Review paper

Immunity of the liver – selected data

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Abstract

The liver being the organ continuously exposed to various antigens, coming by way of blood around the body has developed mechanisms to ensure its protection immune response. This organ is rich in immune cells, which in addition to the action themselves, secretes numbers of pro-and anti-inflammatory cytokines, and non-immune cells with immune functions, which also take part in the defense of the liver. Moreover, the hepatocytes, are also capable of modulating the immune response through the production of complement components and expression of TLR receptors.

Key words: *liver, hepatocytes, immune cells.*

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Introduction

Liver as an organ participating in metabolism is exposed to continuous effects of various antigens, reaching it principally through the portal vein system from the digestive system and via hepatic artery from the entire body [1-4]. It was evidenced that blood inflowing to this organ is rich with nutrients, but also with bacterial degradation products, including PAMPs (pathogen associated molecular patterns), MAMPs (microbe-associated molecular patterns) and LPS (lipopolysaccharides) of Gram-negative bacteria, and toxins and antigens principally originating from the digestive system [5]. Therefore, the organ, in order to have the immunological function, is rich with immune system (IS) cells and cells not belonging to the IS that have immunological functions. It must be mentioned that nutrients reaching liver are metabolised there by hepatocytes, while various antigens and bacterial degradation products are removed by elements forming the liver immune system [5, 6], and which after activation generate many pro- and anti-inflammatory factors that modulate the body's immunological response. This last process is also participated in by hepatocytes, which, by synthesis of components of the complement and expression of TLR (Toll-like receptors) and other immune system's proteins, activate the immune system [2].

Liver and the immune system cells

In the liver, apart from hepatocytes – principally in charge of metabolism and detoxication, although also immunological processes, there are cells not being an element of the immune system that have immunological functions, and the immune system cells that principally ensure immunity in this organ. The latter elements are typical immune system cells represented by macrophages (Browicz-Kupffer cells – KC), dendritic cells (DC), mast cells, granulocytes and NK and NKT cells, as well as lymphocytes T, B and their subpopulations [4, 7]. In turn, in the group of cells that do not belong to immune system cells that have functions related to liver immunity. Nemeth *et al*. [7], list hepatic stellate cells (HSC) also known as Ito cells, sinusoidal endothelial cells (LSECs), cholangiocytes and hepatocytes.

Browicz-Kupffer cells are settled macrophages – derivative of monocytes, which from the time of settling in the liver act as antigen presenting cells (APC) and take part in the process of immunological response, including phagocytosis [4]. It was evidenced that the cells are the main source of TNF-α, IL 12, 18 and IFN-γ – cytokines that support production of TNF-α, as well as IL-10, which inhibits generation of TNF-α [4, 5]. In the case of DC cells, it was evidenced that they differentiate both from myeloid series cells and lymphoid cells, which results in the fact that their populations have many functions [8], although it is adopted that in the liver, during a bacterial and viral infection, they are responsible for presentation of the antigen to lymphocytes T [8]. Furthermore, in the liver, there are mast cells that are both tryptase- and chymase-positive, which take part in pathogenesis of diseases referring to cholesta-

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sis and fibrosis of the liver, yet their role is rather unknown [7]. In turn, granulocytes flow in to the liver principally in acute hepatitis and as a result of impact of chemotactic factors principally secreted by KC of this organ [7]. In the healthy condition, granulocytes in the liver are scarce, as they constitute just 1% of the entire pool of the immune system cells [7]. Other cellular elements of the immune system in the liver include NK and NKT cells, which reveal strong cytotoxic properties as a result of PAMP recognition by PRRs receptors. NK cells are natural killers responsible for cytotoxicity without the participation of antibodies, complement, and act without the restriction of MHC particles [9]. In turn, NKT cells, having both the properties of T and NK cells, reveal immunoregulatory properties to other cytotoxic cells, as well as activate cidal properties of such cells to tumour cells [9]. In turn, lymphocytes T and their subpopulations, as well as lymphocytes B, are elements whose role in "building" liver immunity is very important. Studies evidenced that subpopulations of lymphocytes T, present in the liver, are mainly lymphocytes Th1/Tc1, characterised with the capacity of quick secretion of pro-inflammatory factors, such as IFN-γ, TNF-α and IL-2, which substances are also produced after the action of cytokines secreted by hepatocytes and KC cells [10]. It was recorded that among all lymphocytes T in the liver, about 5% are cells that produce cytokines typical of subpopulations of lymphocytes Th2/Tc2. It was also evidenced that among subpopulations of lymphocytes T in the liver, there are also lymphocytes with receptors TCR$\alpha\beta$ and TCR$\gamma\delta$, and lymphocytes Th0, as well as LAK cells, although the role of such elements is not fully known. Also, the occurrence of lymphocytes T_{reg} in the liver was described, as well as of T cells with receptor CD4+ that produce IL-17 – namely lymphocytes Th17. It was evidenced that lymphocytes Treg are the basic element responsible for maintaining the body's tolerance, by inhibiting activation of lymphocytes Th1, Th2 and the response of lymphocytes Th17. In turn, Th17 cells are principally responsible for damage to the tissue caused by auto-immunological processes [7]. Facts related to lymphocytes T and their subpopulations in the liver point to high heterogeneity of such cells, which have various functions [10]. In the case of lymphocytes B, it was recorded that such cells constitute approx. 10% of lymphocytes in this organ [7], and are principally functionally related to the activity of lymphocytes B2 of the spleen, and have an important role in the liver regeneration processes. In turn, lymphocytes B1 that are present in the liver are activated independently of lymphocytes T, and are characterised with low capacity to secrete immunoglobulins of class M, also referred to as natural antibodies [7]. Furthermore, it was evidenced that the number of lymphocytes B in the liver increases in the case of hepatitis C (HCV), which is probably related to the suppressive state of the immune system, recorded in chronic infections of the liver [7].

In turn, cells not belonging to the immune system which, however, have immunological functions in the liver, include hepatic stellate cells (HSC) that appear and are present in liver damage conditions, principally in the cases of fibrosis of this organ, and are responsible for inducing inflammatory state and stimulation of the response related to lymphocytes T and B [2]. It was evidenced that HSC cells functioning as APC cells, during bacterial infection, promote immunological response conditioned with lymphocytes T [11]. In turn, sinusoidal endothelial cells (LSECs) are elements whose role in immunity is related to and conditioned with the condition of the liver and the type of infection [5]. Such cells can eliminate products of metabolic transformations and toxins from the digestive system without causing inflammation [5], although they also induce the response of lymphocytes T during a viral infection [3]. In the case of cholangiocytes present in the liver, it was evidence that they are capable of synthesising PRR receptors and producing many proteins of antibacterial properties, as well as cytokines and chemokines, which decides on their participation in the immunity of the organ [7]. In turn, the role of hepatocytes as an element creating liver immunity, as mentioned earlier, is related to secretion of components of the complement, expression of TLR receptors, as well as other proteins of the immune system, such as acute phase proteins.

It is assumed that the presence and activation of immune system cells and cells not being elements of the immune system in the liver results from the fact that the system is continuously exposed to contact with a large number of various antigens; however, according to the homeostasis theory, the condition of immunological tolerance prevails in this organ. It was evidenced that reactivity of immune system cells in the liver i.a. towards bacterial MAMPs of commensal origin, is weakened by the development of the condition caused by the repeated stimulation of the cells of the organ, referred to as endotoxic tolerance. Furthermore, this condition is achieved by cooperation of population of APC cells i.a. with KC and DC, and factors regulating the immune system, among which one must list IL-10 and TGF-β produced by KC, LSEC and lymphocytes T_{reg} [1, 7]. Regardless of this situation, immune system cells of the liver, as a result of impact of bacterial degradation products from the digestive system, show increase in expression of many particles related to inflammation, such as e.g. CD54 and CD106 [5]. It must also be added that the activity of immune system cells of the liver should be high, as this organ is very much exposed to the action of many pathogenic microorganisms, like in humans – hepatitis virus B or C and *Listeria* monocytogenes, as well as parasite *Plasmodium* spp. [2, 5], while in animals - the RHD virus, as well as L. monocytogenes [12]. It must also be added that the described elements forming immunity, principally immune system cells of the liver, not only themselves decide on the immunity of this organ, but also contribute

and activate the response also related to elements such as B cells, which principally create acquired immunity [5]. This is evidenced by the fact that elimination of the infected hepatocytes and releasing factors regulating replication of various pathogens is principally due to products of lymphocytes B – immunoglobuline, although also to the activity of lymphocytes T [13]. In turn, in viral infections, it was evidenced that there is quick maturation of LSEC cells, and as a consequence activation and induction of response of lymphocytes T with receptor CD8+ [3]. In turn, after contact with PAMPs particles such as: nucleic acids, and as a result of inflammasome impact – multi-protein complexes comprising NLR receptor, caspase 1 and adaptor proteins ASC (apoptosis- associated speck- like protein containing a CARD), DC cells stimulate lymphocytes T [8, 14]. It must be added that e.g. induction of lymphocytes T by mature DC cells is also directly related to increased expression of co-stimulating particles (CD80, CD86, IL-12 and IFN-α/β), which facilitate differentiation of lymphocytes T into effector cells, as well as activate lymphocytes B [8].

Liver and non-cellular components of the immune system

In the liver, 80% all cells of this organ are formed by hepatocytes, which apart from the basic metabolic role, owing to the synthesis of the components of the complement system and production of pathogen recognizing receptors (PRR), of which probably the TLR (Toll-like receptors) are the most important, have the capacity of modulating and strengthening the immunological response [2, 7]. The properties are controlled by liver-specific transcription factors such as: HNF-1 (hepatocyte nuclear factor), NF-1 (nuclear factor 1) and C/EBP (CCAAT enhancer binding proteins). It was also evidenced that during immunological response in the liver, as a result of impact of such cytokines as IL-6, IL-1, TNF-α and IFN-γ, hepatocytes are additionally stimulated towards increased secretion of components of the complement system and PRR receptors – actually TLR [2]. Detailed tests indicated that the liver principally produces such components of the complement system as: C1r/s, C2, C4 and Cbp - creating elements of classic complement path, C3 and factor B – being components of alternative path for complement activation, as well as MASP 1-3 (mannan-binding lectin-associated serine pro tease 1-3) and MBL 19 (mannan binding lectin associated protein 19) – which affect lectin path of complement activation, although also components common to all activation paths, namely component C5, C6, C8 and C9 [15]. It must be added that components of the complement are also produced by immune system cells and endothelial cells, although this is not much as compared to their synthesis by liver cells. Furthermore, it was evidenced that hepatocytes secrete proteins that regulate activation of the complement system, present in the plasma, such as factor I, H – being components of properdin system, as well as inhibitor of C1 component [2, 15]. The discussed elements of the complement system [2, 15] are not only important in immunological response and decide on innate immunity, but also participate in pathogenesis of various liver diseases, such as: fibrosis and cirrhosis. As already mentioned, hepatocytes are also a source of PRR receptor production, which during infection also activate the complement system and participate in opsonisation of microorganisms – the process necessary to initiate the phagocytosis process. Many of such PRR markers, including TLR, synthesised in liver cells, and released to the circulatory system – has an important role not only in local immunity, but also in the immunity of the entire organism [2]. Among the most important PRR receptors, there are TLR receptors, recognising PAMPs, 18 of which have been identified so far (namely TLR 1-13, 14, 15, 21-23) [16], 13 of which are present in humans (TLR 1-13). It must also be added that e.g. TLR4 and TLR2 receptors, identified in hepatocytes and immune system cells present in the liver, are involved in the endotoxin elimination processes and processes of generation and secretion of pro- and anti-inflammatory cytokines and oxidation stress [17]. It was determined that during the cirrhosis, there are changes to TLR-2 and TLR-4 expression, not only in hepatocytes, but also in monocytes of peripheral blood. It was also evidenced that the induction of lymphocytes T with CD8+ as a result of e.g. infection of hepatocytes occurs by stimulation of TLR-9. It is the more interesting, as the ligand for TLR-9 receptor are the unmethylated DNA sequences, which suggests intermediate path for lymphocytes T induction, and not directly by the RNA virus, whose receptor is TLR-3. Moreover, it was evidenced that, owing to expression of MHC-1 and CD1b, hepatocytes are capable of direct antigen presentation to T cells and NKT cells [7]. It must also be mentioned that hepatocytes are also a source of many other proteins, such as e.g. acute phase proteins, which play a key role in natural immunity, and also affect reduction of tissue damage by inactivation of protease release by pathogens or dead cells of the body [2].

Conclusion

To conclude on the presented data regarding liver immunity, it must be stated that this is an organ with significant capacity of immunity activation. Elements conditioning such functions include both hepatocytes and immune system cells (KC, DC, mast cells, granulocytes, NK, NKT, lymphocytes T, B and their subpopulations), as well as cells not being elements of the immune system, which have immunological functions (HSC, LSECs, cholangiocytes). The listed elements decide not only about local immunity in the liver, but also on the immunity of the entire organism, also during viral, bacterial and parasitic infection. Moreover, owing to the immune system cells,

there is not only quick response of innate immunity to permeating pathogens, but also as a result of their activation, immunity occurring slightly later in time is affected, namely acquired immunity related, among others, to immunoglobulins.

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