Journal of Mind and Medical Sciences

Volume 6 | Issue 1 Article 10

2019

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Recommended Citation

Coste, Sorina Cezara; Popovici, Ionela; Stefan, Andreea Maria; Breaban, Iulia; Sitar Taut, Adela; Tarmure Sarlea, Simina; Cozma, Angela; Sampelean, Dorel; Orasan, Olga Hilda; Negrean, Vasile; and Procopciuc, Lucia Maria (2019) "Immune and Inflammatory Pathways in Non-Alcoholic Steatohepatitis (NASH). An update," *Journal of Mind and Medical Sciences*: Vol. 6 : Iss. 1 , Article 10.
DOI: 10.22543/7674.61.P5257
Available at: https://scholar.valpo.edu/jmms/vol6/iss1/10

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https://scholar.valpo.edu/jmms/
https://proscholar.org/jmms/
ISSN: 2392-7674

J Mind Med Sci. 2019; 6(1): 52-57
doi: 10.22543/7674.61.P5257

Received for publication: July 11, 2018
Accepted: October 10, 2018

Review

Immune and Inflammatory Pathways in Non-Alcoholic Steatohepatitis (NASH). An update

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Abstract

Non-alcoholic steatohepatitis (NASH), also known as fatty liver disease (FLD), is a major public health problem. It is considered to be the hepatic manifestation of the metabolic syndrome. Chronic inflammation of the liver is an essential key in the progression from simple hepatic steatosis to steatohepatitis, the evolutionary stage of fatty liver disease. Moreover, the innate immune system plays a crucial role in the progression of hepatic inflammation. For this reason, it is of utmost importance to elucidate the connections between immune mechanisms, Toll-like receptor cytokine signalling, in order to find new effective treatments.

Further studies are necessary to test theories presented in this paper. The elucidation of mechanisms underlying the progression of hepatic steatosis towards steatohepatitis is essential for the development of useful diagnosis and treatment for medical practice.

Keywords : non-alcoholic steatohepatitis, NASH pathogenesis, immune mechanism, Toll-like receptors (TLRs), Interleukin-17 (IL-17)

Highlights

- ✓ One of the possible mechanisms responsible for the activation of the immune system through intestinal microbiota is the activation of IL17 axis.
- ✓ Another possibility is represented by activation of the TLRs, with further studies being necessary to clarify these perspectives.

To cite this article: Coste SC, Popovici I, Stefan AM, Breaban I, Taut AS, Sarlea ST, Cozma A, Sampelean D, Orasan OH, Negrean V, Procopciuc LM. Immune and Inflammatory Pathways in Non-Alcoholic Steatohepatitis (NASH). An update. *J Mind Med Sci.* 2019; 6(1): 52-57. DOI: 10.22543/7674.61.P5257

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Introduction

NASH is a disease considered to be the liver manifestation of the metabolic syndrome (MS) (1). Its incidence and prevalence are continually increasing worldwide. The prevalence of NASH in the European general population is between 20-30% and reaches 90% among patients with associated obesity (2). NASH has the potential of advancing to hepatic cirrhosis and increases the risk of developing hepatocellular carcinoma (HHC) (2). Due to the alarming increase in the incidence of obesity associated with NASH and its potential to progress towards severe chronic hepatic diseases (hepatic cirrhosis and HHC), it has been estimated that NASH will become one of the main causes of liver transplant (3). Sustained inflammatory process in the liver is essential for the progression from NAFLD to NASH.

Recent medical research has reported important progress in understanding the immune and inflammatory mechanisms involved in NASH (4).

Discussions

Hepatic cell population

The liver is made up of a variety of cells involved in the propagation of the inflammatory process. Hepatocytes represent 60-80% of the total liver cell population and are responsible for the metabolic process, biosynthesis, biliary secretion, and detoxification. Apart from these, in the liver, there are also cells with a role in immunity, such as Kupffer cells (KC) responsible for innate immunity, macrophages, and natural killer (NK) cells. After liver injury, other cells are recruited. Some examples are neutrophils, leukocytes, monocytes, and macrophages, also responsible for the innate immune response. The acquired immune response belongs to T NK cells and B cells. Other cell types that contribute to the production of inflammation and fibrosis are hepatic stellate cells (HSC) and sinusoidal endothelial cells (5).

Toll-like receptors (TLRs) and interleukin 17 (IL-17)

In the liver, TLRs are expressed through Kupffer cells, hepatocytes, stellate cells, and sinusoidal endothelial cells. They are found in different cellular locations. TLR 2, 4, 5, 6, and 11 have extracellular location, while TLR 3, 7, 8, and 9 are expressed intracellularly in endosomes, lysosomes, and the endoplasmic reticulum (6). TLR 4 is the most studied TLR (7). From the family of ten TLRs discovered in humans, TLR4 was the first to be identified (8).

IL-17 is the generic name for a cytokine family composed of 6 members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F). Interleukin 17A, which names the family, is secreted in the skin, liver, and mucous membranes (9).

NASH pathogenesis

The theory of the two aggressions or the theory of multiple hepatic aggressions has been formulated. The first aggression in NASH is caused by modifications in the metabolism of fatty acids, which leads to accumulation of lipids in hepatocytes and to the occurrence of hepatic steatosis. Lipopolysaccharides (LPSs), oxidative stress, cytokine production, and other pro-inflammatory mediators represent the second aggression that sustains the progression of steatosis to steatohepatitis (10).

Obesity and NASH pathogenesis

Adipose tissue is considered to have an endocrine and immunological function (11).

The incidence of overweight and obesity has increased worldwide, from 857 million in 1980 to 2.1 trillion in 2013 (12). Obesity is associated with atherosclerosis in cardiovascular diseases, Alzheimer's disease, type-2 diabetes mellitus, and metabolic syndrome (13). The incidence of metabolic syndrome is continually increasing, because of unhealthy lifestyle changes in the general population – an increasing consumption of fast foods, high-fat diets and processed foods, a sedentary life style, and lack of physical exercise (14).

In obesity, there is dysfunctional adipose tissue resulting from the infiltration of macrophages and hypertrophic adipocytes (15). The liver is the major target for adipose tissue accumulation and, thus, the occurrence of steatohepatitis. Therefore, adipose tissue is considered to have a major role in NASH.

Different studies conducted on laboratory mice with obesity have shown that pro-inflammatory pathways are activated in the fat tissue in both obesity and NASH. Their activation involves a multifactorial process and includes the presence of oxidative stress which leads to hypoxia and adipocytes death (16), changes in the intestinal microbiota with increased intestinal permeability, and metabolic endotoxemia (17, 18). Obesity and NAFLD progression are associated with dysbiosis in the intestinal microbiota (19). Furthermore, experimental studies on animal models with diet-induced obesity have shown that intestinal microbiota is essential in the development of obesity and that it could play an important role in modulating NAFLD progression (20).

Two of the most common mechanisms in NASH pathogenesis involve the immune and inflammatory

pathways. The inflammatory pathways are represented by cytokines with a pro-inflammatory role (interleukins (IL), while increased free fatty acid (FFA) concentration or bacterial products (lipopolysaccharide-LPS) activate the innate immune system from adipocytes and macrophages through Toll-like receptors (TLRs) (Figure 1) and ultimately lead to inflammation (18). Also, the increasing level of free fatty acids in blood circulation leads to their growth in the portal system, thus contributing to the development of NAFLD or NASH (15).

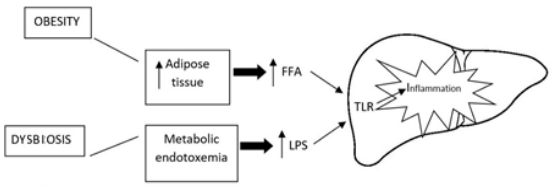

Figure 1. Toll-like receptor (TLR) activation

As a consequence of activating the above pro-inflammatory pathways, adipocyte death occurs, producing cytokines and chemokines with a key role in the inflammatory process. Also, as a secondary consequence, other immune cells are recruited: neutrophils, eosinophils, dendritic cells, natural-killer (NK) cells, T cells, B cells etc. (13).

Changes in the intestinal microbiota, TLR pathways and NASH pathogenesis

One of the main concerns of the scientific community is the role of intestinal microbiota and probiotics in liver diseases. It is known that patients with NAFLD present an increase in intestinal permeability and an increased incidence of bacterial development in the small intestine compared to patients without liver disease (21). Bacterial translocation promotes the inflammatory process of the liver by activating TLRs (22). There are two known patterns for TLR activation: pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).

PAMPs originate from certain exogenous pathogens responsible for the emergence of inflammation and contain lipids, lipoproteins, nucleic acids, and proteins. They are expressed by bacteria, viruses, parasites, and fungi (6). This pathway contributes to the inflammatory process in NASH by signaling the pathogen recognition receptors (PRRs), leading to the activation of innate and acquired immune systems. PAMPs are recognized by numerous PRRs receptors, including Toll-like receptors (TLRs) (6).

DAMPs, similar to PAMPs, are endogenous molecules released by destroyed cells that trigger a sterile inflammatory response. In NASH, there is chronic inflammation resulting from the presence of DAMP. Similar to PAMPs, DAMPs activate both types of immunity, i.e., acquired and innate, and PRRs, out of which the most characteristic are TLRs (23). The DAMP receptors responsible for TLR activation are hyaluronic acid, fibrinogen, and thermal shock proteins (23).

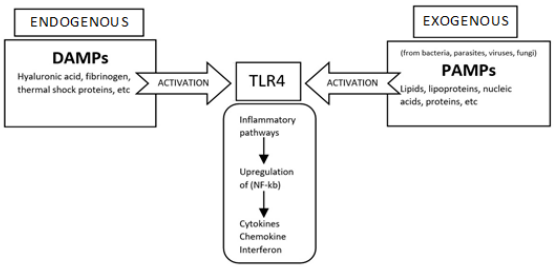

Figure 2. TLRs recognize a wide range of PAMPs. Once a molecular pattern has been recognized by TLR, it initiates signals with a role in activating the inflammatory and antiviral responses. Some examples are the activation of the Kappa B Nuclear transcription factor (NF-kb) and the regulatory factors of interferon which determine the transcription of inflammatory cytokines, chemokine or type-1 interferon (6)

Different studies have attempted to elucidate the role of TLR4 in NASH. Patients or laboratory mice with NASH presented increased serum levels of polysaccharides, which would suggest an increased activation of TLR4 (24). It is also supposed that fructose could increase activation of TLR4 by its influence on microbiota and intestinal permeability. It is a risk factor for steatosis and steatohepatitis (25).

The activation of TLR4 and sensitization of hepatic stellate cells could be the key connection between the inflammatory process and the emergence of fibrosis in NASH or other forms of chronic hepatitis. The explanation could be the involvement of hepatic stellate cells in regulating the extracellular matrix and the regeneration of liver tissue (8).

Immune cells and IL-17 contribution to NASH pathogenesis

The innate immune response, consisting of Kupffer cells (KC), neutrophils, dendritic cells (DCs), and natural killer cells (NKT) plays an important role in the pathogenesis of NASH in NAFLD (26). Having characteristics of both innate and acquired immune cells, NKTs are considered to be the link between the two immune systems. NKTs are found predominantly in the

liver and regulate the immune response through the secretion of cytokines TH1 and TH2 (27). T helper 17 cells (TH17) are a subdivision of T cells that secrete IL-17 and play a role in mediating the immune response by modulating the clearance of pathogens and the inflammatory response of tissues.

In acute or chronic liver disease, KCs are activated by PAMPs and DAMPs and release cytokines with pro-inflammatory roles, such as tumor necrosis factor (TNFa), interleukin-6 (IL-6), and interleukin-1b (IL-1b), responsible for the activation of T cells, stellate cells which eventually lead to apoptosis (26). The activation of neutrophils determines the release of pro-inflammatory cytokines and myeloperoxidase responsible for the occurrence of oxidative stress in the liver (28). Neutrophil high concentrations compared to lymphocytes have a role in the progression of NASH (29). A decrease in DCs results in the unfavorable evolution of NASH, suggesting that DCs play an important role in steatohepatitis (30). Natural killer T cells (NKT) are a subdivision of lymphocytes presenting markers for NK cells: CD161 and CD94 and T cell receptors (27).

Recent studies have shown the importance of TH17 cells in autoimmune liver disease, viral hepatitis, alcoholic steatohepatitis, and hepatocarcinoma (31). Tang et al. (32) demonstrated an increase in the number of TH17 cells at the hepatic level after 8 weeks of hypercaloric diet as well as the fact that these cells are associated with the progression of hepatic steatosis and inflammation through the production of Interleukin 17 (IL-17).

A delayed or ineffective immune response results in viral, bacterial, or fungal infections. But a heightened response can be harmful, as observed in autoimmune diseases: rheumatoid arthritis, type-1 diabetes, psoriasis, and inflammatory bowel diseases (33). The pathogenesis of these autoimmune disorders is related to the excessive production of pro-inflammatory cytokines: TNF-alpha, IL-6, IFN-gamma, IL-23 etc. (34).

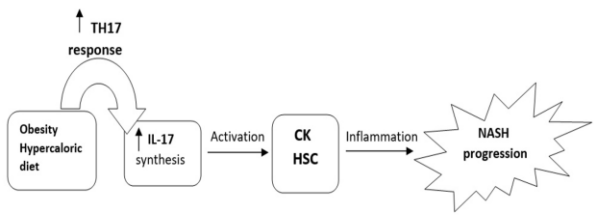

Figure 3. IL-17 role in the pathogenesis of NASH

Special interest has been paid to interleukin 17 (IL-17) which plays an important role in the pathogenesis of NASH (Figure 3) (35). The classical conceptualization claims that under the action of certain stimuli, ThCD4 + lymphocytes are differentiated in TH1 lymphocytes and TH2 lymphocytes. It has recently been found that under the influence of IL-23, ThCD4 + lymphocytes differentiate in a specific cell type whose main action is to release IL-17, in addition to tumor necrosis factor (TNF) and granulated monocyte colonies stimulation factor (GM-CSF) (9). The lymphocytes of this distinct subset of TH1 and TH2 were called Th17 lymphocytes. Apart from Th17 lymphocytes, additional synthesis sources of IL-17 are lymphocytes THCD8 + neutrophils, NK and NKT cells, macrophages etc. (36). Increased levels of IL-17A were discovered in liver disorders such as alcoholic steatohepatitis (37), viral hepatitis B and C (9, 38), primary biliary cirrhosis (39), hepatocellular carcinoma (40). The increased expression of IL-17A is also found in patients with obesity and is associated with an increased infiltration of adipose tissue with TH17 (41).

Conclusions

One of the possible mechanisms responsible for the activation of the immune system through intestinal microbiota is the activation of IL17 axis. The other one is the activation of the TLRs. Further studies are necessary to test these possibilities.

The elucidation of mechanisms underlying the progression of hepatic steatosis towards steatohepatitis is essential for the development of useful diagnosis and treatment for medical practice.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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