patients with an unconfirmed diagnosis, patients with NASH had an increased M1/M2 ratio of macrophages in the peripheral blood. An increase in the M1/M2 ratio in the peripheral blood was also found in patients with portal hypertension compared with patients without portal hypertension. The M1/M2 ratio of macrophages in the peripheral blood was positively correlated with the severity of steatosis [113].

In conditions of lipotoxicity hepatocytes release exosomes that can activate macrophages by delivering various contents, including mitochondrial DNA and TNF-related apoptosis-inducing ligand [114–116]. Hepatocyte-derived exosomes may also promote fibrosis resolution through the inhibition of macrophage activation and cytokine secretion, suppression of HSC activation, induction of the extracellular matrix, and its degradation and remodeling [115]. Exosomes, which are apoptotic bodies, also comprise noncoding RNAs that can regulate macrophage polarization. Thus, hepatocyte-derived exosomal miR-192-5p plays a critical role in the activation of proinflammatory macrophages and NAFLD progression by modulating Rictor/Akt/FoxO1 signaling [116]. Macrophage polarization can also be regulated by miR-148a, which acts by inhibiting Krüppel-like factor 6 (KLF6), which plays a key role in fibrogenesis [117], and STAT3, which alleviates the symptoms arising during the development of hepatic fibrosis [118]. Early hepatic fibrosis stages may be associated with a change or, to be precise, a downregulation of miR-122a, which targets a *KLF6* gene transcript [119]. A previous study demonstrated that the activation of an axis, m^6A-catalytic enzyme methyltransferase-like 3 [(*METTL3*)/

metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*; a lncRNA)/polypyrimidine tract-binding protein 1 (PTBP1; an RNA-binding protein)/ubiquitin-specific peptidase 8 (USP8; a deubiquitinating enzyme)/transforming growth factor β-activated kinase 1 (TAK1, a kinase)], may promote pyroptosis and M1 polarization of hepatic macrophages [120]. Neutrophils and macrophages may also release exosomes that subsequently modify liver function. For instance, miR-223 is one of the most common microRNAs expressed in neutrophils and macrophages and plays a key role in controlling inflammation in various diseases, including liver diseases [121]. When activated, neutrophils can deliver exosomal miR-223 to macrophages [122, 123] or hepatocytes [124], thereby suppressing NASH and hepatic fibrosis. In addition, miR-223 can be transferred to various cells, including hepatocytes, with macrophage-derived exosomes [125, 126]. For instance, Hou et al. [127] demonstrated that IL-6 may induce the secretion of miR-223-enriched exosomes by macrophages and neutrophils in mice. Reaching hepatocytes within these exosomes, miR-223 downregulates several target genes, including the transcriptional coactivator with PDZ-binding motif (*Taz*) gene, cryopyrin (*Nlrp3*) gene, and chemokine 10 with C-X-C motif gene (also known as IFNγ-induced protein 10; *Cxcl10*). The overexpression of these genes promotes fibrosis in NASH [128–131].

Bi et al. [132] revealed the role of miR-155-5p in macrophage polarization in CC14-induced fibrosis and LC. These authors showed that the number of M1 macrophages was associated with lymphangiogenesis and fibrosis severity. The levels of miR-155-5p in the liver and peripheral blood increased gradually as fibrosis worsened. *In vitro* experiments have shown that SOCS1, a target of miR-155-5p, regulates the polarization of macrophages to the M1 phenotype through the JAK1/STAT1 pathway [132]. Thus, changes in the expression of noncoding RNAs may influence macrophage polarization in the liver [120]. This opens up prospects for using the expression level of these molecules as both a diagnostic and prognostic criterion for NAFLD progression.

Neutrophils

A connection exists between NAFLD pathogenesis and neutrophils [133, 134]. Being the first cells to reach the site of damage or inflammation, neutrophils recruit other immune cells, such as monocytes, to the site. Interestingly, the presence of neutrophils and macrophages in portal infiltrates correlated with NASH progression [135]. The activity of these cells in patients' peripheral blood increases as NAFLD progresses. In patients with steatosis (NAFL), the number of neutrophils with surface markers of their activation CD62L and TLR4 was nearly the same as that in the peripheral blood of healthy donors [136]. These cells with the said surface markers were significantly increased in patients with NASH. Moreover, CD11b (neutrophil activation marker) expression increased in patients with steatosis [137].

The activation of stellate cells in steatohepatitis is likely associated with the infiltration of neutrophils into the liver. This assumption is supported by the fact that the downregulation of chemokine ligand 1 (C-X-C motif) or intercellular adhesion molecule-1 (ICAM-1) reduced the infiltration of neutrophils into the liver, organ damage, and fibrosis [137]. Coculture of HSCs and neutrophils induced the activation of the latter and enhanced their viability. A crosstalk between neutrophils and HSCs is required to maintain the oxidative/proinflammatory loop (i.e., by means of NADPH oxidase activity in neutrophils) that promotes liver fibrosis [137]. Neutrophils synthesize myeloperoxidase (MPO), a lysosomal enzyme essential for hydrogen peroxide conversion to hypochlorous acid. In patients with NASH, MPO-mediated oxidative cell damage is related to the overexpression of chemokines in the liver (e.g., IL-18 and GROl), which appears to facilitate the recruitment of inflammatory cells to this organ. The ratio of neutrophils to lymphocytes (N/L) has been suggested as a predictive marker of steatohepatitis and fibrosis in patients with NAFLD [138]. In patients with NAFLD, the N/L ratio is strongly associated with histological severity [138]. For each one-unit increase in the N/L ratio, the likelihood of having NASH in patients with NAFLD increased by 70% and the likelihood of having fibrosis increased by 50%. Moreover, neutrophils may produce a positive effect by phagocytizing DCs and defending against bacterial infection.

CONCLUSION

Currently, the search for minimally invasive biomarkers that make it possible to distinguish between NAFLD forms and the severity of liver fibrosis is urgently needed. The ratio of proinflammatory and anti-inflammatory cells, particularly *Treg/Th17* cells and M1 (proinflammatory) and M2 (anti-inflammatory) macrophages, which may depend on the microenvironment (levels of proinflammatory cytokines, chemokine, and growth factors) (Figure 1) play a substantial role in NAFLD pathogenesis and disease progression. Proinflammatory stimuli may cause stellate cells and hepatocytes to undergo epithelial–mesenchymal transition and activate myofibroblasts, thereby promoting extracellular matrix deposition and hepatic fibrosis. Thus, immune mechanisms play an important role in the pathogenesis and progression of NAFLD. The ratio of immune cells in the peripheral blood and liver may be a marker of these processes. However, the literature thus far contains very little information on variations in the profile of immunocompetent cells in relation to NAFLD progression and NASH severity. Most studies investigating the role of immune cells in the pathogenesis of NAFLD have been conducted using animals with experimentally induced steatosis or steatohepatitis and cell cultures. The use of liver biopsy samples from patients with NAFLD is challenging

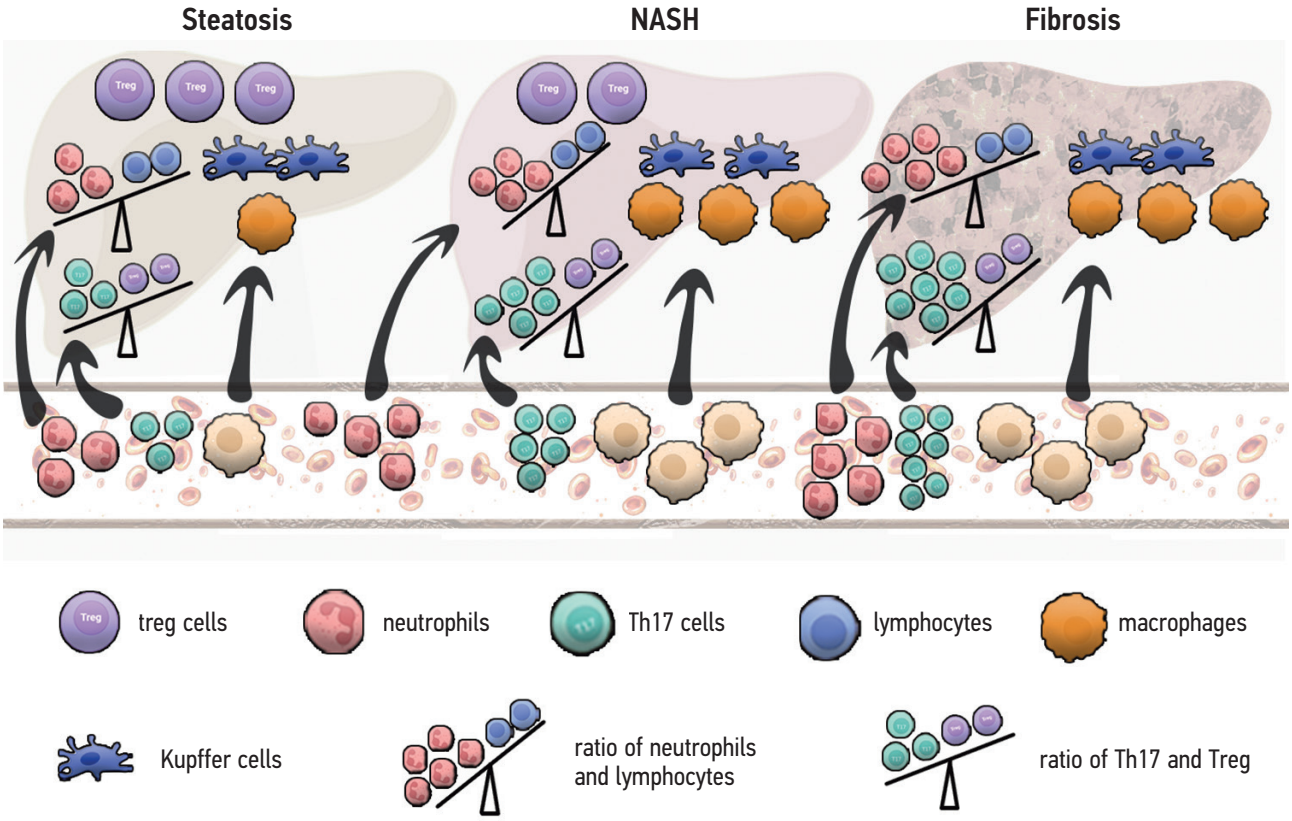

Fig. 1. Changes in the immune cell profile during nonalcoholic fatty liver disease (NAFLD) progression
The number of hepatic Tregs declined during the course of steatosis development and decreased further as steatosis evolves into nonalcoholic steatohepatitis (NASH). Disease progression is accompanied by the depletion of the hepatic Treg pool. The risk of NASH and fibrosis development in patients with NAFLD increases as the hepatic neutrophil/lymphocyte ratio increases. The presence of neutrophils in portal infiltrates correlates with NAFLD progression. The balance between Treg and Th17 cells maintains immune homeostasis. An increase in Th17 cell count may promote hepatic steatosis and inflammation in NAFLD and accelerate the transition from simple steatosis to steatohepatitis. Liver injury scores, severity of hepatic fibrosis, and expression of inflammation markers are higher in patients with a higher Th17/Treg ratio. In NASH, liver injury caused by an excess of lipids and damage/death of hepatocytes triggers the activation of resident Kupffer cells with subsequent secretion of proinflammatory cytokines and chemokines and intensified recruitment of monocytes from the bloodstream. As NASH progresses, monocyte-derived macrophages gradually begin to prevail over the pool of resident macrophages.

Рис. 1. Изменения профиля иммунных клеток при прогрессировании неалкогольной жировой болезни печени (НАЖБП)
Количество печёночных Treg-клеток снижается по мере развития стеатоза и ещё больше — по мере того, как стеатоз развивается в неалкогольный стеатогепатит (НАСГ). Прогрессирование заболевания сопровождается истощением пула Treg в печени. Риск развития НАСГ и фиброза у пациентов с НАЖБП возрастает по мере увеличения соотношения нейтрофилов/лимфоцитов в печени. Наличие нейтрофилов в портальных инфильтратах коррелирует с прогрессированием НАЖБП. Иммунный гомеостаз поддерживается балансом между клетками Treg и Th17. Увеличение числа Th17 может способствовать стеатозу и воспалению печени при НАЖБП и ускорять переход от простого стеатоза к стеатогепатиту. Оценка повреждения печени, степень фиброза печени и экспрессия маркёров воспаления выше у пациентов с более высоким соотношением Th17/Treg. При НАСГ повреждение печени, вызванное избытком липидов и повреждением/гибелью гепатоцитов, запускает активацию резидентных клеток Купфера с последующей секрецией провоспалительных цитокинов и хемокинов и усиленным рекрутированием моноцитов из кровотока. По мере прогрессирования НАСГ моноцитарная часть макрофагов постепенно начинает преобладать над пулом резидентных макрофагов.

because this procedure is prescribed to a relatively small number of patients already with severe disease. From this viewpoint, information on the phenotypes of immune cells in the peripheral blood of healthy and sick people is valuable for the search for minimally invasive markers of NAFLD progression. In our opinion, the most convenient diagnostic and prognostic indicator is the ratio of peripheral Th17/Tregs. First, the Th17/Treg count in the liver of patients with NAFLD correlates with their number in the peripheral blood. In addition, data on the relationship between changes in the profile of these cells and the clinical features of NAFLD and severity of liver fibrosis remain limited. Although other cells of innate and adaptive immunity, such as macrophages, neutrophils, NKT cells, and $CD8^+$ cytotoxic lymphocytes, play an equally important role in the pathogenesis of this disease, assessing their number in the liver is difficult. In addition, these data are

limited and contradictory. The immune cell balance in the liver is associated with changes in the expression of noncoding RNAs involved in the regulation of cell signaling pathways and their differentiation. In this regard, studies of the expression pattern of circulating noncoding RNAs are very promising for the search for additional molecular markers of changes in the immune cell balance during NAFLD progression.

ADDITIONAL INFORMATION

Funding source. The work was carried out within the framework of the state assignment on the topic No. FMEN-2022-0009 (state registration No. 122031100064-4) on the equipment of the Core Facility of the Karelian Research Centre of the Russian Academy of Sciences.

Competing interests. The authors declare that they have no competing interests.

Authors' contribution. L.V. Topchieva — collection and analysis of literary sources, preparation and writing of the text of the article, editing the article; I.V. Kurbatova — literature review, collection and analysis of literary sources, preparation and writing of the article; O.P. Dudanova — literature review, article editing; A.V. Vasileva — collection and analysis of literary sources, design of drawings; G.A. Zhulai — literature review, article editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved the final version before publication).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Источник финансирования. Работа выполнена в рамках государственного задания по теме № FMEN-2022-0009 (номер гос. регистрации 122031100064-4) на оборудовании Центра коллективного пользования Федерального исследовательского центра Карельский научный центр Российской академии наук.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Л.В. Топчиева — сбор и анализ литературных источников, подготовка и написание текста статьи, редактирование статьи; И.В. Курбатова — обзор литературы, сбор и анализ литературных источников, подготовка и написание текста статьи; О.П. Дуданова — обзор литературы, редактирование статьи; А.В. Васильева — сбор и анализ литературных источников, дизайн рисунков; Г.А. Жулай — обзор литературы, редактирование статьи. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

REFERENCES

1. Lazebnik LB, Golovanova EV, Turkina SV, et al. Non-alcoholic fatty liver disease in adults: clinic, diagnostics, treatment. Guidelines for therapists, third version. *Experimental and Clinical Gastroenterology Journal*. 2021;(1):4–52. EDN: KJLOJV doi: 10.31146/1682-8658-ecg-185-1-4-52

2. Powell EE, Wong VWS, Rinella M. Non-alcoholic fatty liver disease. *Lancet*. 2021;397(10290):2212–2224. doi: 10.1016/S0140-6736(20)32511-3

3. Ratziu V, Charlotte F, Heurtier A, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology*. 2005;128(7):1898–1906. doi: 10.1053/j.gastro.2005.03.084

4. Duvnjak M, Tomasic V, Gomercic M, et al. Therapy of nonalcoholic fatty liver disease: current status. *J Physiol Pharmacol*. 2009;60 Suppl. 7:57–66.

5. Mancini M, Prinster A, Annuzzi G, et al. Sonographic hepatic-renal ratio as indicator of hepatic steatosis: comparison with 1H magnetic resonance spectroscopy. *Metabolism*. 2009;58(12):1724–1730. doi: 10.1016/j.metabol.2009.05.032

6. Ajmera V, Loomba R. Imaging biomarkers of NAFLD, NASH, and fibrosis. *Mol Metab*. 2021;50:101167. doi: 10.1016/j.molmet.2021.101167

7. Bahcecioglu IH, Yalniz M, Ataseven H, et al. Levels of serum hyaluronic acid, TNF-alpha and IL-8 in patients with nonalcoholic steatohepatitis. *Hepatogastroenterology*. 2005;52(65):1549–1553.

8. Kwok R, Tse YK, Wong GLH, et al. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease — the role of transient elastography and plasma cytokeratin-18 fragments. *Aliment Pharmacol Ther*. 2014;39(3):254–269. doi: 10.1111/apt.12569

9. Giannini C, Feldstein AE, Santoro N, et al. Circulating levels of FGF-21 in obese youth: associations with liver fat content and markers of liver damage. *J Clin Endocrinol Metab*. 2013;98(7):2993–3000. doi: 10.1210/jc.2013-1250

10. Tang LJ, Ma HL, Eslam M, et al. Among simple non-invasive scores, Pro-C3 and ADAPT best exclude advanced fibrosis in Asian patients with MAFLD. *Metabolism*. 2022;128:154958. doi: 10.1016/j.metabol.2021.154958

11. Yoneda M, Mawatari H, Fujita K, et al. Type IV collagen 7s domain is an independent clinical marker of the severity of fibrosis in patients with nonalcoholic steatohepatitis before the cirrhotic stage. *J Gastroenterol*. 2007;42(5):375–381. doi: 10.1007/s00535-007-2014-3

12. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and FibroTest. *Hepatology*. 2007;46(1):32–36. doi: 10.1002/hep.21669

13. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology*. 2007;45(4):846–854. doi: 10.1002/hep.21496

14. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38(2):518–526. doi: 10.1053/jhep.2003.50346

15. Yilmaz Y, Dolar E, Ulukaya E, et al. Soluble forms of extracellular cytokeratin 18 may differentiate simple steatosis from nonalcoholic steatohepatitis. *World J Gastroenterol*. 2007;13(6):837–844. doi: 10.3748/wjg.v13.i6.837
16. Daniels SJ, Leeming DJ, Eslam M, et al. ADAPT: an algorithm incorporating PRO-C3 accurately identifies patients with NAFLD and advanced fibrosis. *Hepatology*. 2019;69(3):1075–1086. doi: 10.1002/hep.30163
17. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;156(5):1264–1281.e4. doi: 10.1053/j.gastro.2018.12.036
18. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43(6):1317–1325. doi: 10.1002/hep.21178
19. Al-Qarni R, Iqbal M, Al-Otaibi M, et al. Validating candidate biomarkers for different stages of non-alcoholic fatty liver disease. *Medicine (Baltimore)*. 2020;99(36):e21463. doi: 10.1097/MD.0000000000021463
20. Watt J, Kurth MJ, Reid CN, et al. Non-alcoholic fatty liver disease — a pilot study investigating early inflammatory and fibrotic biomarkers of NAFLD with alcoholic liver disease. *Front Physiol*. 2022;15:13:963513. doi: 10.3389/fphys.2022.963513
21. Chen Z, Ke X, Wang X, et al. LncRNA JPX contributes to Treg/Th17 imbalance in allergic rhinitis via targeting the miR-378g/CCL5 axis. *Immunopharmacol Immunotoxicol*. 2022;44(4):519–524. doi: 10.1080/08923973.2022.2055566
22. Dongiovanni P, Meroni M, Longo M, et al. MiRNA signature in NAFLD: a turning point for a non-invasive diagnosis. *Int J Mol Sci*. 2018;19(12):3966. doi: 10.3390/ijms19123966
23. Rohilla S, Kaur S, Puria R. Long non-coding RNA in non-alcoholic fatty liver disease. *Adv Clin Chem*. 2022;110:1–35. doi: 10.1016/bs.acc.2022.06.001
24. Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell*. 2009;136(2):215–233. doi: 10.1016/j.cell.2009.01.002
25. Li Y, Jiang HT, Han LB, et al. MiR-195 regulates CD40 to maintain Th17/Treg balance in rats with non-alcoholic fatty liver disease. *Biomed Pharmacother*. 2020;124:109930. doi: 10.1016/j.biopha.2020.109930
26. Mehana NA, Ghaiad HR, Hassan M, et al. LncRNA MEG3 regulates the interplay between Th17 and Treg cells in Behçet's disease and systemic lupus erythematosus. *Life Sci*. 2022;309:120965. doi: 10.1016/j.lfs.2022.120965
27. Liu XL, Pan Q, Cao HX, et al. Lipotoxic hepatocyte-derived exosomal microRNA 192-5p activates macrophages through Rictor/Akt/Forkhead Box transcription factor O1 signaling in nonalcoholic fatty liver disease. *Hepatology*. 2020;72(2):454–469. doi: 10.1002/hep.31050
28. Schuster S, Cabrera D, Arrese M, Feldstein AE. Triggering and resolution of inflammation in NASH. *Nat Rev Gastroenterol Hepatol*. 2018;15(6):349–364. doi: 10.1038/s41575-018-0009-6
29. Yu MC, Chen CH, Liang X, et al. Inhibition of T-cell responses by hepatic stellate cells via B7-H1-mediated T-cell apoptosis in mice. *Hepatology*. 2004;40(6):1312–1321. doi: 10.1002/hep.20488
30. Hernandez-Gea V, Friedman SL. Pathogenesis of liver fibrosis. *Annu Rev Pathol*. 2011;6:425–456. doi: 10.1146/annurev-pathol-011110-130246
31. Xu L, Xu C, Yu C, et al. Association between serum growth hormone levels and nonalcoholic fatty liver disease: a cross-sectional study. *PLoS One*. 2012;7(8):e44136. doi: 10.1371/journal.pone.0044136
32. Zhao L, Qiu DK, Ma X. Th17 cells: the emerging reciprocal partner of regulatory T cells in the liver. *J Dig Dis*. 2010;11(3):126–133. doi: 10.1111/j.1751-2980.2010.00428.x
33. Ma X, Hua J, Mohamood AR, et al. A high-fat diet and regulatory T cells influence susceptibility to endotoxin-induced liver injury. *Hepatology*. 2007;46(5):1519–1529. doi: 10.1002/hep.21823
34. Tang Y, Bian Z, Zhao L, et al. Interleukin-17 exacerbates hepatic steatosis and inflammation in non-alcoholic fatty liver disease. *Clin Exp Immunol*. 2011;166(2):281–290. doi: 10.1111/j.1365-2249.2011.04471.x
35. Vonghia L, Ruyssers N, Schrijvers D, et al. CD4+RORγt++ and Tregs in a mouse model of diet-induced nonalcoholic steatohepatitis. *Mediators Inflamm*. 2015;2015:239623. doi: 10.1155/2015/239623
36. Rau M, Schilling A-K, Meertens J, et al. Progression from non-alcoholic fatty liver to nonalcoholic steatohepatitis is marked by a higher frequency of Th17 cells in the liver and an increased Th17/Resting regulatory T cell ratio in peripheral blood and in the liver. *J Immunol*. 2016;196(1):97–105. doi: 10.4049/jimmunol.1501175
37. Zhou Y, Zhang H, Yao Y, et al. CD4+ T cell activation and inflammation in NASH-related fibrosis. *Front Immunol*. 2022;13:967410. doi: 10.3389/fimmu.2022.967410
38. Seike T, Mizukoshi E, Yamada K, et al. Fatty acid-driven modifications in T-cell profiles in non-alcoholic fatty liver disease patients. *J Gastroenterol*. 2020;55(7):701–711. doi: 10.1007/s00535-020-01679-7
39. Wang X, Li W, Fu J, et al. Correlation between T-Lymphocyte subsets, regulatory T Cells, and hepatic fibrosis in patients with nonalcoholic fatty liver. *Evid Based Complement Alternat Med*. 2022;2022:6250751. doi: 10.1155/2022/6250751
40. Karimi E, Azari H, Tahmasebi A, et al. LncRNA-miRNA network analysis across the Th17 cell line reveals biomarker potency of lncRNA NEAT1 and KCNQ1OT1 in multiple sclerosis. *J Cell Mol Med*. 2022;26(8):2351–2362. doi: 10.1111/jcmm.17256
41. Wu M, Sun J, Wang L, et al. The lncRNA HOTAIR via miR-17-5p is involved in arsenite-induced hepatic fibrosis through regulation of Th17 cell differentiation. *J Hazard Mater*. 2023;443(Pt B):130276. doi: 10.1016/j.jhazmat.2022.130276
42. Lu LF, Thai TH, Calado DP, et al. Foxp3-dependent microRNA155 confers competitive fitness to regulatory T Cells by targeting SOCS1 protein. *Immunity*. 2009;30(1):80–91. doi: 10.1016/j.immuni.2008.11.010
43. Dong J, Warner LM, Lin LL, et al. miR-155 promotes T reg cell development by safeguarding medullary thymic epithelial cell maturation. *J Exp Med*. 2021;218(2):e20192423. doi: 10.1084/jem.20192423
44. Hu J, Huang S, Liu X, et al. miR-155: an important role in inflammation response. *J Immunol Res*. 2022;2022:7437281. doi: 10.1155/2022/7437281
45. Kim HJ, Park SO, Byeon HW, et al. T cell-intrinsic miR-155 is required for Th2 and Th17-biased responses in acute and chronic airway inflammation by targeting several different transcription factors. *Immunology*. 2022;166(3):357–379. doi: 10.1111/imm.13477
46. O'Connell RM, Kahn D, Gibson WSJ, et al. MicroRNA-155 promotes autoimmune inflammation by enhancing inflammatory T cell development. *Immunity*. 2010;33(4):607–619. doi: 10.1016/j.immuni.2010.09.009

47. Rodriguez A, Vigorito E, Clare S, et al. Requirement of bic/microRNA-155 for normal immune function. *Science*. 2007;316(5824):608–611. doi: 10.1126/science.1139253
48. Luedde T, Schwabe RF. NF-kappaB in the liver — linking injury, fibrosis and hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol.* 2011;8(2):108–118. doi: 10.1038/nrgastro.2010.213
49. Crispe IN. Hepatic T cells and liver tolerance. *Nat Rev Immunol.* 2003;3(1):51–62. doi: 10.1038/nri981
50. Herkel J, Schuchmann M, Tiegs G, Lohse AW. Immune-mediated liver injury. *J Hepatol*. 2005;42(6):920–923. doi: 10.1016/j.jhep.2005.02.009
51. Tyshchuk EV, Mikhailova VA, Selkov SA, Sokolov DI. Natural killer cells: origin, phenotype, function. *Medical Immunology (Russia)*. 2021;23(6):1207–1228. EDN: QILUOK doi: 10.15789/1563-0625-NKC-2330
52. Rhost S, Sedimbi S, Kadri N, Cardell SL. Immunomodulatory type II natural killer T lymphocytes in health and disease. *Scand J Immunol*. 2012;76(3):246–255. doi: 10.1111/j.1365-3083.2012.02750.x
53. Taniguchi M, Seino K, Nakayama T. The NKT cell system: bridging innate and acquired immunity. *Nat Immunol*. 2003;4(12):1164–1165. doi: 10.1038/ni1203-1164
54. Bendelac A, Savage PB, Teyton L. The biology of NKT cells. *Annu Rev Immunol*. 2007;25:297–336. doi: 10.1146/annurev.immunol.25.022106.141711
55. Exley M, Garcia J, Balk SP, Porcelli S. Requirements for CD1d recognition by human invariant V alpha 24+ CD4-CD8- T cells. *J Exp Med.* 1997;186(1):109–120. doi: 10.1084/jem.186.1.109
56. Arrenberg P, Halder R, Kumar V. Cross-regulation between distinct natural killer T cell subsets influences immune response to self and foreign antigens. *J Cell Physiol*. 2009;218(2):246–250. doi: 10.1002/jcp.21597
57. Kumar V, Delovitch TL. Different subsets of natural killer T cells may vary in their roles in health and disease. *Immunology*. 2014;142(3):321–336. doi: 10.1111/imm.12247
58. Maricic I, Marrero I, Eguchi A, et al. Differential activation of hepatic invariant nkt cell subsets plays a key role in progression of nonalcoholic steatohepatitis. *J Immunol*. 2018;201(10):3017–3035. doi: 10.4049/jimmunol.1800614
59. Girardi E, Maricic I, Wang J, et al. Type II natural killer T cells use features of both innate-like and conventional T cells to recognize sulfatide self antigens. *Nat Immunol.* 2012;13(9):851–856. doi: 10.1038/ni.2371
60. Arrenberg P, Halder R, Dai Y, et al. Oligoclonality and innate-like features in the TCR repertoire of type II NKT cells reactive to a beta-linked self-glycolipid. *Proc Natl Acad Sci U S A.* 2010;107(24):10984–10989. doi: 10.1073/pnas.1000576107
61. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology*. 2011;141(5):1572–1585. doi: 10.1053/j.gastro.2011.09.002
62. Matsuda JL, Naidenko OV, Gapin L, et al. Tracking the response of natural killer T cells to a glycolipid antigen using CD1d tetramers. *J Exp Med*. 2000;192(5):741–754. doi: 10.1084/jem.192.5.741
63. Bendelac A, Rivera MN, Park SH, Roark JH. Mouse CD1-specific NK1 T cells: development, specificity, and function. *Annu Rev Immunol*. 1997;15:535–562. doi: 10.1146/annurev.immunol.15.1.535
64. Jahng A, Maricic I, Aguilera C, et al. Prevention of autoimmunity by targeting a distinct, noninvariant CD1d-reactive T cell population reactive to sulfatide. *J Exp Med.* 2004;199(7):947–957. doi: 10.1084/jem.20031389
65. Gu X, Chu Q, Ma, et al. New insights into iNKT cells and their roles in liver diseases. *Front Immunol.* 2022;13:1035950. doi: 10.3389/fimmu.2022.1035950
66. Tang T, Sui Y, Lian, et al. Pro-inflammatory activated Kupffer cells by lipids induce hepatic NKT cells deficiency through activation-induced cell death. *PLoS One*. 2013;8(12):e81949. doi: 10.1371/journal.pone.0081949
67. Hou X, Hao X, Zheng M, et al. CD205- TLR9-IL-12 axis contributes to CpG-induced oversensitive liver injury in HBsAg transgenic mice by promoting the interaction of NKT cells with Kupffer cells. *Cell Mol Immunol.* 2017;14(8):675–684. doi: 10.1038/cmi.2015.111
68. Cui K, Yan G, Xu C, et al. Invariant NKT cells promote alcohol-induced steatohepatitis through interleukin- 1β in mice. *J Hepatol.* 2015;62(6):1311–1318. doi: 10.1016/j.jhep.2014.12.027
69. Liew PX, Lee WY, Kubes P. iNKT cells orchestrate a switch from inflammation to resolution of sterile liver injury. *Immunity*. 2017;47(4):752–765.e5. doi: 10.1016/j.immuni.2017.09.016
70. Wang H, Li L, Li Y, et al. Intravital imaging of interactions between iNKT and Kupffer cells to clear free lipids during steatohepatitis. *Theranostics*. 2021;11(5):2149–2169. doi: 10.7150/thno.51369
71. Han M, Geng J, Zhang S, et al. Invariant natural killer T cells drive hepatic homeostasis in nonalcoholic fatty liver disease via sustained IL-10 expression in CD170+ Kupffer cells. *Eur J Immunol*. 2023;53(11):e2350474. doi: 10.1002/eji.202350474
72. Arrenberg P, Maricic I, Kumar V. Sulfatide-mediated activation of type II natural killer T cells prevents hepatic ischemic reperfusion injury in mice. *Gastroenterology*. 2011;140(2):646–655. doi: 10.1053/j.gastro.2010.10.003
73. Halder RC, Aguilera C, Maricic I, Kumar V. Type II NKT cell-mediated anergy induction in type I NKT cells prevents inflammatory liver disease. *J Clin Invest.* 2007;117(8):2302–2312. doi: 10.1172/JCI31602
74. Maricic I, Sheng H, Marrero I, et al. Inhibition of type I natural killer T cells by retinoids or following sulfatide-mediated activation of type II natural killer T cells attenuates alcoholic liver disease in mice. *Hepatology*. 2015;61(4):1357–1369. doi: 10.1002/hep.27632
75. Mathews S, Feng D, Maricic I, et al. Invariant natural killer T cells contribute to chronic-plus-binge ethanol-mediated liver injury by promoting hepatic neutrophil infiltration. *Cell Mol Immunol.* 2016;13(2):206–216. doi: 10.1038/cmi.2015.06
76. Guebre-Xabier M, Yang S, Lin HZ, et al. Altered hepatic lymphocyte subpopulations in obesity-related murine fatty livers: potential mechanism for sensitization to liver damage. *Hepatology*. 2000;31(3):633–640. doi: 10.1002/hep.510310313
77. Ma X, Hua J, Li Z. Probiotics improve high fat diet-induced hepatic steatosis and insulin resistance by increasing hepatic NKT cells. *J Hepatol*. 2008;49(5):821–830. doi: 10.1016/j.jhep.2008.05.025
78. Satoh M, Andoh Y, Clingan CS, et al. Type II NKT cells stimulate diet-induced obesity by mediating adipose tissue infammation, steatohepatitis and insulin resistance. *PLoS One*. 2012;7(2):e30568. doi: 10.1371/journal.pone.0030568
79. Sutti S, Jindal A, Locatelli I, et al. Adaptive immune responses triggered by oxidative stress contribute to hepatic infammation in NASH. *Hepatology.* 2014;59(3):886–897. doi: 10.1002/hep.26749
80. Wolf MJ, Adili A, Piotrowitz K, et al. Metabolic activation of intrahepatic CD8+ T cells and NKT cells causes nonal coholic steato-

hepatitis and liver cancer via cross-talk with hepatocytes. *Cancer Cell*. 2014;26(4):549–564. doi: 10.1016/j.ccell.2014.09.003
81. Syn WK, Agboola KM, Swiderska M, et al. NKT-associated hedgehog and osteopontin drive fbrogenesis in nonalcoholic fatty liver disease. *Gut*. 2012;61(9):1323–1329. doi: 10.1136/gutjnl-2011-301857
82. Syn WK, Oo YH, Pereira TA, et al. Accumula tion of natural killer T cells in progressive nonalcoholic fatty liver disease. *Hepatology.* 2010;51(6):1998–2007. doi: 10.1002/hep.23599
83. Li Z, Lin H, Yang S, Diehl AM. Murine leptin deficiency alters kupffer cell production of cytokines that regulate the innate immune system. *Gastroenterology*. 2002;123(4):1304–1310. doi: 10.1053/gast.2002.35997
84. Elinav E, Pappo O, Sklair-Levy M, et al. Adoptive transfer of regulatory NKT lymphocytes ameliorates non-alcoholic steatohepatitis and glucose intolerance in ob/ob mice and is associated with intrahepatic CD8 trapping. *J Pathol*. 2006;209(1):121–128. doi: 10.1002/path.1950
85. Kremer M, Thomas E, Milton RJ, et al. Kupffer cell and interleukin-12-dependent loss of natural killer T cells in hepatosteatosis. *Hepatology*. 2010;51(1):130–141. doi: 10.1002/hep.23292
86. Li Z, Soloski MJ, Diehl AM. Dietary factors alter hepatic innate immune system in mice with nonalcoholic fatty liver disease. *Hepatology*. 2005;42(4):880–885. doi: 10.1002/hep.20826
87. Syn WK, Choi SS, Liaskou E, et al. Osteopontin is induced by hedgehog pathway activation and promotes fibrosis progression in nonalcoholic steatohepatitis. *Hepatology*. 2011;53(1):106–115. doi: 10.1002/hep.23998
88. Tajiri K, Shimizu Y, Tsuneyama K, Sugiyama T. Role of liver-infiltrating CD3+CD56+ natural killer T cells in the pathogenesis of nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol*. 2009;21(6):673–680. doi: 10.1097/MEG.0b013e32831bc3d6
89. Miyagi T, Takehara T, Uemura A, et al. Absence of invariant natural killer T cells deteriorates liver infammation and fbrosis in mice fed high-fat diet. *J Gastroenterol*. 2010;45(12):1247–1254. doi: 10.1007/s00535-010-0272-y
90. Zheng S, Yang W, Yao D, et al. A comparative study on roles of natural killer T cells in two diet-induced non-alcoholic steatohepatitis-related fibrosis in mice. *Ann Med*. 2022;54(1):2233–2245. doi: 10.1080/07853890.2022.2108894
91. Cuño-Gómiz C, de Gregorio E, Tutusaus A, et al. Sex-based differences in natural killer T cell-mediated protection against diet-induced steatohepatitis in Balb/c mice. *Biol Sex Differ*. 2023;14(1):85. doi: 10.1186/s13293-023-00569-w
92. Diedrich T, Kummer S, Galante A, et al. Characterization of the immune cell landscape of patients with NAFLD. *PLoS One*. 2020;15(3):e0230307. doi: 10.1371/journal.pone.0230307
93. Adler M, Taylor S, Okebugwu K, et al. Intrahepatic natural killer T cell populations are increased in human hepatic steatosis. *World J Gastroenterol*. 2011;17(13):1725–1731. doi: 10.3748/wjg.v17.i13.1725
94. Caballano-Infantes E, García-García A, Lopez-Gomez C, et al. Differential iNKT and T cells activation in non-alcoholic fatty liver disease and drug-induced liver injury. *Biomedicines*. 2022;10(1):55. doi: 10.3390/biomedicines10010055
95. Stepanova OI, Bazhenov DO, Khokhlova EV, et al. The role of subpopulations of cd8+ t lymphocytes in the development of pregnancy. *Medical Immunology (Russia).* 2018;20(5):621–638. EDN: YLTKRF doi: 10.15789/1563-0625-2018-5-621-638
96. Ghazarian M, Revelo XS, Nøhr MK, et al. Type I interferon responses drive intrahepatic T cells to promote metabolic syndrome. *Sci Immunol*. 2017;2(10):eaai7616. doi: 10.1126/sciimmunol.aai7616
97. Haas JT, Vanghia L, Mogilenko DA, et al. Transcriptional network analysis implicates altered hepatic immune function in NASH development and resolution. *Nat Metab.* 2019;1(6):604–614. Corrected and republished from: *Nat Metab.* 2019;1(7):744. doi: 10.1038/s42255-019-0076-1
98. Breuer DA, Pacheco MC, Washington MK, et al. CD8+ T cells regulate liver injury in obesity-related nonalcoholic fatty liver disease. *Am J Physiol Gastrointest Liver Physiol*. 2020;318(2):G211–G224. doi: 10.1152/ajpgi.00040.2019
99. Hammerich L, Tacke F. Hepatic inflammatory responses in liver fibrosis. *Nat Rev Gastroenterol Hepatol.* 2023;20(10):633–646. doi: 10.1038/s41575-023-00807-x
100. Koda Y, Teratani T, Chu PS, et al. CD8+ tissue-resident memory T cells promote liver fibrosis resolution by inducing apoptosis of hepatic stellate cells. *Nat Commun*. 2021;12(1):4474. doi: 10.1038/s41467-021-24734-0
101. Zhang Q, Wang J, Huang F, et al. Leptin induces NAFLD progression through infiltrated CD8+ T lymphocytes mediating pyroptotic-like cell death of hepatocytes and macrophages. *Dig Liver Dis.* 2021;53(5):598–605. doi: 10.1016/j.dld.2020.10.025
102. Sutti S, Albano E. Adaptive immunity: an emerging player in the progression of NAFLD. *Nat Rev Gastroenterol Hepatol*. 2020;17(2):81–92. doi: 10.1038/s41575-019-0210-2
103. Bhattacharjee J, Kirby M, Softic S, et al. Hepatic natural killer T-cell and CD8+ T-cellsignatures in mice with nonalcoholic steatohepatitis. *Hepatol Commun*. 2017;1(4):299–310. doi: 10.1002/hep4.1041
104. Musso G, Gambino R, Cassader M. Recent insights into hepatic lipid metabolism in non-alcoholic fatty liver disease (NAFLD). *Prog Lipid Res*. 2009;48(1):1–26. doi: 10.1016/j.plipres.2008.08.001
105. Neuschwander-Tetri BA. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: the central role of nontriglyceride fatty acid metabolites. *Hepatology*. 2010;52(2):774–788. doi: 10.1002/hep.23719
106. Tacke F. Targeting hepatic macrophages to treat liver diseases. *J Hepatol*. 2017;66(6):1300–1312. doi: 10.1016/j.jhep.2017.02.026
107. Tacke F, Zimmermann HW. Macrophage heterogeneity in liver injury and fibrosis. *J Hepatol*. 2014;60(5):1090–1096. doi: 10.1016/j.jhep.2013.12.025
108. Krenkel O, Tacke F. Liver macrophages in tissue homeostasis and disease. *Nat Rev Immunol*. 2017;17(5):306–321. doi: 10.1038/nri.2017.11
109. Zimmermann HW, Seidler S, Nattermann J, et al. Functional contribution of elevated circulating and hepatic non-classical CD14+CD16+ monocytes to inflammation and human liver fibrosis. *PLoS One*. 2010;5(6):e11049. doi: 10.1371/journal.pone.0011049
110. Wang Y, Gao L. Monocyte-derived KCs (MoKCs) contribute to the KC pool in NASH. *Cell Mol Immunol*. 2021;18(3):518–519. doi: 10.1038/s41423-020-00606-3
111. Tran S, Baba I, Poupel L, et al. Impaired Kupffer cell self-renewal alters the liver response to lipid overload during non-alcoholic steatohepatitis. *Immunity*. 2020;53(3):627–640.e5. doi: 10.1016/j.immuni.2020.06.003
112. Leroux A, Ferrere G, Godie V, et al. Toxic lipids stored by Kupffer cells correlates with their pro-inflammatory phenotype at

an early stage of steatohepatitis. *J Hepatol*. 2012;57(1):141–149. doi: 10.1016/j.jhep.2012.02.028

113. Vonghia L, Magrone T, Verrijken A, et al. Peripheral and hepatic vein cytokine levels in correlation with non-alcoholic fatty liver disease (NAFLD)-related metabolic, histological, and haemodynamic features. *PLoS One*. 2015;10(11):e0143380. doi: 10.1371/journal.pone.0143380

114. Garcia-Martinez I, Santoro N, Chen Y, et al. Hepatocyte mitochondrial DNA drives nonalcoholic steatohepatitis by activation of TLR9. *J Clin Invest*. 2016;126(3):859–864. doi: 10.1172/JCI83885

115. Hirsova P, Ibrahim SH, Krishnan A, et al. Lipid-induced signaling causes release of inflammatory extracellular vesicles from hepatocytes. *Gastroenterology*. 2016;150(4):956–967. doi: 10.1053/j.gastro.2015.12.037

116. Chen J, Gu X, Zhou L, et al. Long non-coding RNA-HOTAIR promotes the progression of sepsis by acting as a sponge of miR-211 to induce IL-6R expression. *Exp Ther Med*. 2019;18(5):3959–3967. doi: 10.3892/etm.2019.8063

117. Watanabe K, Ohnishi S, Manabe I, et al. KLF6 in nonalcoholic fatty liver disease: role of fibrogenesis and carcinogenesis. *Gastroenterology*. 2008;135(1):309–312. doi: 10.1053/j.gastro.2008.06.014

118. Tian S, Zhou X, Zhang M, et al. Mesenchymal stem cell-derived exosomes protect against liver fibrosis via delivering miR-148a to target KLF6/STAT3 pathway in macrophages. *Stem Cell Res Ther*. 2022;13(1):330. doi: 10.1186/s13287-022-03010-y

119. Tsai WC, Hsu SD, Hsu CS, et al. MicroRNA-122 plays a critical role in liver homeostasis and hepatocarcinogenesis. *J Clin Invest*. 2012;122(8):2884–2897. doi: 10.1172/JCI63455

120. Shu B, Zhou YX, Li H, et al. The METTL3/MALAT1/PTBP1/USP8/TAK1 axis promotes pyroptosis and M1 polarization of macrophages and contributes to liver fibrosis. *Cell Death Discov*. 2021;7(1):368. doi: 10.1038/s41420-021-00756-x

121. Ye D, Zhang T, Lou G, Liu Y. Role of miR-223 in the pathophysiology of liver diseases. *Exp Mol Med*. 2018; 50(9):1–12. doi: 10.1038/s12276-018-0153-7

122. Guillot A, Tacke F. The unexpected role of neutrophils for resolving liver inflammation by transmitting microRNA-223 to macrophages. *Hepatology*. 2020;71(2):749–751. doi: 10.1002/hep.30925

123. Calvente CJ, Tameda M, Johnson CD, et al. Neutrophils contribute to spontaneous resolution of liver inflammation and fibrosis via microRNA-223. *J Clin Invest*. 2019;129(10):4091–4109. doi: 10.1172/JCI122258

124. He Y, Hwang S, Cai Y, et al. MicroRNA-223 ameliorates nonalcoholic steatohepatitis and cancer by targeting multiple inflammatory and oncogenic genes in hepatocytes. *Hepatology*. 2019;70(4):1150–1167. doi: 10.1002/hep.30645

125. Aucher A, Rudnicka D, Davis DM. MicroRNAs transfer from human macrophages to hepato-carcinoma cells and inhibit proliferation. *J Immunol*. 2013;191(12):6250–6260. doi: 10.4049/jimmunol.1301728

126. Ismail N, Wang Y, Dakhlallah D, et al. Macrophage microvesicles induce macrophage differentiation and miR-223 transfer. *Blood*. 2013; 121(6):984–995. doi: 10.1182/blood-2011-08-374793

127. Hou X, Yin S, Ren R, et al. Myeloid-cell–specific IL-6 signaling promotes microRNA-223-enriched exosome production to attenuate NAFLD-associated fibrosis. *Hepatology*. 2021;74(1):116–132. doi: 10.1002/hep.31658

128. Wang X, Sommerfeld MR, Jahn-Hofmann K, et al. A therapeutic silencing RNA targeting hepatocyte TAZ prevents and reverses fibrosis in nonalcoholic steatohepatitis in mice. *Hepatol Commun*. 2019;3(9):1221–1234. Corrected and republished from: *Hepatol Commun*. 2019;4(1):134. doi: 10.1002/hep4.1405

129. Wang X, Zheng Z, Caviglia JM, et al. Hepatocyte TAZ/WWTR1 promotes inflammation and fibrosis in nonalcoholic steatohepatitis. *Cell Metab*. 2016;24(6):848–862. doi: 10.1016/j.cmet.2016.09.016

130. Wree A, McGeough MD, Inzaugarat ME, et al. NLRP3 inflammasome driven liver injury and fibrosis: roles of IL-17 and TNF in mice. *Hepatology*. 2018;67(2):736–749. doi: 10.1002/hep.29523

131. Mridha AR, Wree A, Robertson AAB, et al. NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. *J Hepatol*. 2017;66(5):1037–1046. doi: 10.1016/j.jhep.2017.01.022

132. Bi J, Liu J, Chen X, et al. MiR-155-5p-SOCS1/JAK1/STAT1 participates in hepatic lymphangiogenesis in liver fibrosis and cirrhosis by regulating M1 macrophage polarization. *Hum Exp Toxicol*. 2023;42:9603271221141695. doi: 10.1177/09603271221141695

133. Arrese M, Cabrera D, Kalergis AM, Feldstein AE. Innate Immunity and Inflammation in NAFLD/NASH. *Dig Dis Sci*. 2016;61(5):1294–1303. doi: 10.1007/s10620-016-4049-x

134. Hwang S, Yun H, Moon S, et al. Role of neutrophils in the pathogenesis of nonalcoholic steatohepatitis. *Front Endocrinol (Lausanne)*. 2021;12:751802. doi: 10.3389/fendo.2021.751802

135. Gadd VL, Skoien R, Powell EE, et al. The portal inflammatory infiltrate and ductular reaction in human nonalcoholic fatty liver disease. *Hepatology*. 2014;59(4):1393–1405. doi: 10.1002/hep.26937

136. Lauszus JS, Eriksen PL, Hansen MM, et al. Activation and functional priming of blood neutrophils in non-alcoholic fatty liver disease increases in non-alcoholic steatohepatitis. *Clin Exp Gastroenterol*. 2021;14:441–449. doi: 10.2147/CEG.S329424

137. Zhou Z, Xu MJ, Cai Y, et al. Neutrophil-hepatic stellate cell interactions promote fibrosis in experimental steatohepatitis. *Cell Mol Gastroenterol Hepatol*. 2018;5(3):399–413. doi: 10.1016/j.jcmgh.2018.01.003

138. Alkhouri N, Morris-Stiff G, Campbell C, et al. Neutrophil to lymphocyte ratio: a new marker for predicting steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease. *Liver Int*. 2012;32(2):297–302. doi: 10.1111/j.1478-3231.2011.02639.x

СПИСОК ЛИТЕРАТУРЫ

1. Лазебник Л.Б., Голованова Е.В., Туркина С.В., и др. Неалкогольная жировая болезнь печени у взрослых: клиника, диагностика, лечение. Рекомендации для терапевтов, третья версия // Экспериментальная и клиническая гастроэнтерология. 2021. № 1. С. 4–52. EDN: KJLOJV doi: 10.31146/1682-8658-ecg-185-1-4-52

2. Powell E.E., Wong V.W.S., Rinella M. Non-alcoholic fatty liver disease // Lancet. 2021. Vol. 397, N 10290. P. 2212–2224. doi: 10.1016/S0140-6736(20)32511-3

3. Ratziu V., Charlotte F., Heurtier A., et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease //

Gastroenterology. 2005. Vol. 128, N 7. P. 1898–1906. doi: 10.1053/j.gastro.2005.03.084
4. Duvnjak M., Tomasic V., Gomercic M., et al. Therapy of nonalcoholic fatty liver disease: current status // J Physiol Pharmacol. 2009. Vol. 60, Suppl. 7. P. 57–66.
5. Mancini M., Prinster A., Annuzzi G., et al. Sonographic hepatic-renal ratio as indicator of hepatic steatosis: comparison with 1H magnetic resonance spectroscopy // Metabolism. 2009. Vol. 58, N 12. P. 1724–1730. doi: 10.1016/j.metabol.2009.05.032
6. Ajmera V., Loomba R. Imaging biomarkers of NAFLD, NASH, and fibrosis // Mol Metab. 2021. Vol. 50. P. 101167. doi: 10.1016/j.molmet.2021.101167
7. Bahcecioglu I.H., Yalniz M., Ataseven H., et al. Levels of serum hyaluronic acid, TNF-alpha and IL-8 in patients with nonalcoholic steatohepatitis // Hepatogastroenterology. 2005. Vol. 52, N 65. P. 1549–1553.
8. Kwok R., Tse Y.K., Wong G.L., et al. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease — the role of transient elastography and plasma cytokeratin-18 fragments // Aliment Pharmacol Ther. 2014. Vol. 39, N 3. P. 254–269. doi: 10.1111/apt.12569
9. Giannini C., Feldstein A.E., Santoro N., et al. Circulating levels of FGF-21 in obese youth: associations with liver fat content and markers of liver damage // J Clin Endocrinol Metab. 2013. Vol. 98, N 7. P. 2993–3000. doi: 10.1210/jc.2013-1250
10. Tang L.J., Ma H.L., Eslam M., et al. Among simple non-invasive scores, Pro-C3 and ADAPT best exclude advanced fibrosis in Asian patients with MAFLD // Metabolism. 2022. Vol. 128. P. 154958. doi: 10.1016/j.metabol.2021.154958
11. Yoneda M., Mawatari H., Fujita K., et al. Type IV collagen 7s domain is an independent clinical marker of the severity of fibrosis in patients with nonalcoholic steatohepatitis before the cirrhotic stage // J Gastroenterol. 2007. Vol. 42, N 5. P. 375–381. doi: 10.1007/s00535-007-2014-3
12. Vallet-Pichard A., Mallet V., Nalpas B., et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and FibroTest // Hepatology. 2007. Vol. 46, N 1. P. 32–36. doi: 10.1002/hep.21669
13. Angulo P., Hui J.M., Marchesini G., et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD // Hepatology. 2007. Vol. 45, N 4. P. 846–854. doi: 10.1002/hep.21496
14. Wai C.T., Greenson J.K., Fontana R.J., et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C // Hepatology. 2003. Vol. 38, N 2. P. 518–526. doi: 10.1053/jhep.2003.50346
15. Yilmaz Y., Dolar E., Ulukaya E., et al. Soluble forms of extracellular cytokeratin 18 may differentiate simple steatosis from nonalcoholic steatohepatitis // World J Gastroenterol. 2007. Vol. 13, N 6. P. 837–844. doi: 10.3748/wjg.v13.i6.837
16. Daniels S.J., Leeming D.J., Eslam M., et al. ADAPT: an algorithm incorporating PRO-C3 accurately identifies patients with NAFLD and advanced fibrosis // Hepatology. 2019. Vol. 69, N 3. P. 1075–1086. doi: 10.1002/hep.30163
17. Castera L., Friedrich-Rust M., Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease // Gastroenterology. 2019. Vol. 156, N 5. P. 1264–1281. doi: 10.1053/j.gastro.2018.12.036
18. Sterling R.K., Lissen E., Clumeck N., et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection // Hepatology. 2006. Vol. 43, N 6. P. 1317–1325. doi: 10.1002/hep.21178
19. Al-Qarni R., Iqbal M., Al-Otaibi M., et al. Validating candidate biomarkers for different stages of non-alcoholic fatty liver disease // Medicine (Baltimore). 2020. Vol. 99, N 36. P. e21463. doi: 10.1097/MD.0000000000021463
20. Watt J., Kurth M.J., Reid C.N., et al. Non-alcoholic fatty liver disease — a pilot study investigating early inflammatory and fibrotic biomarkers of NAFLD with alcoholic liver disease // Front Physiol. 2022. Vol. 13. P. 963513. doi: 10.3389/fphys.2022.963513
21. Chen Z., Ke X., Wang X., et al. LncRNA JPX contributes to Treg/Th17 imbalance in allergic rhinitis via targeting the miR-378g/CCL5 axis // Immunopharmacol Immunotoxicol. 2022. Vol. 44, N 4. P. 519–524. doi: 10.1080/08923973.2022.2055566
22. Dongiovanni P., Meroni M., Longo M., et al. MiRNA signature in NAFLD: a turning point for a non-invasive diagnosis // Int J Mol Sci. 2018. Vol. 19, N 12. P. 3966. doi: 10.3390/ijms19123966
23. Rohilla S., Kaur S., Puria R. Long non-coding RNA in non-alcoholic fatty liver disease // Adv Clin Chem. 2022. Vol. 110. P. 1–35. doi: 10.1016/bs.acc.2022.06.001
24. Bartel D.P. MicroRNAs: target recognition and regulatory functions // Cell. 2009. Vol. 136, N 2. P. 215–233. doi: 10.1016/j.cell.2009.01.002
25. Li Y., Jiang H.T., Han L.B., et al. MiR-195 regulates CD40 to maintain Th17/Treg balance in rats with non-alcoholic fatty liver disease // Biomed Pharmacother. 2020. Vol. 124. P. 109930. doi: 10.1016/j.biopha.2020.109930
26. Mehana N.A., Ghaiad H.R., Hassan M., et al. LncRNA MEG3 regulates the interplay between Th17 and Treg cells in Behçet's disease and systemic lupus erythematosus // Life Sci. 2022. Vol. 309. P. 120965. doi: 10.1016/j.lfs.2022.120965
27. Liu X.L., Pan Q., Cao H.X., et al. Lipotoxic hepatocyte-derived exosomal microRNA 192-5p activates macrophages through Rictor/Akt/Forkhead Box transcription factor O1 signaling in nonalcoholic fatty liver disease // Hepatology. 2020. Vol. 72, N 2. P. 454–469. doi: 10.1002/hep.31050
28. Schuster S., Cabrera D., Arrese M., Feldstein A.E. Triggering and resolution of inflammation in NASH // Nat Rev Gastroenterol Hepatol. 2018. Vol. 15, N 6. P. 349–364. doi: 10.1038/s41575-018-0009-6
29. Yu M.C., Chen C.H., Liang X., et al. Inhibition of T-cell responses by hepatic stellate cells via B7-H1-mediated T-cell apoptosis in mice // Hepatology. 2004. Vol. 40, N 6. P. 1312–1321. doi: 10.1002/hep.20488
30. Hernandez-Gea V., Friedman S.L. Pathogenesis of liver fibrosis // Annu Rev Pathol. 2011. Vol. 6. P. 425–456. doi: 10.1146/annurev-pathol-011110-130246
31. Xu L., Xu C., Yu C., et al. Association between serum growth hormone levels and nonalcoholic fatty liver disease: a cross-sectional study // PLoS One. 2012. Vol. 7, N 8. P. e44136. doi: 10.1371/journal.pone.0044136
32. Zhao L., Qiu D.K., Ma X. Th17 cells: the emerging reciprocal partner of regulatory T cells in the liver // J Dig Dis. 2010. Vol. 11, N 3. P. 126–133. doi: 10.1111/j.1751-2980.2010.00428.x
33. Ma X., Hua J., Mohamood A.R., et al. A high-fat diet and regulatory T cells influence susceptibility to endotoxin-induced liver injury // Hepatology. 2007. Vol. 46, N 5. P. 1519–1529. doi: 10.1002/hep.21823

34. Tang Y., Bian Z., Zhao L., et al. Interleukin-17 exacerbates hepatic steatosis and inflammation in non-alcoholic fatty liver disease // Clin Exp Immunol. 2011. Vol. 166, N 2. P. 281–290. doi: 10.1111/j.1365-2249.2011.04471.x
35. Vonghia L., Ruyssers N., Schrijvers D., et al. CD4+RORγt++ and tregs in a mouse model of diet-induced nonalcoholic steatohepatitis // Mediators Inflamm. 2015. Vol. 2015. P. 239623. doi: 10.1155/2015/239623
36. Rau M., Schilling A.-K., Meertens J., et al. Progression from nonalcoholic fatty liver to nonalcoholic steatohepatitis is marked by a higher frequency of Th17 cells in the liver and an increased Th17/resting regulatory T cell ratio in peripheral blood and in the liver // J Immunol. 2016. Vol. 196, N 1. P. 97–105. doi: 10.4049/jimmunol.1501175
37. Zhou Y., Zhang H., Yao Y., et al. CD4+ T cell activation and inflammation in NASH-related fibrosis // Front. Immunol. 2022. Vol. 13. P. 967410. doi: 10.3389/fimmu.2022.967410
38. Seike T., Mizukoshi E., Yamada K., et al. Fatty acid-driven modifications in T-cell profiles in non-alcoholic fatty liver disease patients // J Gastroenterol. 2020. Vol. 55, N 7. P. 701–711. doi: 10.1007/s00535-020-01679-7
39. Wang X., Li W., Fu J., et al. Correlation between T-Lymphocyte subsets, regulatory T Cells, and hepatic fibrosis in patients with non-alcoholic fatty liver // Evid Based Complement Alternat Med. 2022. Vol. 2022, P. 6250751. doi: 10.1155/2022/6250751
40. Karimi E., Azari H., Tahmasebi A., et al. LncRNA-miRNA network analysis across the Th17 cell line reveals biomarker potency of lncRNA NEAT1 and KCNQ1OT1 in multiple sclerosis // J Cell Mol Med. 2022. Vol. 26, N 8. P. 2351–2362. doi: 10.1111/jcmm.17256
41. Wu M., Sun J., Wang L., et al. The lncRNA HOTAIR via miR-17-5p is involved in arsenite-induced hepatic fibrosis through regulation of Th17 cell differentiation // J Hazard Mater. 2023. Vol. 443(Pt B). P. 130276. doi: 10.1016/j.jhazmat.2022.130276
42. Lu L.F., Thai T.H., Calado D.P., et al. Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein // Immunity. 2009. Vol. 30, N 1. P. 80–91. doi: 10.1016/j.immuni.2008.11.010
43. Dong J., Warner L.M., Lin L.L., et al. miR-155 promotes T reg cell development by safeguarding medullary thymic epithelial cell maturation // J Exp Med. 2021. Vol. 218, N 2. P. e20192423. doi: 10.1084/jem.20192423
44. Hu J., Huang S., Liu X., et al. MiR-155: an important role in inflammation response // J Immunol Res. 2022. Vol. 2022. P. 7437281. doi: 10.1155/2022/7437281
45. Kim H.J., Park S.O., Byeon H.W., et al. T cell-intrinsic miR-155 is required for Th2 and Th17-biased responses in acute and chronic airway inflammation by targeting several different transcription factors // Immunology. 2022. Vol. 166, N 3. P. 357–379. doi: 10.1111/imm.13477
46. O'Connell R.M., Kahn D., Gibson W.S., et al. MicroRNA-155 promotes autoimmune inflammation by enhancing inflammatory T cell development // Immunity. 2010. Vol. 33, N 4. P. 607–619. doi: 10.1016/j.immuni.2010.09.009
47. Rodriguez A., Vigorito E., Clare S., et al. Requirement of bic/microRNA-155 for Normal Immune Function // Science. 2007. Vol. 316, N 5824. P. 608–611. doi: 10.1126/science.1139253
48. Luedde T., Schwabe R.F. NF-kappaB in the liver — linking injury, fibrosis and hepatocellular carcinoma // Nat Rev Gastroenterol Hepatol. 2011. Vol. 8, N 2. P. 108–118. doi: 10.1038/nrgastro.2010.213
49. Crispe I.N. Hepatic T cells and liver tolerance // Nat Rev Immunol. 2003. Vol. 3, N 1. P. 51–62. doi: 10.1038/nri981
50. Herkel J., Schuchmann M., Tiegs G., Lohse A.W. Immune-mediated liver injury // J Hepatol. 2005. Vol. 42, N 6. P. 920–923. doi: 10.1016/j.jhep.2005.02.009
51. Тыщук Е.В., Михайлова В.А., Сельков С.А., Соколов Д.И. Естественные киллеры: происхождение, фенотип, функции // Медицинская иммунология. 2021. Т. 23, № 6. С. 1207–1228. EDN: QILUOK doi: 10.15789/1563-0625-NKC-2330
52. Rhost S., Sedimbi S., Kadri N., Cardell S.L. Immunomodulatory type II natural killer T lymphocytes in health and disease // Scand J Immunol. 2012. Vol. 76, N 3. P. 246–255. doi: 10.1111/j.1365-3083.2012.02750.x
53. Taniguchi M., Seino K., Nakayama T. The NKT cell system: bridging innate and acquired immunity // Nat Immunol. 2003. Vol. 4, N 12. P. 1164–1165. doi: 10.1038/ni1203-1164
54. Bendelac A., Savage P.B., Teyton L. The biology of NKT cells // Annu Rev Immunol. 2007. Vol. 25. P. 297–336. doi: 10.1146/annurev.immunol.25.022106.141711
55. Exley M., Garcia J., Balk S.P., Porcelli S. Requirements for CD1d recognition by human invariant V alpha 24+ CD4-CD8- T cells // J Exp Med. 1997. Vol. 186, N 1. P. 109–120. doi: 10.1084/jem.186.1.109
56. Arrenberg P., Halder R., Kumar V. Cross-regulation between distinct natural killer T cell subsets influences immune response to self and foreign antigens // J Cell Physiol. 2009. Vol. 218, N 2. P. 246–250. doi: 10.1002/jcp.21597
57. Kumar V., Delovitch T.L. Different subsets of natural killer T cells may vary in their roles in health and disease // Immunology. 2014. Vol. 142, N 3. P. 321–336. doi: 10.1111/imm.12247
58. Maricic I., Marrero I., Eguchi A., et al. Differential activation of hepatic invariant NKT cell subsets plays a key role in progression of nonalcoholic steatohepatitis // J Immunol. 2018. Vol. 201, N 10. P. 3017–3035. doi: 10.4049/jimmunol.1800614
59. Girardi E., Maricic I., Wang J., et al. Type II natural killer T cells use features of both innate-like and conventional T cells to recognize sulfatide self antigens // Nat Immunol. 2012. Vol. 13, N 9. P. 851–856. doi: 10.1038/ni.2371
60. Arrenberg P., Halder R., Dai Y., et al. Oligoclonality and innate-like features in the TCR repertoire of type II NKT cells reactive to a beta-linked self-glycolipid // Proc Natl Acad Sci U S A. 2010. Vol. 107, N 24. P. 10984–10989. doi: 10.1073/pnas.1000576107
61. Gao B., Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets // Gastroenterology. 2011. Vol. 141, N 5. P. 1572–1585. doi: 10.1053/j.gastro.2011.09.002
62. Matsuda J.L., Naidenko O.V., Gapin L., et al. Tracking the response of natural killer T cells to a glycolipid antigen using CD1d tetramers // J Exp Med. 2000. Vol. 192, N 5. P. 741–754. doi: 10.1084/jem.192.5.741
63. Bendelac A., Rivera M.N., Park S.H., Roark J.H. Mouse CD1-specific NK1 T cells: development, specificity, and function // Annu Rev Immunol. 1997. Vol. 15. P. 535–562. doi: 10.1146/annurev.immunol.15.1.535
64. Jahng A., Maricic I., Aguilera C., et al. Prevention of autoimmunity by targeting a distinct, noninvariant CD1d-reactive T cell population reactive to sulfatide // J Exp Med. 2004. Vol. 199, N 7. P. 947–957. doi: 10.1084/jem.20031389

65. Gu X., Chu Q., Ma, et al. New insights into iNKT cells and their roles in liver diseases // Front Immunol. 2022. Vol. 13. P. 1035950. doi: 10.3389/fimmu.2022.1035950
66. Tang T., Sui Y., Lian, et al. Pro-inflammatory activated Kupffer cells by lipids induce hepatic NKT cells deficiency through activation-induced cell death // PLoS One. 2013. Vol. 8, N 12. P. e81949. doi: 10.1371/journal.pone.0081949
67. Hou X., Hao X., Zheng M., et al. CD205- TLR9-IL-12 axis contributes to CpG-induced oversensitive liver injury in HBsAg transgenic mice by promoting the interaction of NKT cells with Kupffer cells // Cell Mol Immunol. 2017. Vol. 14, N 8. P. 675–684. doi: 10.1038/cmi.2015.111
68. Cui K., Yan G., Xu C., et al. Invariant NKT cells promote alcohol-induced steatohepatitis through interleukin- 1β in mice // J Hepatol. 2015. Vol. 62, N 6. P. 1311–1318. doi: 10.1016/j.jhep.2014.12.027
69. Liew P.X., Lee W.Y., Kubes P. iNKT cells orchestrate a switch from inflammation to resolution of sterile liver injury // Immunity. 2017. Vol. 47, N 4. P. 752–765. doi: 10.1016/j.immuni.2017.09.016
70. Wang H., Li L., Li Y., et al. Intravital imaging of interactions between iNKT and Kupffer cells to clear free lipids during steatohepatitis // Theranostics. 2021. Vol. 11, N 5. P. 2149–2169. doi: 10.7150/thno.51369
71. Han M., Geng J., Zhang S., et al. Invariant natural killer T cells drive hepatic homeostasis in nonalcoholic fatty liver disease via sustained IL-10 expression in CD170+ Kupffer cells // Eur J Immunol. 2023. Vol. 53, N 11. P. e2350474. doi: 10.1002/eji.202350474
72. Arrenberg P., Maricic I., Kumar V. Sulfatide-mediated activation of type II natural killer T cells prevents hepatic ischemic reperfusion injury in mice // Gastroenterology. 2011. Vol. 140, N 2. P. 646–655. doi: 10.1053/j.gastro.2010.10.003
73. Halder R.C., Aguilera C., Maricic I., Kumar V. Type II NKT cell-mediated anergy induction in type I NKT cells prevents inflammatory liver disease // J Clin Invest. 2007. Vol. 117, N 8. P. 2302–2312. doi: 10.1172/JCI31602
74. Maricic I., Sheng H., Marrero I., et al. Inhibition of type I natural killer T cells by retinoids or following sulfatide-mediated activation of type II natural killer T cells attenuates alcoholic liver disease in mice // Hepatology. 2015. V. 61, N 4. P. 1357–1369. doi: 10.1002/hep.27632
75. Mathews S., Feng D., Maricic I., et al. Invariant natural killer T cells contribute to chronic-plus-binge ethanol-mediated liver injury by promoting hepatic neutrophil infiltration // Cell Mol Immunol. 2016. Vol. 13, N 2. P. 206–216. doi: 10.1038/cmi.2015.06
76. Guebre-Xabier M., Yang S., Lin H.Z., et al. Altered hepatic lymphocyte subpopulations in obesity-related murine fatty livers: potential mechanism for sensitization to liver damage // Hepatology. 2000. Vol. 31, N 3. P. 633–640. doi: 10.1002/hep.510310313
77. Ma X., Hua J., Li Z. Probiotics improve high fat diet-induced hepatic steatosis and insulin resistance by increasing hepatic NKT cells // J Hepatol. 2008. Vol. 49, N 5. P. 821–830. doi: 10.1016/j.jhep.2008.05.025
78. Satoh M., Andoh Y., Clingan C.S., et al. Type II NKT cells stimulate diet-induced obesity by mediating adipose tissue infammation, steatohepatitis and insulin resistance // PLoS One. 2012. Vol. 7, N 2. P. e30568. doi: 10.1371/journal.pone.0030568
79. Sutti S., Jindal A., Locatelli I., et al. Adaptive immune responses triggered by oxidative stress contribute to hepatic infammation in NASH // Hepatology. 2014. Vol. 59, N 3. P. 886–897. doi: 10.1002/hep.26749
80. Wolf M.J., Adili A., Piotrowitz K., et al. Metabolic activation of intrahepatic CD8+ T cells and NKT cells causes nonalcoholic steatohepatitis and liver cancer via cross-talk with hepatocytes // Cancer Cell. 2014. Vol. 26, N 4. P. 549–564. doi: 10.1016/j.ccell.2014.09.003
81. Syn W.K., Agboola K.M., Swiderska M., et al. NKT-associated hedgehog and osteopontin drive fbrogenesis in nonalcoholic fatty liver disease // Gut. 2012. Vol. 61, N 9. P. 1323–1329. doi: 10.1136/gutjnl-2011-301857
82. Syn W.K., Oo Y.H., Pereira T.A., et al. Accumula tion of natural killer T cells in progressive nonalcoholic fatty liver disease // Hepatology. 2010. Vol. 51, N 6. P. 1998–2007. doi: 10.1002/hep.23599
83. Li Z., Lin H., Yang S., Diehl A.M. Murine leptin deficiency alters kupffer cell production of cytokines that regulate the innate immune system // Gastroenterology. 2002. Vol. 123, N 4. P. 1304–1310. doi: 10.1053/gast.2002.35997
84. Elinav E., Pappo O., Sklair-Levy M., et al. Adoptive transfer of regulatory NKT lymphocytes ameliorates non-alcoholic steatohepatitis and glucose intolerance in ob/ob mice and is associated with intrahepatic CD8 trapping // J Pathol. Vol. 209, N 1. P. 121–128. doi: 10.1002/path.1950
85. Kremer M., Thomas E., Milton R.J., et al. Kupffer cell and interleukin-12-dependent loss of natural killer T cells in hepatosteatosis // Hepatology. 2010. Vol. 51, N 1. P. 130–141. doi: 10.1002/hep.23292
86. Li Z., Soloski M.J., Diehl A.M. Dietary factors alter hepatic innate immune system in mice with nonalcoholic fatty liver disease // Hepatology. 2005. Vol. 42, N 4. P. 880–885. doi: 10.1002/hep.20826
87. Syn W.K., Choi S.S., Liaskou E., et al. Osteopontin is induced by hedgehog pathway activation and promotes fibrosis progression in nonalcoholic steatohepatitis // Hepatology. 2011. Vol. 53, N 1. P. 106–115. doi: 10.1002/hep.23998
88. Tajiri K., Shimizu Y., Tsuneyama K., Sugiyama T. Role of liver-infiltrating CD3+CD56+ natural killer T cells in the pathogenesis of nonalcoholic fatty liver disease // Eur J Gastroenterol Hepatol. 2009. V. 21, N 6. P. 673–680. doi: 10.1097/MEG.0b013e32831bc3d6
89. Miyagi T., Takehara T., Uemura A., et al. Absence of invariant natural killer T cells deteriorates liver infammation and fbrosis in mice fed high-fat diet // J Gastroenterol. 2010. Vol. 45, N 12. P. 1247–1254. doi: 10.1007/s00535-010-0272-y
90. Zheng S., Yang W., Yao D., et al. A comparative study on roles of natural killer T cells in two diet-induced non-alcoholic steatohepatitis-related fibrosis in mice // Ann Med. 2022. Vol. 54, N 1. P. 2233–2245. doi: 10.1080/07853890.2022.2108894
91. Cuño-Gómiz C., de Gregorio E., Tutusaus A., et al. Sex-based differences in natural killer T cell-mediated protection against diet-induced steatohepatitis in Balb/c mice // Biol Sex Differ. 2023. Vol. 14, N 1. P. 85. doi: 10.1186/s13293-023-00569-w
92. Diedrich T., Kummer S., Galante A., et al. Characterization of the immune cell landscape of patients with NAFLD // PLoS One. 2020. P. 15, N 3. P. e0230307. doi: 10.1371/journal.pone.0230307
93. Adler M., Taylor S., Okebugwu K., et al. Intrahepatic natural killer T cell populations are increased in human hepatic steatosis // World J Gastroenterol. 2011. Vol. 17, N 13. P. 1725–1731. doi: 10.3748/wjg.v17.i13.1725
94. Caballano-Infantes E., García-García A., Lopez-Gomez C., et al. Differential iNKT and T cells activation in non-alcoholic fatty liver disease and drug-induced liver injury // Biomedicines. 2021. Vol. 10, N 1. P. 55. doi: 10.3390/biomedicines10010055

95. Степанова О.И., Баженов Д.О., Хохлова Е.В., и др. Молекулярно-генетические механизмы регуляции ангиогенеза // Медицинская иммунология. 2018. Т. 20, № 5. С. 621–638. EDN: YLTKRF doi: 10.15789/1563-0625-2018-5-621-638
96. Ghazarian M., Revelo X.S., Nøhr M.K., et al. Type I interferon responses drive intrahepatic T cells to promote metabolic syndrome // Sci Immunol. 2017. Vol. 2, N 10. P. eaai7616. doi: 10.1126/sciimmunol.aai7616
97. Haas J.T., Vanghia L., Mogilenko D.A., et al. Transcriptional network analysis implicates altered hepatic immune function in NASH development and resolution // Nat Metab. 2019. Vol. 1, N 6. P. 604–614. Corrected and republished from: Nat Metab. 2019. Vol. 1, N 7. P. 744. doi: 10.1038/s42255-019-0076-1
98. Breuer D.A., Pacheco M.C., Washington M.K., et al. CD8+ T cells regulate liver injury in obesity-related nonalcoholic fatty liver disease // Am J Physiol Gastrointest Liver Physiol. 2020. Vol. 318, N 2. P. G211–G224. doi: 10.1152/ajpgi.00040.2019
99. Hammerich L., Tacke F. Hepatic inflammatory responses in liver fibrosis // Nat Rev Gastroenterol Hepatol. 2023. Vol. 20, N 10. P. 633–646. doi: 10.1038/s41575-023-00807-x
100. Koda Y., Teratani T., Chu P.S., et al. CD8+ tissue-resident memory T cells promote liver fibrosis resolution by inducing apoptosis of hepatic stellate cells // Nat Commun. 2021. Vol. 12, N 1. P. 4474. doi: 10.1038/s41467-021-24734-0
101. Zhang Q., Wang J., Huang F., et al. Leptin induces NAFLD progression through infiltrated CD8+ T lymphocytes mediating pyroptotic-like cell death of hepatocytes and macrophages // Dig Liver Dis. 2021. Vol. 53, N 5. P. 598–605. doi: 10.1016/j.dld.2020.10.025
102. Sutti S., Albano E. Adaptive immunity: an emerging player in the progression of NAFLD // Nat Rev Gastroenterol Hepatol. 2020. Vol. 17, N 2. P. 81–92. doi: 10.1038/s41575-019-0210-2
103. Bhattacharjee J., Kirby M., Softic S., et al. Hepatic natural killer T-cell and CD8+ T-cellsignatures in mice with nonalcoholic steatohepatitis // Hepatol Commun. 2017. Vol. 1, N 4. P. 299–310. doi: 10.1002/hep4.1041
104. Musso G., Gambino R., Cassader M. Recent insights into hepatic lipid metabolism in non-alcoholic fatty liver disease (NAFLD) // Prog Lipid Res. 2009. Vol. 48, N 1. P. 1–26. doi: 10.1016/j.plipres.2008.08.001
105. Neuschwander-Tetri B.A. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: the central role of nontriglyceride fatty acid metabolites // Hepatology. 2010. Vol. 52, N 2. P. 774–788. doi: 10.1002/hep.23719
106. Tacke F. Targeting hepatic macrophages to treat liver diseases // J Hepatol. 2017. Vol. 66, N 6. P. 1300–1312. doi: 10.1016/j.jhep.2017.02.026
107. Tacke F., Zimmermann H.W. Macrophage heterogeneity in liver injury and fibrosis // J Hepatol. 2014. Vol. 60, N 5. P. 1090–1096. doi: 10.1016/j.jhep.2013.12.025
108. Krenkel O., Tacke F. Liver macrophages in tissue homeostasis and disease // Nat Rev Immunol. 2017. Vol. 17, N 5. P. 306–321. doi: 10.1038/nri.2017.11
109. Zimmermann H.W., Seidler S., Nattermann J., et al. Functional contribution of elevated circulating and hepatic nonclassical CD14+CD16+ monocytes to inflammation and human liver fibrosis // PLoS One. 2010. Vol. 5, N 6. P. e11049. doi: 10.1371/journal.pone.0011049
110. Wang Y., Gao L. Monocyte-derived KCs (MoKCs) contribute to the KC pool in NASH // Cell Mol Immunol. 2021. Vol. 18, N 3. P. 518–519. doi: 10.1038/s41423-020-00606-3
111. Tran S., Baba I., Poupel L., et al. Impaired Kupffer cell self-renewal alters the liver response to lipid overload during non-alcoholic steatohepatitis // Immunity. 2020. Vol. 53, N 3. P. 627–640. doi: 10.1016/j.immuni.2020.06.003
112. Leroux A., Ferrere G., Godie V., et al. Toxic lipids stored by Kupffer cells correlates with their pro-inflammatory phenotype at an early stage of steatohepatitis // J Hepatol. 2012. Vol. 57, N 1. P. 141–149. doi: 10.1016/j.jhep.2012.02.028
113. Vonghia L., Magrone T., Verrijken A., et al. Peripheral and hepatic vein cytokine levels in correlation with non-alcoholic fatty liver disease (NAFLD)-related metabolic, histological, and haemodynamic features // PLoS One. 2015. Vol. 10, N 11. P. e0143380. doi: 10.1371/journal.pone.0143380
114. Garcia-Martinez I., Santoro N., Chen Y., et al. Hepatocyte mitochondrial DNA drives nonalcoholic steatohepatitis by activation of TLR9 // J Clin Invest. 2016. Vol. 126, N 3. P. 859–864. doi: 10.1172/JCI83885
115. Hirsova P., Ibrahim S.H., Krishnan A., et al. Lipid-induced signaling causes release of inflammatory extracellular vesicles from hepatocytes // Gastroenterology. 2016. Vol. 150, N 4. P. 956–967. doi: 10.1053/j.gastro.2015.12.037
116. Chen J., Gu X., Zhou L., et al. Long non-coding RNA-HOTAIR promotes the progression of sepsis by acting as a sponge of miR-211 to induce IL-6R expression // Exp Ther Med. 2019. Vol. 18, N 5. P. 3959–3967. doi: 10.3892/etm.2019.8063
117. Watanabe K., Ohnishi S., Manabe I., et al. KLF6 in non-alcoholic fatty liver disease: role of fibrogenesis and carcinogenesis // Gastroenterology. 2008. Vol. 135, N 1. P. 309–312. doi: 10.1053/j.gastro.2008.06.014
118. Tian S., Zhou X., Zhang M., et al. Mesenchymal stem cell-derived exosomes protect against liver fibrosis via delivering miR-148a to target KLF6/STAT3 pathway in macrophages // Stem Cell Res Ther. 2022. Vol. 13, N 1. P. 330. doi: 10.1186/s13287-022-03010-y
119. Tsai W.C., Hsu S.D., Hsu C.S., et al. MicroRNA-122 plays a critical role in liver homeostasis and hepatocarcinogenesis // J Clin Invest. 2012. Vol. 122, N 8. P. 2884–2897. doi: 10.1172/JCI63455
120. Shu B., Zhou Y.-X., Li H., et al. The METTL3/MALAT1/PTBP1/USP8/TAK1 axis promotes pyroptosis and M1 polarization of macrophages and contributes to liver fibrosis // Cell Death Discov. 2021. Vol. 7, N 1. P. 368. doi: 10.1038/s41420-021-00756-x
121. Ye D., Zhang T., Lou G., Liu Y. Role of miR-223 in the pathophysiology of liver diseases // Exp Mol Med. 2018. Vol. 50, N 9. P. 1–12. doi: 10.1038/s12276-018-0153-7
122. Guillot A., Tacke F. The unexpected role of neutrophils for resolving liver inflammation by transmitting microRNA-223 to macrophages // Hepatology. 2020. Vol. 71, N 2. P. 749–751. doi: 10.1002/hep.30925
123. Calvente C.J., Tameda M., Johnson C.D., et al. Neutrophils contribute to spontaneous resolution of liver inflammation and fibrosis via microRNA-223 // J Clin Invest. 2019. Vol. 129, N 10. P. 4091–4109. doi: 10.1172/JCI122258
124. He Y., Hwang S., Cai Y., et al. MicroRNA-223 ameliorates non-alcoholic steatohepatitis and cancer by targeting multiple inflammatory and oncogenic genes in hepatocytes // Hepatology. 2019. Vol. 70, N 4. P. 1150–1167. doi: 10.1002/hep.30645

125. Aucher A., Rudnicka D., Davis D.M. MicroRNAs transfer from human macrophages to hepato-carcinoma cells and inhibit proliferation // J Immunol. 2013. V. 191, N 12. P. 6250–6260. doi: 10.4049/jimmunol.1301728
126. Ismail N., Wang Y., Dakhlallah D., et al. Macrophage microvesicles induce macrophage differentiation and miR-223 transfer // Blood. 2013. Vol. 121, N 6. P. 984–995. doi: 10.1182/blood-2011-08-374793
127. Hou X., Yin S., Ren R., et al. Myeloid-cell–specific IL-6 signaling promotes microRNA-223-enriched exosome production to attenuate NAFLD-associated fibrosis // Hepatology. 2021. Vol. 74, N 1. P. 116–132. doi: 10.1002/hep.31658
128. Wang X., Sommerfeld M.R., Jahn-Hofmann K., et al. A therapeutic silencing RNA targeting hepatocyte TAZ prevents and reverses fibrosis in nonalcoholic steatohepatitis in mice // Hepatol Commun. 2019. Vol. 3, N 9. P. 1221–1234. Corrected and republished from: Hepatol Commun. 2019. Vol. 4, N 1. P. 134. doi: 10.1002/hep4.1405
129. Wang X., Zheng Z., Caviglia J.M, et al. Hepatocyte TAZ/WWTR1 promotes inflammation and fibrosis in nonalcoholic steatohepatitis // Cell Metab. 2016. Vol. 24, N 6. P. 848–862. doi: 10.1016/j.cmet.2016.09.016
130. Wree A., McGeough M.D., Inzaugarat M.E., et al. NLRP3 inflammasome driven liver injury and fibrosis: roles of IL-17 and TNF in mice // Hepatology. 2018. Vol. 67, N 2. P. 736–749. doi: 10.1002/hep.29523
131. Mridha A.R., Wree A., Robertson A.A.B., et al. NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice // J Hepatol. 2017. Vol. 66, N 5. P. 1037–1046. doi: 10.1016/j.jhep.2017.01.022
132. Bi J., Liu J., Chen X., et al. MiR-155-5p-SOCS1/JAK1/STAT1 participates in hepatic lymphangiogenesis in liver fibrosis and cirrhosis by regulating M1 macrophage polarization // Hum Exp Toxicol. 2023. Vol. 42. P. 9603271221141695. doi: 10.1177/09603271221141695
133. Arrese M., Cabrera D., Kalergis A.M., Feldstein A.E. Innate Immunity and Inflammation in NAFLD/NASH // Dig Dis Sci. 2016. Vol. 61, N 5. P. 1294–1303. doi: 10.1007/s10620-016-4049-x
134. Hwang S., Yun H., Moon S., et al. Role of neutrophils in the pathogenesis of nonalcoholic steatohepatitis // Front Endocrinol (Lausanne). 2021. Vol. 12. P. 751802. doi: 10.3389/fendo.2021.751802
135. Gadd V.L., Skoien R., Powell E.E., et al. The portal inflammatory infiltrate and ductular reaction in human nonalcoholic fatty liver disease // Hepatology. 2014. Vol. 59, N 4. P. 1393–1405. doi: 10.1002/hep.26937
136. Lauszus J.S., Eriksen P.L., Hansen M.M., et al. Activation and functional priming of blood neutrophils in non-alcoholic fatty liver disease increases in non-alcoholic steatohepatitis // Clin Exp Gastroenterol. 2021. Vol. 14, P. 441–449. doi: 10.2147/CEG.S329424
137. Zhou Z., Xu M.-J., Cai Y., et al. Neutrophil-hepatic stellate cell interactions promote fibrosis in experimental steatohepatitis // Cell Mol Gastroenterol Hepatol. 2018. Vol. 5, N 3. P. 399–413. doi: 10.1016/j.jcmgh.2018.01.003
138. Alkhouri N., Morris-Stiff G., Campbell C., et al. Neutrophil to lymphocyte ratio: a new marker for predicting steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease // Liver Int. 2012. Vol. 32, N 2. P. 297–302. doi: 10.1111/j.1478-3231.2011.02639.x

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