REVIEW ARTICLE

CONTENTS

Features of immune reactivity of the spleen and mechanisms of organ damage under the influence of animal venom toxins including scorpions (review)

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ABSTRACT

Aim: To establish features of immune reactivity of the spleen and mechanisms of organ damage under the influence of animal venom toxins including scorpions.

Materials and Methods: A thorough literature analysis was conducted on the basis of PubMed, Google Scholar, Web of Science, and Scopus databases. When processing the search results, we chose the newest publications up to 5 years old or the most thorough publications that vividly described the essence of our topic.

Conclusions: Spleen plays a leading role in the implementation of the body's defense processes, the elimination of structural elements affected by toxins, and the restoration of immune homeostasis. Its participation in the formation of the immune response can be accompanied by qualitative and quantitative changes in histological organization. Morpho-functional changes in the spleen under the action of animal venom toxins currently require careful study, because from the information available in the literature today, it is not possible to clearly construct a complete picture of lesions of certain components of the organ at the microscopic or submicroscopic levels. Therefore, this direction of research in the medical field is currently relevant, taking into account the existence of a large number of poisonous animals, including scorpions.

KEY WORDS: spleen, immune response, lymphocytes, dendritic cells, scorpion venom

Wiad Lek. 2024;77(1):120-125. doi: 10.36740/WLek202401115 DOI

INTRODUCTION

The spleen belongs to the peripheral organs of hematopoiesis and immune response, ensuring the performance of numerous vital functions. According to the structural organization, the organ is represented by red and white pulp. It is known that the red pulp occupies a larger part of the spleen. Its main role is the careful differentiation of old, dead or opsonized blood cells that are delivered from the bloodstream to the marginal zone by terminal arterioles [1]. Despite the fact that the adaptive processes of the immune response to antigens are initiated in the white pulp, the red pulp still possesses immune effector properties. The latter consists in the fact that numerous leukocytes, including neutrophils, monocytes, and histiocytes are in the red pulp and are resident for it. The population of these cells of the myeloid line is able to undergo dynamic changes in quantity and migration under the conditions of the development of inflammatory processes, ensuring a rapid reaction of the body to an acute injury and the formation of an immune response. In addition, plasmablasts enter the red pulp from the white pulp, since there is a much higher gradient of CXCL12 chemokines (chemokines of the CXC subfamily encoded by the CXCL12 gene). Further plasma cells ensure the formation of immunoglobulins that enter the systemic bloodstream and are able to resist foreign antigens. It should be noted that CD8+ T-cells of the immune system are also present in the red pulp. They are transported here for inspection and purification, but are effector components of immune system [2].

The white pulp of the spleen is considered one of the main centers of antigen-dependent differentiation of lymphocytes. It is represented by lymphoid tissue. According to the compartmentalization of the white pulp, zones of accumulation of T- and B-cells are distinguished here. T-cell zone or periarterial zone is represented by T-lymphocytes, macrophages [3]. The last

ones provide antigen presentation and, together with interdigitate cells, participate in the antigen-dependent proliferation of T-lymphocytes. Interdigitate cells of the spleen have numerous processes that provide them with communication processes and the creation of a microenvironment for T-lymphocytes. According to their morphological structure, they are close to the cells of the mononuclear phagocyte system. It was established that under the conditions of the development of acute processes in the body, the phagocytic activity of interdigitate cells increases several times, which is accompanied by a change in their organization at the submicroscopic level towards macrophages [4, 5].

Germinal centers or B-zones are formed by B-lymphocytes, macrophages and dendritic cells. Phagocytosed antigens and their determinants in this zone are presented to T-lymphocytes, and subsequently antigen-dependent differentiation of B-lymphocytes leads to the formation of plasma cells that migrate to the red pulp for the purpose of antibody production [6].

According to the data of scientific research, concentration and clear distribution of T- and B-lymphocytes in the white pulp is determined by the presence of certain molecules in the zones. Thus, the T-zone mainly contains CCR7 (a mammalian β-chemokine receptor of the class of integral membrane proteins) and its two ligands – CCL19 and CCL21. Loss of CCR7 leads to a chaotic dispersion of T cells throughout the spleen tissue. B-zones are organized due to the presence of CXCL13 (chemokine ligand 13 or B-lymphocyte chemoattractant) [7].

AIM

The aim of the study was to establish features of immune reactivity of the spleen and mechanisms of organ damage under the influence of animal venom toxins including scorpions.

MATERIALS AND METHODS

A thorough literature analysis was conducted on the basis of PubMed, Google Scholar, Web of Science, and Scopus databases. When searching for information on the peculiarities of the spleen structure, the immune reactivity of the organ in response to the action of damaging factors, the influence of scorpion venom toxins on its structure and functions, we used the following combinations of keywords: «spleen», «immune response», «lymphocytes», «dendritic cells», «scorpion venom». When processing the search results, we chose the newest publications up to 5 years old or the most thorough publications that vividly described the essence of our topic. After conducting a detailed review of the abstracts of the articles and getting acquainted with their full content, 40 sources were selected that fully corresponded to the results of the request.

REVIEW AND DISCUSSION

Violations of the normal functioning of the body under the influence of damaging factors (injuries, poisoning due to the action of toxins of various origins, viral, bacterial diseases, etc.) activate in the tissue of the spleen many PRR receptors (pattern recognition receptors) on the surface of the plasmolemma of myeloid line cells, which in turn stimulates T-cells through the presentation of antigens by macrophages and the subsequent secretion of cytokines, triggering phagocytosis. PRRs in the spleen are represented by TLRs, NOD-like receptors (NLRs), RIG-I-like receptors (RLRs) and C-type lectin receptors (CLRs) [8]. TLRs recognize extracellular or phagocytosed pathogen-associated molecular structures (PAMPs – pathogen associated molecular patterns) [9]. A number of cytosolic NLRs are sensitive to products of microbial origin that penetrate into the cell (bacterial flagellins) and to compounds released in the host's body during trauma, stress and called molecular structures associated with damage (DAMP – damage-associated molecular patterns). CLRs act as markers for dendritic cells, helping them to recognize carbohydrate determinants and internalize pathogens (in particular, the exoskeleton of insects). PRRs are selectively expressed on the surface of different types of spleen cells, ensuring the formation of both an early and an adaptive immune response [10].

Dendritic cells (DCs) are key participants in the formation and regulation of the response of the immune defense system in the spleen. They are often the subject of discussions among representatives of the scientific community, especially regarding their classification. The reason for the differences is their special ability – dynamic and overlapping expression of T-cell markers (the possibility of production of the same markers by different subspecies of dendritic cells) [11]. According to the data research, CD4+ and CD8+ markers are known. However, other experimental findings indicate that there are a certain number of cells of the myeloid lineage that also have the properties of their expression, but they do not perform the functions of classical DCs. The discovery of specific transcription factors made it possible to understand the peculiarities of their organization and to separate them from monocytes. Splenic DCs are of bone marrow origin, with a high migration rate. Immature DCs are able to capture antigens from the bloodstream, but do not have the ability to present them and activate T cells [12]. They only

absorb antigens by phagocytosis or pinocytosis, and later undergo a multistage maturation process. Mature DCs are structures with already absorbed antigenic material. They can induce T-lymphocytes, which is accompanied by a high degree of expression of HLA antigens and other aditional stimulating molecules. In the T-zones of the white pulp of the spleen, DCs induce naïve, antigen-specific T-helpers to differentiate into type 2 T-helpers, which in turn promotes B-cell proliferation and antibody production. Classical dendritic cells (cDCs) of the spleen carry the transcription factor ZBTB46 on their surface and act exclusively as professional antigen-presenting cells [13]. They can be divided into cDC1 (classic dendritic cells 1) and cDC2 (classic dendritic cells 2) [14]. All cDC1 ensure the expression of XCR1 (X-C motif of chemokine receptors 1), which according to its chemical structure is a protein encoded by the gene of the same name and is involved in intracellular signaling processes. The vast majority of cDC1 is located in the white pulp, but is also found in the red pulp and marginal zone. cDC1 often have CD103 receptors, which are also called integrins α-E, belong to membrane glycoproteins (E-cadherin receptors). Under immunization conditions, all cDC1 activate CD8+ T cells [15].

cDC2 are located at the border of the white and red pulp, ensuring the expression of SIRPα (signal regulatory protein α) and CD11b [16]. The latter belongs to proteins of the integrin superfamily (integrin α-M), which participates in the processes of interaction between monocytic cells, mediates the absorption of particles opsonized by complement, as it recognizes the sequence of C3b amino acids. In addition, CD11b is a receptor for fibrinogen, factor X, ICAM-1 [17].

Some experimental models demonstrate the presence of atypical DCs in the spleen. They are identified using receptors B22a (CD45R – signaling molecules necessary for the activation of T cells and are members of the tyrosine phosphatase family) and PDCA-1 (plasmocytoid dendritic cell antigen-1) [18]. Atypical DCs carry TLR7 and TLR9 on the surface of the plasmalemma, which enables them to identify pathogens, including viruses. After activation, these cells extremely quickly secrete large amounts of type I interferons, IL-12, IL-18, increase the levels of NK cells, stimulate apoptosis of infected cells, enhance cross-priming (induction of naïve CD8+ T cells and their transition into activated cytotoxic cells). Cross-priming allows DCs to involve in the antigenic presentation of exogenous antigens class I MHC molecules (usually they do not participate in these processes). The use of class I MHC allows DCs to remain uninfected, providing an immune response by activated cytotoxic T-lymphocytes against the affected body cells [19].

Macrophages in the spleen, which are resident cells, are involved in the protection of the tissue of the organ, as they provide phagocytosis, maintenance of homeostasis, cleaning from remnants of apoptotic material, and regulation of the function of neighboring cells. They also respond to damage, stress, or infection by stimulating the production of numerous cytokines and activating leukocytes [20]. Several types of macrophages have been identified in the spleen, each of which is responsible for the normal functioning of individual anatomical structures and expresses its own types of PRRs and scavenger receptors (SRs). [21]. In particular, in the marginal zone, marginal zone macrophages – MZM and marginal metallophilic macrophages – MMM are distinguished. Both types are characterized by the expression of SIGN-R1 and CD169 (sialoadhesins) [22]. The last ones play an important role in the detection and absorption of microorganisms containing residues of sialic acids. The aforementioned macrophages are involved in cleansing the spleen of cells that have undergone apoptosis. It has been established that MZM and MMM are of bone marrow origin and are important for the induction of immune tolerance to MHC self-antigens. In the bone marrow, they mature under the influence of the macrophage colony-stimulating factor, since they have common features of ontogenesis with blood monocytes [23, 24].

The scientists note that there are currently available data on the participation of NK cells in the innate and adaptive immune response of the spleen. The vast majority of these cells are concentrated in the red pulp, however, they can migrate to the white pulp under conditions of infection, contribute to T-lymphocyte polarization, TNF-α production, and DCs differentiation [25]. NK cells protect against viral infections (due to the presence of PRR), are involved in the recognition of tumor and damaged cells of the body. The latter fact is possible due to the expression of NKG2D, which is a transmembrane protein of the superfamily of C-type lectins, and its levels on the surface of the plasmalemma increase under the influence of such cytokines as IL-15, IL-12, and IFN-γ. This receptor is responsible for the detection and elimination of transformed, dead cells, since its ligands are induced as a result of infection, damage or genomic stress [26].

Under normal conditions, monocytes are also present in the spleen tissue. There is information in scientific sources that, as a rule, monocytes after interaction with foreign agents in the blood are able to penetrate the marginal zone of the spleen and stimulate the activity of resident macrophages. Also known are the effects of monocytes, such as disposal of cells that have undergone apoptosis, stimulation of TGF-β, IL-10 production. During the development of an inflammatory response, chemokine receptors β (CCR2), activated by cytokines MCP-1 and MCP-3, recruit monocytes from the red bone marrow to the spleen. Further, they can differentiate into several types of

cells of the myeloid lineage, including non-classical DCs. It should be noted that the red pulp of the spleen acts as a so-called depot for undifferentiated monocytes, which can be involved in the processes of immune reactivity in other organs [27].

The adaptive immune response in the spleen is provided by T- and B-cells, which belong to the key effector structures of the organ. Their localization may change depending on the functional state. B cells are canonical T-dependent immunoglobulin-producing cells. The so-called naïve B-lymphocytes are localized in the follicles of the white pulp, however, after activation, they are able to move within the light and dark zones of the germinal centers. Chemokine receptors of the fifth type (CXCR5) direct the movement of B cells to the light zone, where they interact with T cells [28], and receptors of the fourth type (CXCR4) direct them to the dark zone, where B lymphocytes undergo proliferation [29].

CD4+ T cells concentrate on the outer border of the periarterial lymphoid sinuses, next to the follicles. Their function is to stimulate the synthesis of antibodies by B-lymphocytes (high-affinity antibodies) due to the production of specific cytokines (IL-21) and direct co-stimulation. Often this type of cells is called T-follicular helpers. During the activation of the immune response, CD4+ increase the expression of CXCR5 so that B cells can quickly reach the T-B border. B-lymphocytes, in turn, under these conditions actively express β-chemokine receptors (CCR7) [30, 31].

CD8+ or naïve T lymphocytes reside in the central compartments of the periarterial lymphoid sinuses of the white pulp of the spleen, awaiting antigenic presentation. After priming, activated cytotoxic T-cells migrate through the B and marginal zones, reaching the red pulp, where they are involved in the processes of destroying infected cells and cleaning the tissue of the organ. Over time, individual memory T cells return to the sites of primary localization. However, some memory T cells still remain within the red pulp [32, 33].

The analysis of scientific publications made it possible to establish the fact of the existence of hybrid cells in the spleen or innate lymphocytes. One of the most common are NKT cells and γδ T cells, which belong to specialized structures, express the TCR receptor and are able to recognize glycolipid antigens on the surface of antigen-presenting cells, such as MZM [34]. Activated NKT cells produce proinflammatory cytokines and can stimulate DCs to cross-priming of CD8+ T lymphocytes. γδ T cells also possess the properties of rapid cytokine secretion, PRR expression, and direct lysis of infected cells. They are a minor population in the spleen, but are important for the early immune response. NKT and γδ T cells are required for Th1 polarization. This process is possible due to the production of IFN-γ, TNF-α, IL-12, which also activate cDC1 [35, 36].

Another type of hybrid spleen cells are innate lymphoid cells (ILCs). They got their name due to the fact that they are characterized by a common ontogenesis with cells of the lymphoid line, but unlike them, they do not have T-cell receptors [37]. Currently, several types of ILCs are known, their classification depends on the profile of cytokine secretion. The last ones are produced by them in response to damage or infection. ILC-2 produce IL-5, IL-9, IL-13. ILC-3 are able to activate cells of the marginal zone of the spleen, neutrophils through the production of TNF-α, lymphotoxin, GM-CSF and provide costimulation processes of CD4+ T cells in interaction with IL-2, IL-6, macrophage inflammatory protein 1-α (MIP1α) [38].

According to experimental research, the components of scorpion venom have a pronounced effect on the structures of both innate and acquired immunity. Today, more and more frequent studies are devoted to the study of morpho-functional changes in immune defense organs during bites of poisonous animals. Scientists show considerable interest in histological and biochemical changes of the spleen under the influence of zootoxins. The systematization of information from scientific sources made it possible to reach a conclusion about the high sensitivity of the spleen to the action of factors of various genesis. Scientists believe that knowledge of the histological indicators of this organ, as special biomarkers, will allow a better understanding of the integral impact of the environment on the human body. In scientometric databases, an extremely limited amount of information was found on the effect of scorpion toxins on the structure of the spleen of mammals [39]. The vast majority of experiments are devoted to the study of its participation in the development of inflammatory processes during bites of poisonous animals. There are also few reports on this issue. Thus, Costa-Arce J. et al. [40] established that the venom of Centruroides limpidus scorpions leads to an increase in the production and secretion of IFN-γ, IL-4, IL-17, IL-10 in the spleen of mice by T-helpers. The authors proved that most of the toxins that had such an effect belong to blockers of potential-dependent Na+ and K+ channels. To implement their pathological effects, they use the specified T-lymphocyte channels as molecular targets. The researchers also concluded that these toxins were not active in the proliferation of T-helper cells in the spleen.

CONCLUSIONS

As stated above, the spleen plays a leading role in the implementation of the body's defense processes, the elimination of structural elements affected by toxins, and the restoration of immune homeostasis. Its participation in the formation of the immune response can be accompanied by qualitative and quantitative

changes in histological organization. Morpho-functional changes in the spleen under the action of animal venom toxins currently require careful study, because from the information available in the literature today, it is not possible to clearly construct a complete picture of lesions of certain components of the organ at the microscopic or submicroscopic levels. Therefore, this direction of research in the medical field is currently relevant, taking into account the existence of a large number of poisonous animals, including scorpions.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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RECEIVED: 03.05.2023
ACCEPTED: 20.11.2023

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