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Immune mechanisms in the pathogenesis of acute peritonitis

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Abstract

Acute inflammation of the peritoneum − peritonitis - often develops after injury to hollow visceral organs, intestinal necrosis, failure of anastomosis, or tumor processes. Subsequent microbial contamination of the abdominal cavity leads to infection, in response to which immune mechanisms are activated. The pathogenesis of inflammatory processes in the abdominal cavity and their features are largely determined by the structure and function of the peritoneum, as well as its close connection with the omentum. An important point in resolving peritonitis is to maintain the balance of cytokines, the activity of immunocytes and complement functioning in the immune lymphoid clusters of the peritoneum and omentum, and their collaborative action during inflammation. The review presents data on the structure and function of the peritoneum and omentum, the role of neutrophil, macrophage, lymphocytic links of the immune system, as well as those of pro- and anti-inflammatory cytokines and complement in the development and cessation of acute inflammation in the abdominal cavity.

Keywords: peritonitis, peritoneum, omentum, immunocytes, cytokines, complement

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IL, interleukin
LPS, lipopolysaccharide
MTC, mesothelial cell
MS, milk spot
MP, macrophage
MC, monocyte
NG, neutrophilic granulocyte
PMN, polymorphonuclear granulocyte
PF, peritoneal fluid
RPMP, resident peritoneal macrophage
TNF, tumor necrosis factor
NK, natural killer cells

Introduction

Acute peritonitis, the peritoneum inflammation, is often caused by wounds of hollow visceral organs, intestinal necrosis, anastomotic failure, or tumor processes. Subsequent microbial contamination of the abdominal cavity leads to infection, in which response the immune mechanisms are activated [1]. Regardless of the etiology and location of the inflammatory process of the peritoneum, it is the immune system that plays a leading role in its activation and completion [2]. The pathogenesis of inflammatory processes in the abdominal cavity and their features are largely determined

by the structure and functionality of the peritoneum, as well as its close connection with the omentum.

The structure and function of the peritoneum

Peritoneum, the mesothelial membrane lining the abdominal cavity, consists of a thin layer of loose connective tissue covered with a single layer of flat immunoactive mesothelial cells (MTCs) of mesodermal origin, which are characterized by the presence of apical microvilli, fragility, and high plasticity [3]. The abdominal cavity contains, besides visceral organs and lymph nodes, the an omentum and fat deposits with specific lymphoid aggregates, as well as many special single immune cells that act at the junction of innate [4] and adaptive immunity [5]. A unique population of leukocytes patrols the abdominal cavity and migrates to and from the omental milk spots where they encounter antigens or pathogens from the abdominal fluid and react accordingly [6, 7].

The peritoneal cavity contains peritoneal fluid (PF) continuously produced by MTCs and reabsorbed through a large peritoneal surface area. The pancreas ensures the exchange of nutrients, removes pathogenic microorganisms, provides reparative processes and is in equilibrium with plasma [8]. The pancreas has a high fibrinolytic activity, which may restrain the formation of adhesions in response to injury. Growth factors, nutrients, cytokines and chemokines, and leukocytes are continuously exchanged between the pancreas and the blood. The peritoneal membrane, in addition to protecting the abdominal cavity and providing pathways for the entry of nerves, blood and lymphatic vessels, is a “gateway” for pathogenic microorganisms and bacterial toxins that easily penetrate the peritoneum and cause inflammation [3]. The response of the peritoneal cell matrix to

damaging effects includes the recruitment, proliferation, and activation of various hematopoietic and stromal cells. Under physiological conditions, effective reactions are realized, inflammation triggers are eliminated, the inflammation quickly resolves, and normal tissue architecture is restored. However, if inflammatory triggers are not eliminated, fibrosis or scarring develops, and if inflammation increases, a systemic inflammatory response and sepsis develop [9].

A unique feature of inflammatory reactions in the abdominal cavity in response to injury or infection lies in the close relationship and concomitant action of the cellular immune matrices of the peritoneum and omentum.

Immune functions of the omentum

Omentum is a visceral adipose tissue with unique immune functions. It contains lymphoid aggregates called milk spots (MSs), which are clusters of leukocytes much like follicles in secondary lymphoid tissues. Their main function is to provide the immune protection of the peritoneum, which is realized by the recognition and neutralization of antigens, particles, and pathogens from the abdominal cavity and, depending on stimuli, the activation of various immune responses, including inflammation or even fibrosis. Interactions between MS cells and adipocytes regulate their immune and metabolic functions [10]. The role of the omentum in peritoneal immunity was not recognized until the early 1900s, when a British surgeon called it the "abdominal cop" because of its ability to reduce peritonitis activity and promote healing of surgical wounds [11]. The omentum also has remarkable angiogenic, fibrotic, and immune [7] activities, which altogether promote vascularization, accelerate wound healing, and limit infection. MSs function as filters for the pancreas, which makes them ideal for

implementing immune responses to any antigens or pathogens that enter the abdominal cavity [7, 12]. Omental MSs support both innate and adaptive immune responses to peritoneal antigens. For example, inflammation in the abdominal cavity promotes the rapid migration of macrophages into the omentum, a process originally known as the macrophage disappearance response [13]. This process can be triggered by sterile and bacterial irritants, including lipopolysaccharides (LPSs) [14]. The populations of leukocytes in the bladder and other fat-associated lymphoid cells are also quite different from leukocytes in normal lymphoid tissues [15]. Fat-associated lymphoid clusters (FALCs) are atypical lymphoid aggregates found in the mesentery of mice and humans, on the mucous membranes of the peritoneum, mediastinum, and pericardium, and contain a large number of lymphoid cells responsible for innate immune responses. The central cluster of MS is formed by B cells, while macrophages and dendritic cells often accumulate outside the MS and are also found individually throughout the omentum. In the MSs, they are represented by two populations: self-renewing B1 cells, permanently located in the omentum and abdominal cavity [7, 16], and B2 cells, which circulate between the omentum and other lymphoid tissues. The omentum also contains circulating $CD4^+$ and $CD8^+$ cells, albeit at a lower concentration than in normal lymphoid organs, as well as natural killer (NK) cells. Although the studies performed have not specifically tested the role of NK cells in the omentum, the prevalence of these cells in this tissue undoubtedly influences various local immune responses, such as the expansion of leukocytes from adipose tissue cell clusters in response to inflammatory stimuli. Moreover, fat-associated NK cells actively produce IL-10, suggesting that these cells are involved in anti-inflammatory responses [12].

The role of cells of the immune system in the pathogenesis of peritonitis

The host's primary response to invading microorganisms is mediated **by resident peritoneal macrophages** (RPMPs) that comprise up to 90% of peritoneal leukocytes [17], and MTCs, which are responsible for primary phagocytosis and the subsequent activation and recruitment of polymorphonuclear granulocytes (PMNs) and monocytes (MCs) into the abdominal cavity [18]. During the first 24 hours after infection, most bacteria are phagocytosed by representatives of the most numerous permanent pool of large RPMPs (GATA6+) and, to a lesser extent, by small peritoneal macrophages (GATA6–) originating from MCs and playing an important role in inflammatory and infectious processes [19, 20]. At the same time, GATA6+ macrophages release chemokines that attract PMNs that rapidly phagocytize microorganisms [21, 22].

Leukocytes from blood enter the abdominal cavity both in the normal resting state and during the induction of acute inflammation [23]. Their main role in the abdominal cavity is to maintain tissue homeostasis and promote tissue repair. **Neutrophilic granulocytes (NGs)** are the first to enter the inflammation focus, as being a part of the first line of defense against microbes and having a set of antimicrobial effector functions, including phagocytosis, degranulation, and the formation of extracellular traps (nets) [24]. Phagocytosis is rapid and occurs within minutes and is then enhanced in the presence of the complement system, IgG antibodies, or cellular primer [25]. The gradual release of the content of NG granules, which has a high oxidizing and lysing potential, allows for controlled degranulation to chemically incapacitate pathogens while limiting the impact of cytotoxic

molecules on host cells [26].

It was traditionally believed that NGs, the immune cells with a short half-life, are in circulation for 6–8 hours, being present in the focus only in the acute phase of inflammation, and function only as destroyers of pathogens [27]. However, recent results have shown that the function of NGs goes beyond this role. During inflammation, the lifespan of NGs increases several times as they are activated, which ensures their constant presence at the site of infection. This issue is important because it allows NGs to perform complex functions in the tissue, thereby maintaining inflammation, or contributing to its resolution, tissue healing, or the formation of adaptive responses. [28, 29]. NG activation occurs with the help of various cytokines and growth factors and(or) bacterial products [30, 31].

The second most abundant cells in the peritoneum are **B-lymphocytes**. They are a source of natural antibodies (in particular, IgM and IgA) having broad specificity and low affinity for antigens [32]. B-lymphocytes are represented by two populations: B1 and B2 cells. Under the effect of activation signals, B1 cells produce IgM [33] with subsequent migration of these cells to secondary lymphoid organs [34]. B1 cells promote early microbial clearance after infection, regulate the production of polyreactive and low affinity antibodies for innate humoral immunity, and facilitate the transition from innate to adaptive immunity. B2 cells are responsible for the adaptive response to environmental antigens [35, 36]. Peritoneal B1 cells are able to strongly stimulate T-helper cell proliferation and cytokine secretion upon a contact with auto- or allogeneic antigens, in contrast to follicular B2 cells, which are actively involved in the activation of Treg cells [37].

An important role in the pathogenesis of peritonitis is played by **T lymphocytes** represented by several populations in the lymphoid aggregates of the abdominal cavity. And, while T helper 1 (Th1) and Th17 cells induce inflammation and tissue destruction [38], the regulatory T cells (Treg) play an important role in organizing the process of completing inflammation fading and repairing damaged tissues. It has been experimentally shown that in a neutrophil-mediated inflammatory reaction in the course of zymosan-induced peritonitis resolution, the number of Treg cells abruptly increased following a decrease in the number of neutrophils [39]. Data *in vitro* and *in vivo* confirm that activated Treg cells secrete IL-13, which then enhances efferocytosis (uptake of apoptotic cells) by stimulating macrophages (MPs) recruited to the area of inflammation. In addition, it is known that Treg cells through the autocrine-paracrine pathway and by IL-10 also help MPs to produce efferocytosis of apoptotic cells, which prevents the latter from becoming necrotic and pro-inflammatory [40, 41]. IL-10 can also reprogram MP metabolism in a way to promote anti-inflammatory and clearance functions [42].

Pro- and anti-inflammatory cytokines

The coherence of the actions of all cells that constitute the innate response to infection and tissue damage is provided by cytokines, which play a central role in the positive and negative regulation of immune responses and in interaction with other physiological systems, such as the complement system and the hematopoietic system. By interacting with specific receptors on the target cell membrane, cytokines trigger a cascade that leads to the induction, enhancement, or inhibition of the cell's immunological activity. During peritonitis, several cytokines are secreted by

reticuloendothelial cells, MTCs and RPMPs. IL-1β and tumor necrosis factor-α (TNF -α) are the first cytokines that have been identified as the leading players and primary mediators of the inflammatory response in peritoneal inflammation [43, 44]. Since their discovery, many more mediators have been identified that perform both pro- and anti-inflammatory functions both in the peritoneum and in peripheral parts of the body during the macroorganism response to peritonitis.

In peritonitis with an unfavorable outcome, the concentrations of pro-**inflammatory mediators** increase rather consistently in the blood and in peripheral organs, but increase only slightly or decrease in the abdominal cavity. However, the hope of clinicians that the removal of pro-inflammatory cytokines from the bloodstream or their neutralization would prevent the development of severe septic complications and death did not materialize. Prophylactic inhibition of early cytokines such as TNF-α, IL-1β, and IFN-γ slightly improved survival in some models of peritonitis, but genetic deletion of these cytokines resulted in increased mortality [45–47]. Therapeutic inhibition of IL-1β and TNF-α in humans, as shown by the results of a number of studies, including a double-blind randomized study, also had no significant effect on survival in sepsis [48, 49]. Thus, in order to improve survival, it is necessary to prevent the early production of these cytokines by activated cells, rather than to remove them completely.

The recruitment, proliferation, and activation of immune cells are induced by any damage to the peritoneum; as a result, their combined action contributes to tissue repair. But an uncontrolled activation with hyperproduction of pro-inflammatory cytokines can eventually lead not only to progressive damage to the peritoneum, but also to the damage to cells and tissues in peripheral organs [50]. The kinetics of cytokine expression is

critical for mortality from peritonitis. For example, the neutralization of an important component of anti-infective defense, such as IL-12, which is produced in response to LPS impact, has been shown to improve animal survival. But neutralization of this cytokine by antibodies led to a significant deterioration in the host's ability to clear the abdominal cavity from gram-negative bacterial infection, which significantly increased mortality [51].

To prevent the development of a systemic inflammatory response and sepsis, a balance of pro- and **anti-inflammatory cytokines** is needed**.** The latter can have both beneficial and adverse effects on the peritonitis severity and mortality. The beneficial effect of anti-inflammatory cytokines on survival may be predetermined by a reduction in inflammatory damage to tissue (and organs) [52]. It has been shown in models of peritonitis that in genetically modified animals lacking anti-inflammatory cytokines, mortality acutely increased [53], while the therapeutic or prophylactic use of IL-10 or IL-4 prevented these animals from dying [52, 54, 55]. It has been shown that the release of IL-4 and IL-10 is accompanied by a decrease in the pro-inflammatory activity of many cellular factors, which contributes to the resolution of inflammation [56, 57]. The resolution of the inflammation induced by overactive neutrophils requires strict regulation to prevent excessive tissue damage and ensure that acute inflammation does not become chronic. Inactivation of IL-27 that is involved in the negative regulation of granulocytic infiltration and oxidative burst in them leads to a decrease in mortality from peritonitis [58]. But the suppression of NG activity, their complete absence or neutropenia lead to septic complications, and even to death amid immune deficiency [59]. Thus, on the one hand, anti-inflammatory reactions in peritonitis protect the host from excessive inflammation, but on the other hand, they can play a role in the development

of immunosuppression.

The complement system role

The immune mechanisms involved in the pathogenesis of peritonitis are not limited to the cell populations and cytokines listed above. The important role of the complement system should also be noted. The scientific literature, which mainly reflects the results of experimental studies, is quite inconsistent, however, it has been shown that mortality from peritonitis increased to 100% when the factors C1q, C2, C4 of the classical pathway, factor B of the alternative pathway, or factor C3 of the common pathway were insufficient or inhibited [60 , 61]. Animals lacking a powerful complement activator, IgM, showed a decrease in the activity of inflammatory reactions necessary for recovery, and a decrease in survival after induced peritonitis [62]. The proinflammatory nature of C5a in septic peritonitis is highlighted by the fact that the known proinflammatory cytokine IL-6 upregulates C5a receptor expression in various organs in peritonitis in mice [63]. Inhibition of IL-6 decreased C5a receptor expression and increased survival [64]. In addition, the inhibition of C3d was accompanied by a reduction in tissue damage both locally and peripherally [65]. Summarizing the above, we can conclude that both the activation and inhibition of complement play an important role in the elimination of intra-abdominal infection. However, only a balanced, rather than excessive, activation of the complement system is beneficial.

Thus, to ensure the cellular and molecular constancy of the body inner environment, the immune system must work without any impairments of its functions. Despite the fact that immunity is a powerful and multilevel system with pronounced compensatory properties [66], cases of forming

resistance to antigens or excessive reactions are not uncommon [67]. It is impossible to exclude genetically determined individual features of the immune response. A personalized approach to determining the nature of the immune response and outcomes of purulent peritonitis using cluster analysis allowed the authors [68] to identify four groups of patients: cluster 1 includes immunotype characterized by the activation of innate immunity; cluster 2 is the immunotype characterized by humoral response of adaptive immunity; cluster 3 is the immunodeficient immunotype; cluster 4 is unreactive immunotype. The overall severity and adverse outcome of the disease were most often reported in clusters 3 and 4.

Conclusion

In the pathogenesis of peritonitis, an important role is played by the peritoneum, which provides a stable microenvironment under normal conditions, but is subject to the damaging effects of infections, surgical trauma and other events. The peritoneal response to injury includes the recruitment, proliferation, and activation of various hematopoietic and stromal cells. Under physiological conditions, effective responses to injury are organized, inflammation triggers are eliminated, inflammation quickly subsides, and normal tissue architecture is restored. It has been shown that an important point in the resolution of peritonitis is preserving the balance of cytokines, the activity of the immunocytes and complement functioning in the immune lymphoid aggregates of the peritoneum and omentum, and their concomitant action during inflammation. However, if the inflammatory triggers are not removed, fibrosis or scarring occurs, tissue dysfunction develops and ultimately leads to organ failure. Therefore, an important promising task for researchers is to determine the time and target of

interventions that provide a balance between favorable pro-inflammatory effects - infection control, and adverse effects - systemic activation and tissue damage, obligatory considering of an individual immune response.

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