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Review paper

The interplay between Th17 and T-regulatory responses as well as adipokines in the progression of non-alcoholic fatty liver disease

Magdalena Świderska[1], Jerzy Jaroszewicz[2], Agnieszka Stawicka[3], Anna Parfieniuk-Kowerda[3], Adrian Chabowski[1], Robert Flisiak[3]

[1]Department of Physiology, Medical University of Bialystok, Bialystok, Poland
[2]Department of Infectious Diseases and Hepatology, Medical University of Silesia, Bytom, Poland
[3]Department of Infectious Diseases and Hepatology, Medical University of Bialystok, Bialystok, Poland

Abstract

Non-alcoholic fatty liver disease (NAFLD) is a chronic progressive liver disease, coupled with metabolic syndrome, which may progress to non-alcoholic steatohepatitis (NASH). Diabetes, obesity, hypertension, hypercholesterolemia, and hypertriglyceridemia are considered to be the most common causes leading to the incidence of NAFLD. It is assumed that the accumulation of lipid deposits in hepatocytes leads to production of proinflammatory cytokines that triggers the development of liver inflammation. Regulatory T cells (Tregs) play a critical role in regulating inflammatory processes in NASH, while T helper type 17 (Th17) might functionally oppose Treg-mediated responses. In addition, important mediators of hepatic steatosis are fatty hormones known as adipokines. We aimed to describe the significance and interaction between Treg and Th17-related cytokines as well as adipokines in pathogenesis and its potential use as biomarkers of NAFLD, especially with respect to progression to NASH.

Key words: NAFLD, NASH, Treg, Th17, adipokines.

Address for correspondence

Dr. Magdalena Świderska, Department of Physiology, Medical University of Bialystok, 2C Mickiewicza St., 15-222 Bialystok, Poland, phone: +48 85 748 55 85, e-mail: magdalena.swiderska@umb.edu.pl

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease, which affects 6.3% to 33% of worldwide population [1]. The prevalence of NAFLD industrialized countries is estimated for 1/3 of adult population and 25-30% in Europe [2, 3]. Non-alcoholic fatty liver disease is associated with an accumulation of fat in liver despite the lack of secondary causes. Non-alcoholic fatty liver disease includes different histologic and clinic types: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), which is usually associated with ongoing liver fibrosis [2]. Non-alcoholic fatty liver disease may lead to liver cirrhosis with portal hypertension and hepatocellular carcinoma (HCC) [2, 4]. Frequently, NAFLD is con-

nected with higher risk of obesity, cardiovascular diseases, metabolic syndrome, type 2 diabetes, and insulin resistance [2, 4]. It is assumed that among patients with NAFLD, approximately 33% will develop NASH [5]. Cirrhosis may occur in 5-19% of patients diagnosed with NASH [4]. Understanding of the mechanisms, which are responsible for progression from simple steatosis to NASH, may be crucial in diagnostics and planning therapy for patients with progressive disease.

Pathogenesis of NASH is complex with a variety of different processes that may lead to liver damage [4]. The balance between pro- and anti-inflammatory processes plays a crucial role, mediated by both, innate and adaptive immunity. Aforementioned mechanisms are a part of induction and progression of metabolic liver damage [3]. Accumulation of lipid deposits in hepato-

cytes leads to synthesis of proinflammatory cytokines, and finally results in development of hepatitis [6, 7]. Cytokines and chemokines are important mediators of steatosis. The damage of the organ is connected with an increase of tumor necrosis factor (TNF-α) and interleukin 1 beta (IL-1β) synthesis, activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) inflammatory signal as well as IL-12 and IL-23, which induce Th1 and Th17 response [6]. What is more, in NAFLD pathogenesis, hormones called adipokines, are of vast importance. Secretory activity of fatty tissue changes in steatosis, causing the release of adipokines, which participate in insulin resistance development [8]. In patients with NAFLD, an increased concentration TNF-α, IL-6 and resisting is observed as well as decreased concentration of adiponectin. It is possible that retinol binding protein 4 (RBP-4) and hyaluronic acid participate in development of the disease [9]. Nevertheless, the crosslink between immunity and adiponectin as well as profibrogenic pathways leads to progression of disease.

T helper cells (Th)

It is a subgroup of lymphocytes, which participate in adaptive immunity. They release cytokines that activate the immune cells, including cytotoxic T lymphocytes and macrophages. T helper cells (CD4+) may adopt a proinflammatory (Th1) phenotype, which is important for synthesis of interferon (INF-α). Their function is protection from viral, bacterial, and parasites infections. Th1 response is also beneficial for antineoplastic immunity [4, 10]. Furthermore, CD4+ may develop anti-inflammatory phenotype – Th2 characterized by synthesis of IL-4, IL-5, and IL-13 [4, 11]. Differentiation of CD4+ T cells into the Th2 subset is controlled by GATA-3-transcription factor into Th1 subset monitored by T-bet [12]. The balance between Th1 and Th2 is important, and lack or excess of proinflammatory cytokines in relation to deficiency of anti-inflammatory cytokines have been observed in the course of NASH in liver and visceral adipose tissue (Fig. 1) [4, 13, 14]. Impaired balance of Th1/Th2 may result in rapid growth of cytotoxic cells T (CD8+), which may release proinflammatory mediators, participating in recruiting and activation of macrophages into adipose tissue (Fig. 1) [11, 14]. A disruption of Th1/Th2 balance towards the Th1 polarization was demonstrated in diabetic patients. Interestingly, the predominant Th2 response was common in patients with diabetes and NASH [4]. Furthermore, it was shown in mouse model that lipid metabolism alterations observed in NAFLD result in a selective loss of intrahepatic CD4+, but not CD8+ T cells, which can lead to hepatocarcinogenesis.
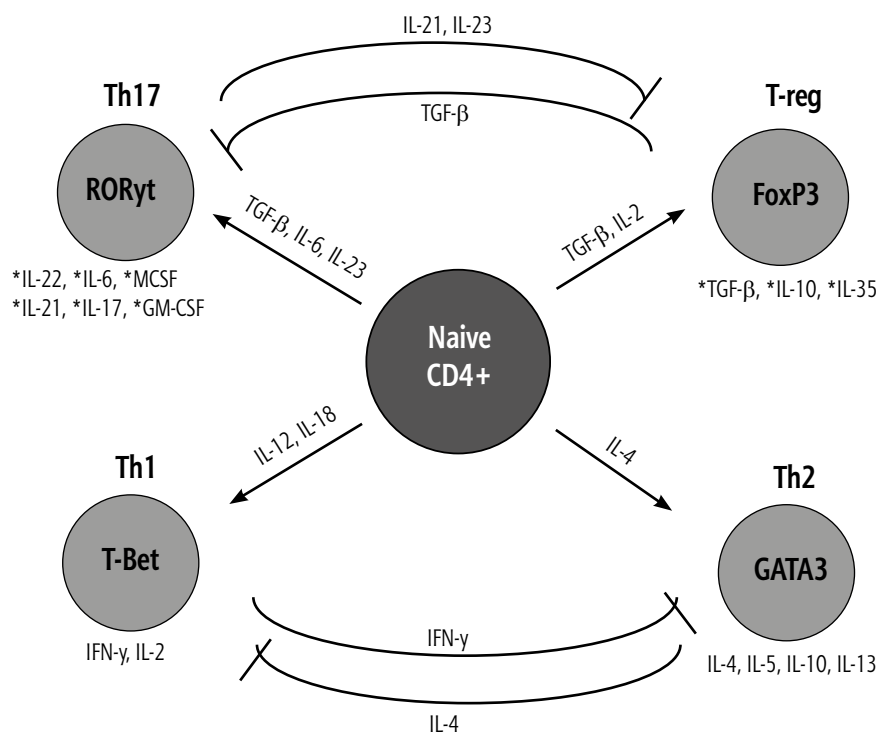

Fig. 1. Showing a putative Th17/Treg/Th1/Th2 regulatory axis. TH0 differentiation pathway indicating cytokines that induce Th17, Treg, T1, T2, differentiation, and major cytokine production; based on [24]

The researchers conclude that there is an association between obesity-induced lipid accumulation and selective loss of CD4+ T cells, which suggested a critical role for the CD4+ T lymphocytes in the progression NAFLD to develop HCC [15].

Th17 interleukin-17 (IL-17)-producing effector CD4+ T (Th17) cells

Lymphocytes T, among others subpopulations, include IL-17 releasing cells that are classified as Th17 type of response. For immunology hemostasis it is important to preserve proper Th17 function, as its lack was observed in many autoimmune infectious and metabolic diseases [11, 10]. Th17 cells release interleukins IL-17A, IL-17F, IL-21, and IL-22 (Fig. 1) [10, 14, 15]. Th17 cells are also proinflammatory cells [16, 17] that participate in bacterial and fungal infections, but may also contribute to nonspecific damage of organs in the course of autoimmune or metabolic diseases [7, 10]. Furthermore, Th17 lymphocytes stimulate the synthesis of proinflammatory cytokines, which in turn stimulate the secretion of chemokines by local cells that leads to the recruitment of neutrophils and macrophages to the area of inflammation. Permanent stimulation of Th17 cells promotes chronic inflammatory activity associated with damage of tissues in autoimmune diseases. Only few reports exist evaluating the significance of Th17 cells in course of NASH in humans [7, 17-19]. It is proved that activation of Th17 cells and increase of IL-17 production promote the progression of the disease from the steatosis to steatosis with inflammation. However, particular influence of Th17 on the pathogenesis of NASH as well as potential application of determination of this immune response markers in diagnostics and prognoses of NASH have not been examined. Among main cytokines associated with type Th17 response are counterbalancing each other IL-17A, IL-17F, and interleukin 21 (IL-21) [16, 19, 20].

Th17 cells play an important role in chronic inflammatory diseases. The increased number of circulating and intrahepatic Th1 cells was found in chronic hepatitis C (CHC) and correlated with the severity of hepatitis [21]. Interleukin 17 probably participates in pathogenesis of liver fibrosis [16, 20]. The highest synthesis among Th17 cells was revealed with regard to IL-17A. It has also higher biologic activity compared to IL-17F. IL-17A is produced mainly by CD4+ Th17 cells, but also by different cells including CD8+ T, natural killer T-cells (NKT), natural killer (NK), eosinophils, neutrophils, and monocytes. IL17A and IL17F transmit the signal through receptors IL-17RA and IL-17RC5 [17]. Animal studies revealed that IL-17

stimulates production of inflammatory cytokines IL-6, IL-1, TNF-α, and TGF-β1. What is more important, IL-17 stimulates hepatic stellate cells (HSC) by increasing the production of type I collagen through signal transducer and activator of transcription 3 (STAT3). Interleukin 17 may serve as attractive target for antifibrotic therapies [17]. The development of Th17 cells is mutually connected with T regulatory (Treg) cells [13].

Th17 cells promote the autoimmunization and tissue damage, while Treg cells act antagonistically. The balance between two subgroups of T cells is crucial for immune homeostasis [13, 16]. The differentiation of Th17 cells may be regulated by nuclear receptors LXR (liver X receptor). Nuclear receptors act like modulators of lipids and cholesterol metabolism through regulation of genes, such as sterol regulating element binding protein 1c (SREBP-1c) and ATP binding cassette transporters-1 (ABCA-1) [16]. Increased values of LDL cholesterol were observed in patients with metabolic syndrome and NASH in comparison to those without steatosis [5]. That is why cholesterol along with LXR receptors may be important for differentiation of T lymphocytes into Th17 cells [5, 10]. Differentiation of Th17 with Th0 is regulated by TGF-β1, IL-6, IL-21, and IL-235. Th17 secretes IL-22 that participates in hepatocytes protection [17].

Concentration of IL-17A correlates with the inflammatory activity of different liver diseases including alcoholic liver disease [22] primary biliary cirrhosis, chronic hepatitis B and C, transplant rejection, and hepatocellular carcinoma [18].

IL-17RA signalization is crucial for progression of the disease from NALFD to NASH [18]. Results of animal studies indicate that not only IL-17A but also IL-17F are important in NAFLD progression [23]. Concentrations of IL-17 and IL-6 are strictly correlated with each other. Interleukin 17 causes significant increase of IL-6 concentration in liver, while IL-6 is necessary in differentiation of naive CD4 T cells into Th17 [19]. The study in mouse model revealed that IL-17 is connected with progression of NAFLD, and IL-17 blocking may be promising therapeutic option for NAFLD [19].

Interleukin 22 may play both protective or pathogenic role in chronic inflammatory diseases, depending on the type and location of the affected tissue [24]. It has been shown that IL-22 was involved the process of stimulation of hepatic fibrogenesis [24, 25]. For example, some studies in mice highlight IL-22 protective role in NASH, but only in the absence of IL-17 [26]. Treatment with recombinant IL-22 in animals mitigates the damage of the liver through activation of signaling tract of STAT3; it also leads to alleviation of oxidative stress. Furthermore, long term administration

of recombinant IL-22 in mice with high fat diet and induced steatosis decreased the level of TNF-α in liver [25]. Increased levels of IL-22 were found in serum and liver tissues in chronic hepatitis C and alcoholic liver disease [22, 24, 25]. Researchers Wu *et al.* [24] in the study of 32 CHC and 64 HCV associated liver cirrhosis patients, demonstrated significant increase ($p < 0.001$) of IL-22 concentration in patients with HCV, in comparison to the control group that was closely associated with the stages of liver fibrosis. Activation of HSCs to release extracellular matrix, a process implicated in liver fibrosis during chronic HCV infection, can be induced by elevated concentrations of IL-22 [24].

T regulatory cells

Another component of immune response with poorly recognized significance in NASH are T regulatory cells (Treg). Those cells play an important role in supporting immune homeostasis by inhibiting proliferation and functions of T effector cells [4, 10, 17]. Tregs consist 5-10% of total number of T CD4+ cells in a healthy human. It is a separate subpopulation of mature T lymphocytes produced in thymus and expressing transcription factor Foxp3 of forkhead family [27].

Tregs are divided into two groups: natural Treg (nTregs) and adaptive or induced Treg (iTreg) [28]. Treg lymphocytes are capable of producing of main anti-inflammatory cytokines, including IL-10 and TGF-β1 [4, 28]. Importantly depletion of Tregs leads to severe systemic autoimmunity [28]. Deficiencies of Treg are frequently connected with mutation of FOXP3 gene on chromosome X [27]. IL-2, TGF-β are important cytokines for Treg production. Participation of TGF-β in Tregs development in thymus is under discussion, but TGF-β is crucial for Treg homeostasis [27]. Treg takes part in prevention of autoreactive cells proliferation, e.g. in autoimmune hepatitis, and also takes part in negative control of different immune responses, e.g. viral hepatitis and HCC, and in organs tolerance after transplantation [11].

What is more, the induction of regulatory T cells can alleviate insulin resistance, which contributes to reducing liver damage. It has been shown that administration of a monoclonal antibody OKT3 (inductive effect of Treg) in patients with NASH during 30 days therapy, resulted in improvement in the immune parameters and good biological effects in the liver of patients with NASH (increase in CD4(+) LAP(+) and CD4(+) CD25(+) LAP(+)), an increase in TGF-β, and a decrease of AST activity in one of the treatment group patients with NASH. Further research on the role of Treg cells in disease development and their application in immunotherapy of patients with NASH is appropriate [29].

Transforming growth factor β

Transforming growth factor β is one of the most important factors for immune regulation [7]. It is produced by different cell types, including lymphocytes, monocytes, and macrophages [7, 28]. Transforming growth factor β appears in at least three strictly connected isoforms TGF-β1, TGF-β2, and TGF-β3 [20, 28]. TGF-β1 is an important antiproliferatic and profibrogenic cytokine. The highest concentration in patients with liver fibrosis among three isoforms shows TGF-β1. In a healthy liver, the main source of TGF-β1 are Kupffer cells, HSCs, and endothelial cells. Transforming growth factor β is expressed exclusively by HSCs [20]. In a large study including 1,322 healthy persons, the frequency of occurrence of NAFLD after 4 years of follow-up was associated with TGF-β3 serum concentration. It was proven that higher levels of TGF-β3 in serum of healthy persons increase risk of steatosis development in further observation [20]. Importantly, anti-inflammatory activity of TGF-β is exerted by stimulation of FOXP3 positive synthesis (forkhead box P3) and development of T regulator cells (Tregs) [7]. Many pathologies such as advanced neoplastic processes or diseases with ongoing fibrosis [20, 28] are connected with increased activity of TGF-β. Abnormal TGF-β1 signalization contributes to the development of PBC through inhibition of inflammatory responses, and an increase of fibrogenesis [30]. The disruption of transduction of TGF-β1 signalization contributes to the development of autoimmune diseases, liver fibrosis, and cancer [31].

Transforming growth factor β regulates the synthesis of extracellular matrix, degradation, and reconstruction, which are important processes in chronic inflammatory liver disorders. Furthermore, TGF-β mediates the transformation of hepatic HSCs into myofibroblasts. Its concentration is increased in patients with NASH in comparison to patients with simple steatosis and healthy persons, which suggests that this cytokine takes part in fibrosis in NASH [20, 28]. Additionally, TGF-β inhibits the differentiation of Th1 and Th2 cells, and contributes to the development of Th17, Th9, and Treg's phenotype [10, 28]. What is interesting, the combination of TGF-β with proinflammatory cytokines, including IL-6 inhibits the production of Treg and stimulates the Th17 cells, acting proinflammatory. Low concentration of TGF-β restrain the expression of IL-23 receptor, which is of a great importance for Th17 cells development, enhancing the expression of Foxp3, and determining the anti-inflammatory Tregs' response [28]. High concentration of TGF-β, along with IL-6 and IL-21, results in increase of IL-23 receptor expression, facilitating Th17

phenotype [28]. Mutual relationship between Treg lymphocytes and Th17 cells constitute the delicate balance between tolerance and activation of immune response [7]. The aforementioned results explain the importance of recognizing the relation between potentially cytotoxic response of Th17 and regulatory Treg in course of NASH.

Interleukin 10

Interleukin 10 (IL-10) is an anti-inflammatory cytokine [32]. It is mainly produced by macrophages, dendric cells, B and Treg lymphocytes, but also by different cells in the liver including hepatocytes, Kupffer cells, and HSCs [25]. Bacteria, viruses, and parasites may stimulate the production of IL-10 through host cells [25]. IL-10 signalization consists of IL10R1-ligand specific and second unit, which occurs also in other cytokines receptors. Binding of IL-10 to IL10R activates the transcriptive factor signal transducer and activator of transcription 3 STAT3 [25]. STAT3 plays significant role in balance of pro- and anti-inflammatory responses [11].

In liver damage induced by alcohol, viruses, autoimmune diseases, or steatosis, IL-10 acts as a protector [33]. Deficiencies of IL-10 expression or IL-10 receptor (IL10R) lead to inflammatory diseases [32]. In animal models of induced liver steatosis IL-10 inhibition, by administering/pre-treated with recombinant murine IL-10 (BD Biosciences, USA) caused the increase of proinflammatory cytokines and despair of insulin signalization [33]. In addition, IL-10 decreases the frequency of occurrence of liver damage after different traumas. It was proven that IL-10 may protect against ischemic liver injury after organ transplantation, thus significantly increase the number of useful livers [34].

Interleukin 6

Interleukin 6 is regarded as inflammatory cytokine. Its concentration increases in obesity and body mass loss leads to the reduction of IL-6 serum concentrations [35, 36]. Increased expression of IL-6 was observed in liver of patients with NASH and was connected to the severity of the disease. Scientists notice strong relation between NASH, insulin resistance, and type 2 diabetes [22]. Furthermore, IL-6 plays important role in inflammatory response and enhances neoplastic processes such as proliferation of cells and anti apoptic process [37].

Tumor necrosis factor α

Tumor necrosis factor α is a proinflammatory cytokine participating in metabolic, inflammatory, proliferative, and also necrotic processes. In response to chronic inflammatory activity in organism, TNF-α is secreted by macrophages, hepatocytes, Kupffer cells, and other types of cells [38]. TNF-α participates in development of steatosis and liver fibrosis in NAFLD [38]. Body mass loss, similarly as in case of IL-6, is connected with the decrease of TNF-α concentration, which in turn, results in a decrease of inflammatory response [36]. Increased level of TNF-α leads to activation of NF-κB that regulates immune and inflammatory response, taking part in apoptosis inhibition [36].

Adipokines

Adipokines are biologically active substances, which participate in hemostasis and blood pressure regulation, lipids and carbohydrates metabolism, atherosclerosis and inflammatory diseases [35, 39]. The family of adipokines is very broad. Adipokines include inter alia: leptin, resistin, RBP-4, lipocalin 2, ANGPTL2, IL-18, CCL2, CXCL5, NAMPT, and adiponectin [35, 38]. They are produced in visceral fatty tissue and secreted into the system of portal vein, and along with blood are transported to the liver. Adipokines expression may differ depending on the location of an adipose tissue depot. What is more, adipocytes are localized in human organism in connection with many different organs including heart, kidneys, bone marrow, lungs, and tunica adventitia of large vessels [35]. An association between impaired secretory function of adipose tissue, adipokines, and immunological cells like Th17, Treg helps to understanding the pathomechanism NAFLD and can identify biomarkers for predicting of disease progression.

Important role of different adipokines in development of various diseases including obesity, diabetes, psoriasis, scleroderma, NAFLD has been already established [31, 35, 38, 39]. Adipopectin and leptin increase insulin sensitivity and act as anti-inflammatory mediators [40]. Adipopectin also inhibits proinflammatory cytokines (including TNF-α) and stimulates anti-inflammatory cytokines (IL-10), which, as consequence, leads to impediment of macrophages function [40]. Adipopectin also alleviates oxidative stress and fibrinogenesis. Decreased level of adipopectin is connected with metabolic syndrome and NAFLD [40].

Leptin

Leptin is a hormone derived from adipocytes, which reflects the nutritional status of organism [40, 41]. Leptin shows proinflammatory and profibrogenic properties of significant importance in pathogenesis of liver diseases including NASH [40]. Increased concentrations of

leptin is correlated with obesity, which initiates proinflammatory mechanisms. Similarly to proinflammatory cytokines, leptin participates in differentiation of Th1 cells in adipose tissue, CD8+ T-cells, macrophages, and mast cells, which stimulate synthesis proinflammatory cytokines (such as TNF-α, IL-6, and IL-12) [41]. Decreased concentrations of leptin in plasma suggests malnutrition and leads to impairment of immune system function [41]. Leptin participates in NASH development contributing to insulin resistance and steatosis, but also in regulation of hepatic HSCs [38]. Leptin level correlates with obesity and steatosis [38], however, further studies are needed in order to confirm the influence of leptin on NAFLD.

Retinol binding protein-4

Retinol binding protein-4 (RBP-4) is a protein responsible for transportation of retinol (vitamin A) stored and synthesized in hepatocytes and adipocytes [39]. Concentration of RBP-4 in serum is frequently increased in insulin resistance in obese patients and type 2 diabetes [35, 38, 42]. Serum concentration of RBP-4 may be associated with inflammatory response in obese patients and may increase in advanced stage of NAFLD [38, 42]. However, the role of RBP4 in pathogenesis of NAFLD is not completely understood.

Angiopoietin Like Protein 2 (ANGPTL)

Angiopoietin Like Protein 2 (ANGPTL) is regarded as adipokine promoting inflammation and insulin resistance. Deficiency of ANGPTL2 leads to alleviation of inflammatory reaction through decreasing the activity of proinflammatory cytokines in adipose tissue and reduction of insulin resistance in mice. Its increased amounts lead to intensification of adipose tissue inflammation and resistance for insulin. It activates the transition of signals through integrins, which induces inflammation via endothelial cells, monocytes, and macrophages [35].

Ghrelin

Ghrelin is a small peptide (28 amino acids), which participates in regulation of appetite, body mass, and energy balance [37]. Importantly, ghrelin influences insulin sensitivity [38]. In an animal study in rats in which liver steatosis was induced by high fat diet, treatment with ghrelin reduced damage caused by steatosis, oxidative stress, and inflammatory state. Authors concluded that ghrelin might have a protective activity in NAFLD [37].

The study by Zwirska-Korczala *et al.* demonstrated that there is no decrease of ghrelin in plasma after a meal in obese women, although it is observed in lean women. The researchers suggest that chronic administration of ghrelin increases weight gain. An increased ghrelin level in plasma and lack of decrease after a meal is characteristic feature of obesity. However, paying attention to the anti-inflammatory ghrelin in obese patients, could have an impact in the progression of metabolic diseases to NASH [43].

Resistin

Resistin is an adipokine produced mainly by nucleated peripheral blood cells [38] and it is composed of 108 amino acids. It is believed that resistin may be a mediator of hepatic insulin resistance [44]. There is a relationship between resistin concentration and obesity. However, its relationship with type 2 diabetes and insulin resistance is not clear [38]. It was found that serum resistin level was directly proportional to body fat mass. In a study of 40 patients with NAFLD it was noted significantly higher resistin-values in comparison with a group of 40 healthy volunteers [44].

Visfatin

Visfatin is mainly secreted by visceral adipose tissue, but also by hepatocytes, lymphocytes, monocytes, and neutrophils [31, 45]. Visfatin level in plasma is associated with the amount of fat tissue, type 2 diabetes, and metabolic syndrome [31]. It has been shown that the concentration of visfatin levels and mRNA levels in a visceral adipose tissue and the liver were increased in a rat model [46]. Authors have suggested strengthening role of visfatin inflammatory response in the formation of visceral adipose tissue rats [46]. Furthermore, visfatin can induce TNF-α, which is associated with obesity and insulin resistance [46, 47]. Insulin resistance is accompanied with increase of visfatin concentration in serum. It is supposed that visfatin resembles the activity of insulin, i.e. inhibits gluconeogenesis in liver and also increases demand for glucose in skeletal muscles and adipose tissue [45]. In different studies, the correlation between visfatin concentration and development of NAFLD has been searched, but not confirmed [31, 45]. In the study [48], serum visfatin levels were significantly associated with NAFLD/NASH. Importantly, the study involving 70 patients with NAFLD showed a relationship between visfatin levels and the degree of liver fibrosis. The researchers suggested the application of visfatin as a non-invasive method for advanced fibrosis allowing to avoid liver biopsy in numerous patients with NAFLD [49]. It has been demonstrated in human studies that visfatin lev-

el in the liver tissue depends on the severity of liver fibrosis. There is no evidence that visfatin expression connects with liver steatosis degree; therefore, the expression of visfatin does not distinguish NASH from NAFLD [47].

Conclusions

In conclusion, it has to be highlighted that immune pathways, especially Th17 and Treg, as well as adipokines are a link between insulin resistance, obesity, and NAFLD. However, the significance of Th17, Treg, and adipokines in the course of NAFLD and progression to NASH requires further extension of research with well characterize group of patients with NAFLD and NASH. It is important to recognize the crucial role of Th17/Treg balance in course of NASH not only in the pathogenesis of the disease, but also as potential target of new therapies.

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Disclosure

Authors report no conflict of interest.

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