Review paper

Immunodeficiency caused by cirrhosis

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Abstract

The syndrome of decreased immunity caused by cirrhosis is a combination of different immunological mechanisms and reactions which result from an advanced stage of the liver disease. The synthesis of proteins of the acute phase becomes impaired, there develop different deficiencies of the complement system, and there ensues a decrease of receptors that are meant to recognize antigens. The negative changes become apparent in the field of cell responses, e.g. there are changes in the amounts of generated monocytes and macrophages, and their phagocytic capabilities and chemotaxic reactions are impacted as well. The humoral response results in distorted synthesis of particular antigen categories. The risk of detrimental immunoresponses with the end result of endotoxemia is not rarely coupled with both local and global infections. The combination of the aforesaid immunodeficiencies worsens the healing chances of cirrhosis sufferers and more often than not it increases the mortality of the affected patients.

Key words: inflammation, immunodeficiency, endotoxemia, cirrhosis.

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Introduction

Regardless of its etiology, cirrhosis as the end stage of a chronic liver illness tends to lead to a syndrome called cirrhosis-associated immune dysfunction syndrome (CAIDS) [1]. In its development, the local immunological response system, i.e. that of the liver, is impaired, whereas the mechanisms responsible for recognition of antigens, the effector mechanisms and their responses are disrupted. As a result of all this, the balance between the pro-inflammatory and anti-inflammatory processes as well as the activation of cells of the immunological system becomes disturbed. Chronic inflammation causes an advanced stage of fibrosis, a significant cirrhosis-linked restructuring and a sequence of serious complications, which may, among other consequences, result in venous hypertension of the hepatic portal vein or encephalopathy of the liver and, eventually, aggravate the already present dysfunction of the liver, which becomes classified as ACLF, i.e. acute-on-chronic liver failure, and they can even trigger the final stage of this failure [2]. The ensuing development of CAIDS incapacitates the habitual efficient protection against different infections and worsens the expected effects of protective vaccinations [3-5].

Immunological function of the liver

The liver of an adult usually weighs about 1.5 kg, of which 70% is made up of cellular elements linked to metabolic and secretion functions (hepatocytes, cells of bile ducts), whereas the remaining 30% is responsible for the immunological functions of the organ. The immunological response cells comprise cells of endothelium, lymphocytes, stellar cells (i.e. liver macrophages) and epithelial cells of bile ducts [6].

Cells of endothelium of hepatic ducts are the first barrier between the blood and hepatocytes [7]. Through the production of different cell adhesion molecules (including ICAM-1, ICAM-2, VCAM-1, antigens HLA – class I and II), they are able to select and intercept activated lymphocytes T (CD4+ and CD8+), which enter the liver, and thus they are able to confront them with exogenic antigens. This reaction results in the genera-

tions of tolerance to the following contacts with antigens (by means of synthesis of cytokines IL-10 and TGF-β). Liposaccharide (LPS; a factor produced by commensal bacterial flora) is an active inhibitor, which hinders endothelial cell generation of new antigens directed against T lymphocytes.

Lymphocytes are present in the liver and number between 5 and 10 million/g as per the mass of the organ. They belong to the subpopulation of toxic lymphocytes (NK, NKT), whereas lymphocytes of populations T and B are few and far between. By means of their natural toxicity (i.e. without any need of antibodies), but through increased numbers of cytokines (interferons IL-12, IL-18, IL-21), NK cells spontaneously eliminate carcinogens and other cells infected with viruses. Uncontrolled increasing activities of NK cells cause inflammatory reactions (viral or auto-aggressive hepatic inflammations). In the liver, there is a large population of lymphocytes, which are characterized by the presence of both receptors typical of NK cells and T cell receptors (TCR), which are able to recognize glycolipid components of the bacterial cell membrane. NKT cells synthesize cytokines Th1 (IL-2, IFN-γ, TNF-α) Th2 (i.e. IL-4) and simultaneously IL-4 and IFN-γ (profile Th0), which are engaged in cytotoxic and immunoregulatory activities. They prevent autoimmunological reactions by blocking the activity of T lymphocytes, which gets triggered by auto-antigens. NKT lymphocytes, which combine some characteristics of T and NK cells, possess features of both adaptive and innate immunoresistance [8].

The peculiar and particular feature of the liver is the presence of a population of T lymphocytes, which, activate γδ TCR (35% of the total population of T cells). Activated lymphocyte TCR γδ synthesize cytokines of types Th1 and Th2, which exert strong cytotoxic activities that could, at the same time, be linked to antigens and be independent of restriction MHC, thus efficiently countering carcinogenic cells [9]. Due to their recognition of thermic-shock proteins, phospho-antigens and alkylamines (bacterial byproducts), γδ T lymphocytes destroy cells which are infected with bacteria and viruses. They also take part in the regulation of the immune response, e.g. by the production of IFN-γ.

Stellar cells (previously referred to as Kupffer cells), making up about 80% of all the macrophages in the body, are found in the sinusoidal sides of the hepatic ducts and adhere to the endothelium layers [10]. They act as cells secreting antigens. Activated by infection-linked factors, they release acute-phase proteins and cytokines (mainly IL-12 and TNF-α), which switch on NK cells and reactions of type Th1.

Endothelial cells of bile ducts, which cover the external and internal layers of these ducts, regulate the flow of bile from the liver to the duodenum. Due to the secretion of adhesins and co-stimulation molecules, they are able to release antigens. Additionally they are capable of synthesizing chemokines and cytokines. Furthermore, the released bile possesses immunological properties as it contains a significant amount of immunoglobulins, e.g. IgA.

The immunological system of the liver, despite the predominance of potentially cytotoxic cells, possesses very high tolerance to both autoantigens (by products of the commensal bacterial flora, material generated in the course of cellular disintegration) and proper antigens (mainly coming from the digestive system). The prevalence of cells functionally linked to the adaptive resistance system (the cellular immune response) allows the state of tolerance to be maintained and facilitates elimination of the pathogens [11].

The liver is also responsible for synthesis of proteins taking part in innate and adaptive immune responses. They include complement components, the majority of acute-phase proteins (e.g. C-reactive proteins, fibrinogens, procalcitonins) and many receptors linked to the recognition of particular patterns (pattern-recognition receptors – PRRs), for instance Toll-like receptors (TLR). Activation of the proteins leads to opsonization (adhesion of particles to pathogens, which facilitates their phagocytosis), and inflammatory and cytotoxic reactions, which participate in regulation and result in the final immune response.

Cirrhosis-associated immune dysfunction syndrome – development and types

The physiological abilities to recognize antigens and activation of the immune response are mutually linked and coordinated so that the immune response to the pathogen can be as efficient and quick as possible. In the case of cirrhosis, there appear some irregularities of the immunological response. They can change dynamically at different stages of the illness (balanced cirrhosis, decompensated cirrhosis, acute cirrhosis) and they are also dependent on the organ damage and stimulating factors, e.g. bacterial translocation. In the development of CAIDS, the tolerance of monocytes towards endotoxins and bacterial antigens plays a significant role. The tolerance develops as a result of the low density of the above-mentioned factors as well as their penetration through the damaged intestinal barrier [12]. These factors trigger inflammatory reactions and lead to negative mutual coupling, which results in decreasing activity of anti-inflammatory cytokines.
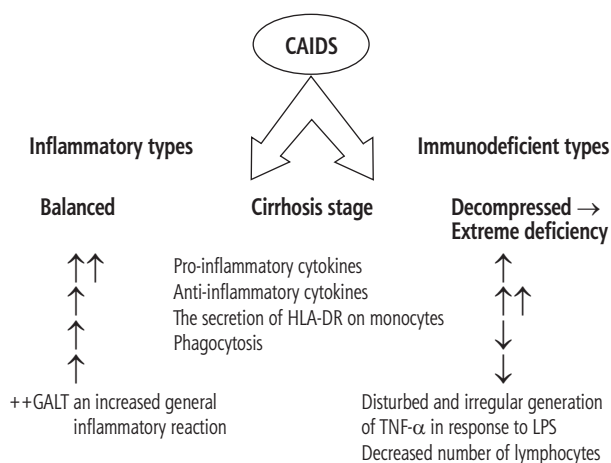
GALT – gut-associated lymphoid tissue (Peyer's patches and mesenteric lymphatic nodes), HLA-DR – proteins of histocompatibility system, secreting antigens against lymphocytes, LPS – lipopolysaccharide, TNF-α – the main cytokine of inflammatory responses

Fig. 1. The types of syndrome cirrhosis-associated immune dysfunction syndrome (CAIDS)

The activated gut-associated lymphoid tissue (GALT) cells and the generated cytokines enter the blood circulation system and aggravate the general inflammatory reaction. This state is called pro-inflammatory type CAIDS [13, 14].

Aggravated stages of cirrhosis coincide with the pre-programmed immune response. The main mechanism of this phenomenon consists in the impeded function of monocytes, i.e. their secretion is inhibited (HLA-DR) and there occurs the impacted release of TNF-α in response to lipopolysaccharide (LPS), the decreased number of T lymphocytes, and inadequate secretion of pro-inflammatory and anti-inflammatory cytokines [15].

In the case of hospitalized patients, the aforementioned changes tend to get discovered quite late, which more often than not is linked to advanced stages of cirrhosis. This category of patients is affected by the ensuing stalemate of the immune system, which bears a striking similarity to analogical developments in the case of sepsis. This developmental stage of CAIDS is characterized by significant immunodeficiency, which, due to bacterial infections, increases the risk of death [16] (Figure 1).

Some of the mechanisms responsible for aggravated cases of cirrhosis-related immunodeficiency

Mechanisms leading to cirrhosis-related immunodeficiency adversely affect the local immunological surveillance exerted by the liver and, thus, negatively impact the general conditions of the organ. Further-more they cause different systemic irregularities and abnormalities, which deregulate the general immune system of individual patients.

Local immunological surveillance and checks exerted by the liver

The liver, among other functions, acts as a bacterial filter. Its phagocytic system (previously known as RES – reticuloendothelial system) plays an important role in the elimination of intestinal bacteria and endotoxins [17]. In the case of cirrhosis patients, the essential functions of RES are debilitated and the number and the efficiency of stellar cells (Kupffer cells, hepatic macrophages) are weakened as well [18, 19]. These syndromes and phenomena coincide with the disturbed synthesis of proteins responsible for the innate immune resistance. They also impact the secretion of receptors responsible for antigen recognition, all of which decreases the antibacterial action of cytophages. These medical conditions are particularly visible in the case of advanced cirrhosis and ascites (characterized by low levels of complements C3, C4, C50 in the serum and effusion fluid) and they tend to result in increased susceptibility to various bacterial infections [20, 21].

In the occurrence of above-mentioned irregularities, a crucial role is played by genetic polymorphisms of receptors responsible for the pattern recognitions of TLR and NOD2. As a result, these receptors are less efficient in binding polysaccharides and/or bacterial endotoxins, which exposes the affected patients to coinciding and/or ensuing infections [22]. In the research carried out by Nischalke and co-authors, analyzing multi-factor aspects [23], some genetic variants of TLR and NOD2 were found to be independent predicators of spontaneous bacterial peritonitis (SBP).

Researchers have presented evidence of a link between excessive iron residues and bacterial infections. Cirrhosis sufferers have often been diagnosed with the syndrome of excessive iron residues (no connection to transferrin), which might, in vivo, inhibit the proliferation and activities of lymphocytes (B and T), particularly of subtype CD4, and result in a disturbed CD4/CD8 ratio [24]. All of this increases the risk of bacterial infections due to the role that the accumulated iron ions play in the bacterial metabolism [25, 26]. Resulting from the increased reaction of free-radical-induced iron ions and the thus accelerated recruitment and activation of stellar cells playing a crucial role in the hepatic fibrosis, the phenomenon of sideronecrosis, i.e. the mortality of hepatocytes, causes advanced hepatic fibrosis regardless of the original etiology [27].

Table 1. Types of hepatic immune cells and their clinical role

Cell types	Roles	Clinical significance
Sinusoidal hepatic endothelial cells	↑ Production of adhesives and interception of activated T lymphocytes Secretion of antigens towards T lymphocytes (CD4 and CD8)	Destruction of present blood-solvable antigens Generation of tolerance for subsequent contacts with antigens
NK lymphocytes NKT lymphocytes	Natural cytotoxic action – destruction without antigens being activated ↑ Production of cytokines Th1, Th2, Th0 Activation of Tc, NK lymphocytes and macrophages	Destruction of carcinogenic cells Destruction of cells infected with viruses Immunoregulation
Th lymphocytes (auxiliary)	Stimulation of production of antigens ↑ Production of cytokines activating B lymphocytes Activation of Tc, NK lymphocytes and macrophages	Stimulation of allergic and inflammatory reactions Immunophagocytosis Destruction of bacteria and parasites Alimentary tolerance
Treg (regulatory) lymphocytes	Activated tolerance against orally applied antigens Inhibition of destruction of the microorganism Inhibition of excessive anti-inflammatory response	Chronic infections Tissue protection from damage Destruction of carcinogenic cells Destruction of cells infected with viruses
Tc (cytotoxic) lymphocytes	↑ Generation of cytokine IFN-γ Activation of macrophages Recognition of antigens without the presence of cells secreting the antigens	Immunoregulation
Tγδ lymphocytes	Activation of cytotoxicity dependent on the antigen types	
B lymphocytes	Production of antigens Recognition and secretion of antigens without participation of MHC Production of cytokines Regulation and activation of dendritic cells and T lymphocytes	First line of protection against microorganisms
Dendritic cells - Epithelial cells of bile ducts	Ability to secrete antigens Production of chemokines and cytokines Secretion of adhesives and co-stimulating molecules Secretion of bile containing immunoglobulins (IgA)	Development of inflammatory reaction Destruction of carcinogenic cells Destruction of cells infected with viruses Activation of cells NK and cells of response type Th1
- Stellar cells (hepatic macrophages)	Production of proteins of acute phase and cytokines (IL-12, TNF-α) Secretion of antigens	

CD4 – particle co-activating auxiliary T lymphocytes, CD8 – particle co-activating cytotoxic T lymphocytes, IFN-γ – interferon gamma, IgA – immunoglobulin A, IL-12 – interleukin 12, Th lymphocytes – auxiliary lymphocytes, Treg lymphocytes – regulatory T lymphocytes, Tc lymphocytes – cytotoxic lymphocytes, Tγδ lymphocytes – subpopulation of T lymphocytes showing presence of receptor TCR with spectrum chains of γ and δ, MHC – main histocompatibility system, NK – natural killer, NKT – natural killer T cells – lymphocytes combining features of NK and T cells, TNF – tumor necrosis factor – an agent causing the extinction of carcinogens alpha

Impaired function of immune cells

Cirrhosis-related immune deficiency can also be a result of certain irregularities linked to the main populations of immune cells present in the whole body (Table 1).

The constant activity of neutrophils is triggered by bacterial endotoxins. However, due to the opsonization of bacteria, their phagocytic properties are hindered and, furthermore, their bactericidal action is impeded by the increased myeloperoxidase and excessive growth of free radicals [28]. The diminished adhesivity to mesothelium and transendothelial migration impact the chemotaxis of neutrophils to the focal points of infection [29]. Because of the cirrhosis-related hyperammonemia and hyponatremia, the size of neutrophils is reduced [30], whereas the coinciding hypersplenism and increased apoptosis lead to neutropenia.

Contrary to the habitual cirrhosis-related granulocytic and lymphocytic leucopenia, the amount of monocytes is increased, which has been evidenced by the research projects conducted by Zimmermann *et al.* [31]. They proved the increased numbers of CD14++ CD16++ cells, which belong to the subgroups of monocytes characterized by strong anti-inflammatory properties, and which can trigger hepatic fibrogenesis. In the case of cirrhosis, monocytes are linked to the diminished secretion of receptors Fc-γ responsible for the recognition of bacterial antigens, which reduces the phagocytic reactions and increases the risk of bacterial infections [32]. The ensuing chronic endotoxemia leads to the development of immunological paralysis, which results in monocytes inducing tolerance towards LPS (liposaccharide) linked to the diminished secretion of HLA-DR [33]. The stimulation by means of the high LPS saturation shows an inverse correlation with the

secretion of HLA-DR, which is facilitated by coinciding high levels of anti-inflammatory cytokines IL-10 and reduced levels of TNF-α (pro-inflammatory cytokines). It has been proved that the reduced secretion of HLA-DR (< 40%) indicates very limited healing chances in the case of acute cirrhosis sufferers [34]. In the case of ascites, there is also increased bacterial transmission of intestinal origin. The application of antibiotics (norfloxacin) leads to normalization of the circulating monocytes and influences the secretion of TNF-α, which improves the relevant functions of the immune system [33-35].

Macrophages, especially stellar cells, play an important role in the pathogenesis and the ensuing stages of cirrhosis. Activated by PAMPs (pathogen-associated molecular patterns, e.g. LPS) and DAMPs (damage-associated molecular patterns – the host's own particles able to initiate and maintain inflammatory responses) stellar cells secrete pro-inflammatory cytokines and chemokines (such as MCP-1) and increase the secretion of adhesive particles, which may result in hepatic fibrosis [36]. The activation of these particles also plays an important role in the stimulation of stellar cells, which take direct part in the reconstruction of extracellular matrix [37]. Produced by activated stellar cells and marrow-generated macrophages, thromboxane A$_2$, an agent narrowing the cells, increases the portal pressure [38]. Reduced numbers of these cells together with their diminished phagocytic activity increase the risk of endotoxemia [39].

Lymphopenia is diagnosed at early stages of cirrhosis. It impacts populations of B and T, both auxiliary (Th) and cytotoxic (Tc), cells [40], and it results from the impeded production of new T lymphocytes, accelerated apoptosis and their shortage caused by a huge load of intestinal antigens. It is also linked to their impeded compensatory proliferation [41]. Some of the already mentioned factors reduce the number of B lymphocytes. As a result, there ensues increased susceptibility to bacterial infections. Because of the impeded function of B lymphocytes, particularly their immunological memory, prophylactic vaccination, normally recommended in the case of cirrhosis, proves to be inadequate and insufficient. The relevant research shows that, in the case of balanced and moderate cirrhosis, the positive responses to vaccination against viral hepatitis were five times higher [42]. It is linked to the impeded production of immunoglobulins. In the case of cirrhosis, there appears overproduction of IgA and reduced production of immunoglobulins G, which are essential for basic immunological memory [43]. Research has also proved a negative influence of long-term alcohol consumption on the production of antigens

and on the population of T cells [44]. Research projects conducted by Rico *et al.* [45] show that the responses of type Th1 together with intensive production of IFN are prevalent in the case of HCV infection, particularly among patients suffering from hypertransaminasemia and aggravated histopathological hepatic damage.

The decreased numbers of NK cells together with their disturbed functioning only deepen and intensify the already present hepatic fibrosis, which subsequently exposes the patient to various infections and might lead to some carcinogenic developments [46].

Disturbed functioning of lymphocytes in the area of the digestive system

GALT, i.e. Peyer's patches and mesenteric lymphatic nodes, are the first defense barrier against intestinal pathogens. In the case of cirrhosis, there is some increased bacterial translocation through the intestinal walls, which triggers the constant activation of GALT cells, the ensuing stimulation of monocytes, and the excessive production of pro-inflammatory and anti-inflammatory cytokines, all of which results in the aggravated inflammatory state. The consecution and continuation of these phenomena fortifies the already deficient functioning of the intestinal barrier [47, 48].

Other mechanisms

Immunodeficiency is also impacted and caused by the impaired natural physiological barriers and iatrogenic factors. The skin of cirrhosis sufferers is thin, fragile and tense as a result of ascites and accompanying swellings, which weakens its protective role against external factors. The already debilitated intestinal peristalsis favors ulceration of the digestive system and allows translocation of bacterial flora from the intestines into the peritoneum or even the blood circulation system. Iatrogenic factors include the procedures of catheterization and endoscopic interventions. The application of certain drugs such as steroids or proton pump inhibitors, coupled with malnutrition, causes indirect debilitation of the immune system as well.

Conclusions

CAIDS is a result of inflammatory conditions, immunodeficient responses and general debilitation of the whole body. These are multi-level immunodeficiencies affecting the local immunological surveillance performed by the liver, and as such they are linked to cellular responses and functions of the receptors. An important role is played by bacterial translocation. An early diag-

nosis of the patient's immunological system problems may be carried out at the level of basic medical care, and the following analytical methods can be applied – morphological analysis together with blood film as well as establishing the levels of electrolytes. Other diagnostic measures such as establishing the level of iron in the blood, the amounts of CD4 lymphocytes and the content of ammonium should be performed within the framework of the specialized medical care. The check-up of these parameters may be of crucial importance for the long-term diagnosis of the patient's state. Additionally, in the case of cirrhosis, the source verification of the diagnosed immunodeficiencies may help to choose and apply appropriate medical strategies and healing methods, which tends to have a particular significance at the final stage of the illness. The knowledge of the most frequent clinical manifestations such as spontaneous peritonitis, infections of the urinary system, pneumonia, skin inflammatory states, fungal infections or an increased risk of diarrhea linked to *Clostridium difficile*, might allow for early recognition and identification of discrete pathologies and the development of infections, and thus a quicker intervention may follow. In this way, the risk of collateral complications may be reduced, the progression of the illness may be delayed and the patients will have better survival chances.

Disclosure

The authors report no conflict of interest.

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