Austin Journal of Clinical Immunology

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Austin Publishing Group

Special Article - Immune System Development

Coordination of Innate and Adaptive Immunity Depending on Neutrophilic Extracellular Traps Formation

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Received: October 09, 2019; **Accepted:** October 23, 2019; **Published:** October 30, 2019

Abstract

Neutrophils are the main cells of innate immunity, which play an important role in early anti-infective protection of the organism, but the mechanisms of the interaction between innate and adaptive immune system are still not clear. A single concept of interaction between innate and adaptive immune system is absent. We propose to consider the interaction of the innate and adaptive immune system upon entering of a pathogen into the human organism in the form of a series of successive stages. The first step consists in the pathogen-induced activation of neutrophils. At this stage, the neutrophils synthesize and secrete IFN-γ and activate the synthesis of NADPH oxidase, myeloperoxidase, arginase. This will start the activation of innate immunity, consisting in the involvement of cytotoxic T-lymphocytes and NK cells to the inflammation site. The second step is the formation of neutrophil extracellular traps that bind, inactivate or damage the pathogens through the action of active forms of oxygen and nitrogen. At this stage is the inhibition of adaptive immunity, caused by a local reduction of arginine concentration, which entails a weakening of the functional activity of T-lymphocytes. In the next stage, acute infectious inflammation decreases the expression of innate immunity receptors (TLR), under the influence of toll-interacting protein and the reactivity of the innate immune system is reduced. Disclosure of neutrophil extracellular traps is limited. Presentation of antigens in the absence of the release of arginase from the neutrophils creates the conditions for activation of adaptive immunity. The sequence of stages of activation of neutrophils or failure in the individual links of this chain of events leads to complications of the inflammatory process.

Keywords: Neutrophils; IFN-γ; Tollip; Arginase; Innate immunity; Adaptive Immunity

Introduction

The protective inflammatory reaction of a person preserves the integrity of the body and is necessary to maintain homeostasis. Neutrophils - the most numerous white blood cells are the most important cells of local immunity and, at the same time, key factors of innate immunity. They are considered to be the first line against injury factor. The innate immunity cell receptors interact with potentially dangerous ligands of exogenous or endogenous origin. The pathogens that enter the body cause an inflammatory reaction that attracts neutrophils from peripheral blood to the tissue. In the focus of inflammation, neutrophils destroy microorganisms using a number of mechanisms, mainly due to phagocytosis, the release of antimicrobial substances and the formation of neutrophilic extracellular traps. The formation of neutrophilic extracellular traps, also called netosis, is a mechanism for the destruction of microorganisms by neutrophils [1,2]. The interaction of neutrophils with microorganisms causes the activation of cells and leads to the release of fibrous network-like structures, consisting of decondensed DNA in complex with cytosolic proteins, enzymes, granule proteins and histones. Such a complex provides a sufficiently high local concentration of antimicrobial components to inactivate and destroy the pathogen, regardless of absorption. Although the mechanism of trap formation is not fully understood, it is known that their formation depends on the activity of neutrophilic NADPH oxidase. In a small number of studies, neutrophilic extracellular traps were found, the opening of which occurs without prior activation of NADPH oxidase. The antibacterial efficiency of such neutrophilic extracellular traps, as expected, was found to be low. In our opinion, these results show that the mechanisms of NADPH oxidase activation and the mechanisms of neutrophilic extracellular traps formation can be different. Or, that the neutrophilic extracellular traps formation after neutrophils activation through Toll-Like Receptors (TLRs) requires some additional factors that are not yet known. In addition to antimicrobial properties, neutrophilic extracellular traps create a barrier that prevents the spread of the pathogen. A large number of studies are devoted to the study of the role of extracellular neutrophils traps in infectious inflammation and it has been shown that both the insufficiency and the excess neutrophils extracellular traps formation are unfavorable for the development of inflammation. Netosis deficiency is due to congenital factors, and can also be induced by pathogens. Excessive netosis leads to tissue damage due to the action of ROS and peptides with pore-forming activity (such as LL-37) and causes hemocoagulation, thrombosis and hemophagia. It is now

Citation: Kazimirskii AN, Salmasi JM and Poryadin GV. Coordination of Innate and Adaptive Immunity Depending on Neutrophilic Extracellular Traps Formation. Austin J Clin Immunol. 2019; 6(1):1037.

becoming clear that there is a link between inflammatory diseases, including infectious diseases, sepsis and autoimmune diseases and networks. Therefore, it is important to re-evaluate inflammatory disorders in terms of neutrophilic networks and incorporate emerging concepts to better understand the mechanisms involved.

Activation of neutrophils in the anti-infection defense of innate immunity

A functional innate immune response is crucial for the correct response of the body and reduction microbial infections. If the innate immune response is dysfunctional and activated in the absence of infection, inflammatory and autoimmune diseases may develop. Therefore, the innate immune response must be strictly controlled in order to avoid an autoimmune response from molecules originating from the host organism. One of the most potent factors in the initial period of acute inflammation is Interferon-γ (IFN-γ). Interferon-γ is a Th1 cytokine mainly produced by T-lymphocytes, NK cells and macrophages in response to Interleukin 12 (IL-12). However, during the primary interaction of the pathogen with neutrophils, intense synthesis of IFN-γ develops with its subsequent secretion without the participation of cells of the adaptive immune system. Neutrophils contain a small supply of IFN-γ, and this supply is rapidly used up during secretion when stimulated by degranulating agents such as formyl peptides. However, after several hours of stimulation with cytokines (IL-2, IL-12, IL-15, IL-18) or LPS, neutrophils activate genome expression and develop their own IFN-γ synthesis. An inhibitor of protein synthesis, cycloheximide, is able to suppress the induction of IFN-γ synthesis by neutrophils. The IFN-γ synthesis is associated with an increase in specific mRNA, which indicates a transcription mechanism [3]. This and some other studies initially led to the suggestion that IFN-γ secretion is secondary, it develops in response to the action of cytokines from the cells of the immune system. But it was further established that neutrophils synthesize IFN-γ even without the influence of cytokines, experiencing only stimulation through innate immunity receptors (TLRs). Moreover, treatment of human neutrophils with IL-4 or IL-13 reduced their ability to neutrophils extracellular traps formation and migrates in the direction of CXCL8 *in vitro*. The blood serum of allergic patients acted similarly on neutrophils of healthy donors [4]. So, when studying the early stages of pneumonia caused by Streptococcus pneumoniae, it was found that early production of IFN-γ regulates bacterial clearance. The synthesis of IFN-γ by neutrophils requires a number of tyrosine kinases and NADPH oxidase and was independent of the presence of TLR2 and TLR4 on the cell membrane and did not require the presence of IL-12. The adapter molecule MyD88 is important for the production of IFN-γ by neutrophils [5]. In experiments on animals infected with Listeria Monocytogenes (LM), it was found that shortly after infection, a large number of IFN-γ-producing neutrophils quickly accumulate in the spleen, blood and abdominal cavity. Both *in vivo* and *in vitro* experiments have shown that neutrophils are an important source of IFN-γ. IFN-γ played a critical protective role against acute LM infection, as evidenced by the poor survival of Ifng -/- mice [6]. However, excessive amounts of IFN-γ-producing by neutrophils during colitis caused by Salmonella Typhimurium negatively, causes severe inflammation, considerable damage to the small intestine and bleeding [7]. Intracellular pathogens also induce accelerated IFN-γ formation. And virus infection does not increase expression of innate immunity receptors (TLRs) in plasmacytoid dendritic cells. Mice infected with the virus of lymphocytic choriomeningitis, developed a strong TLR-independent production of Interferon type I (IFN-I) using RNA helicases and with the participation of Mitochondrial Antiviral Signaling Protein (MAVS) [8]. Viral infection triggers the formation of aggregates of MAVS with prione-like activity [9], which actively stimulates the immune signaling. In control of MAVS-mediated antiviral signaling autophagy plays an important role. Ubiquitin-ligase (RNF34) associated with MAVS in the mitochondrial membrane after viral infection and facilitates autophagic degradation of MAVS, which is required for upgrading of damaged mitochondria during viral infection. RNF34-mediated autophagic degradation of MAVS regulates the innate immune response, mitochondrial homeostasis, and controls intracellular infection [10]. The start of intracellular reactions is initiated after the recognition of viral products through pathogen-associated molecular patterns. Such recognition initiates signaling cascades that activate the intracellular innate immune defense and inflammatory response, which, in turn, facilitates the development of an adaptive immune response. The Retinoic Acid Inducible Gene I (RIG-I) gene I and the RIG-I-Like Receptor (RLR) family of proteins are key receptors for recognition of cytoplasmic pathogens, RNA and some DNA viruses. Activated RIG-I signals interact with the MAVS adapter protein, which leads to a signaling cascade that activates the transcription factors IRF3 and NF-κB. These actions cause the expression of antiviral gene products and the production of interferons type I and III, which lead to an antiviral state in the infected cell and surrounding tissue [11]. The value of Mitochondrial Antiviral Sensor (MAVS) was demonstrated in infected mice of wild-type Ebola Virus (EBOV). MAVS controls the replication of EBOV through the expression of IFN-α, attenuates the inflammatory response in the spleen and prevents liver cells death. MAVWS-/- mice develop severe inflammation, viral replication and decreased synthesis of IFN-I [12]. Infection of genetically modified Myd88/Trif/Mavs(-/-) mice had disrupted signaling of all TLR, RLR(RIG-I, MDA5, LGP2) and IL-1R and other cytokine receptors such as the receptor for IL-18 showed that RSV-infected animals early production of pro-inflammatory mediators was completely absent. However, RSV-specific $CD8^+$ T-lymphocytes were detected in lung tissue and respiratory tract. RSV-infected Myd88/Trif/Mavs(-/-) mouse off the innate immune system overcome the infection, but showed higher viral load and weight loss. These experimental result demonstrate a certain level of redundancy in the immune defense of the organism, and that the involvement of cytotoxic T-lymphocytes and NK cells in the response provided by cells of the infected tissue itself, producing INF-γ [13]. In experimental models of toxoplasmosis (Toxoplasma gondii) was identified the presence of non-lymphoid source of IFN-γ in genetically altered mice lacking all lymphoid cells due to deficiencies of genes 2 and IL-2Rγ_c, activating recombination, which also produced IFN-γ in response to the simplest of the parasite. Flow cytometry and morphological studies have shown that in this experimental model, sources of IFN-γ are neutrophils, but not NK cells and not $CD8^+$ T-lymphocytes [14,15].

The innate response of the immune system on the pathogen develops in several stages. Initially, infected macrophages and dendritic cells recruit and activate neutrophils, synthesizing and

secreting IFN-I (IFN-α and IFN-β). At this stage, the pathogen interacts with the innate immunity receptors (TLR) or intracellular receptors of the RLR (RIG-I, MDA5, LGP2). Group RLR receptors acting as sensors of viral replication in the cell cytoplasm, and detects the viral replication by direct interaction with molecules of double-stranded RNA viral genome. Neutrophils in the peripheral blood enter the focus of inflammation and under the influence of IFN-I are activate and synthesize IFN-γ. The secretion of IFN-γ attracts and activates NK cells and cytotoxic $CD8^+$ T-lymphocytes that are able to recognize (in the presence of specific receptors) and destroy infected cells. During the development of innate immunity reactions, IFN-γ secretions from peripheral blood neutrophils develop and increase functional activity of cytotoxic lymphocytes.

Neutrophils extracellular traps formation and innate immunity inhibition

Although a large number of studies on the role of neutrophils in the anti-infection protection of the human, there is still no complete concept describing the interaction of innate and adaptive immunity. At the same time, some studies indicate that contact interactions of the pathogen with the human cells cause successive stages of neutrophils activation, and their violation extremely negatively affects the outcome of inflammation. The neutrophils extracellular traps formation occurs when the necessary level of neutrophils activation is reached during which the gene is expressed, anti-infection protection enzymes are synthesized, cytokine synthesis develops, and regulatory proteins are synthesized, which include the toll-interacting protein. Toll-interacting protein (Tollip) is an ubiquitin-binding protein that regulates (limits) the innate immune response, including signaling of Toll-like receptors, and is a key negative regulator of innate immunity, prevents excessive inflammatory reactions. Its role was investigated in patients with various diseases and in experimental animal models. Examination of patients with severe inflammation, such as septic colitis, with an unfavorable clinical outcome, found reduced levels of Tollip in the peripheral blood of patients compared to blood samples from healthy donors. Such Tollip-deficient neutrophils had reduced migration ability with respect to the strong chemoattractant N-formyl-methionyl-leucyl-phenylalanine, a product of bacterial proteins degradation, had a weakened potential for the generation of neutrophils extracellular traps and showed a reduced activity of bacterial destruction [16]. Tollip deficiency is associated with an increased risk of developing tuberculosis. Tollip polymorphisms were found in the examined patients, which indicate a mechanism of negative regulation of TLR signaling in the pathogenesis of human tuberculosis [17].

Neuroinflammation in Tollip (-/-) mice was induced by LPS injection into the midbrain region. A significant increase in TNF-α, IL-1β, IL-6 and IFN-γ was recorded. In Tollip (-/-) mice, a higher inducible production of NO synthase was observed both at the mRNA level and at the enzyme level compared to WT mice injected with LPS. The absence of Tollip in animals also exacerbated LPS-induced oxidative damage to the brain [18]. A negative immune regulator, Tollip, inhibits the pro-inflammatory response to Rhinovirus (RV) infection, which contributes to neutrophilic airway inflammation. The ability of Tollip to limit the excess production of IL-8 in the respiratory tract of humans exposed to type 2 cytokines upon RV infection has been demonstrated in primary tracheobronchial epithelial cells of humans, which were obtained using CRISPR/Cas9 technology. Tollip-deficient epithelial cells under the influence of IL-13, IL-33 and RV produced an excess of IL-8, which was accompanied by a decrease in the formation of sST2. IL-8 - a cytokine of innate immunity - a chemoattractant for neutrophils, macrophages, eosinophils, basophils and lymphocytes. ST2 is an IL-33 receptor for IL-1-like cytokines, which is secreted in response to epithelial damage and various pathogens. The soluble form of the ST2 receptor (sST2) interacts with IL-33 and reduces the activation of the main transcriptional pathway of NF-kB, which reduces the inflammatory response [19]. Tollip deficiency causes an accelerated incorporation of the adaptive immune system into the response. In a model of chemically induced colorectal cancer in Tollip (-/-) mice, enhanced immune surveillance of the tumor was observed. Tollip-deficient neutrophils significantly increased T cell activation by enhancing the expression of the costimulatory CD80 molecule and decreasing the expression of the inhibitory PD-L1 molecule. The absence of Tollip in the organism increased the formation of STAT5 and decreased STAT1, the transcription factors that are responsible for the expression of CD80 and PD-L1, respectively [20].

The presented data shows the important role of toll-interacting protein in innate immunity reactions. As neutrophilic extracellular traps disclose, tollip inhibits the expression of innate immunity receptors (TLRs), limiting the interaction of neutrophils with the pathogen. The formation of neutrophilic extracellular traps in this case slows down, which, obviously a mechanism for limiting innate immunity in the early stages of inflammation. The insufficiency of this process entails a prolonged release of enzymes, reactive oxygen species and biologically active substances from the revealed neutrophils extracellular traps and causes tissue damage. The physiological significance of the Toll-interacting protein is to reduce the reactivity of innate immunity. Deficiency of this important regulator of innate immunity leads to premature activation of adaptive immunity and, in some cases, can leads to adverse consequences. Why the inclusion of adaptive immunity occurs with a certain delay remains unclear and requires analysis. The correct answer to this question can be obtained by considering the spectrum of enzymes that produce neutrophils at the neutrophils extracellular traps formation.

Enzymes of neutrophils extracellular traps (the interaction of innate and adaptive immunity)

The main secreted enzymes that enter the site of inflammation during the neutrophilic extracellular traps formation are NADPH oxidase, myeloperoxidase and arginase. The physiological significance of NADPH oxidase and myeloperoxidase is the generation of oxygen and nitrogen radicals in the focus of inflammation, which have a pronounced anti-infection effect. The role of arginase is to inhibition of adaptive immunity [21]. A large number of studies have shown that in the early stages of inflammation, these pre-activated enzymes enter the extracellular space and a violation of this process always causes adverse effects. The research results show that this is an absolutely necessary stage in the interaction of the pathogen with the human's immune system. It should be noted that this stage is limited in time. The physiological limiter to the formation of neutrophils extracellular traps is the toll-interacting protein. The value of arginase entering the focus of inflammation from activated neutrophils during the formation of neutrophils extracellular traps and the resulting

inhibition of adaptive immunity is not entirely clear and attracts the attention of researchers.

The study of patients with acute ischemic stroke revealed a relationship between blood arginase activity, the ratio of Neutrophils/ Lymphocytes (NLR) and the severity of the disease. And the study of patients with traumatic brain injury (24 hours after the injury) has shown an increase in the amount of arginase 1 mRNA and a soluble form of the surface receptor CD100 (sCD100) localized mainly on platelets and T-lymphocytes was detected. In patients' blood was also increased in the content of Matrix Metalloproteinase 9 (MMP9) involved in the remodeling of the extracellular matrix and Myeloid Differentiation factor 2 (MD2, LY96) - glycoprotein, which binds to the extracellular domain of the innate immunity receptor (TLR4), causes its activation and plays an important role in innate immunity [22,23]. An acute stroke alters the systemic immune response in peripheral blood; however, the molecular mechanism by which arginase expression is enhanced is not clear. A study of patients with acute stroke showed that miR-340-5p miRNA binds to the 3'-untranslated region of the arginase-1 gene and inhibits the expression of the arginase gene. Assume that the reduction of miR-340-5p discovered in patients with acute stroke relieves inhibition of gene expression of arginase 1, which subsequently causes her intense synthesis [24]. Using a model of temporary occlusion of the middle cerebral artery in mice, discovered the ability of murine neutrophils to release arginase 1 of pre-formed granules. While there was a decrease in the expression of the Zeta chain (CD3ζ) in T-lymphocytes, which is consistent with a decrease in their functional activity [25]. Acute infectious processes cause a fast increase in the activity of arginase in peripheral blood of patients. In the study of necrotic enterocolitis in children, a significant increase in peripheral blood arginase activity was found and it was demonstrated that infiltrating neutrophils secrete this enzyme [26]. During acute infection in humans was found that the number of neutrophils in the peripheral blood expressing arginase proportional to the severity of the disease. These neutrophils disrupt the expression of the Zeta chain of CD3-cells and the function of T-lymphocytes, contributing to dysfunction of T-cells observed in sepsis [27,28]. The chronic inflammation is also accompanied by increased activity of arginase in inflammation. In tuberculous granulomas, which are a compact, organized clusters of infected and uninfected macrophages, T cells, neutrophils, and other cells showed increased activity of arginase, and the source of this enzyme are macrophages. Induction of arginase blocks the proliferation of T cells, depriving them of their functional activity [29].

The data obtained in their entirety make it possible to argue that the interaction of innate and adaptive immunity experiences certain reciprocal relationships in the initial stage of acute inflammation. The results indicate inhibition of adaptive immunity in the initial stage of acute inflammation associated with the formation of neutrophils extracellular traps. At the stage of traps formation, arginase enters the extracellular environment, a local decrease in arginine concentration occurs, which entails the inhibition of the functional activity of T-lymphocytes and inhibition of antigen presentation processes. At this stage, there is a pronounced activation of innate immunity, which is associated with a simultaneous inhibition of adaptive immunity. As the expression of innate immunity receptors decreases, under the influence of the toll-interacting protein, the reactivity of the innate immunity system decreases. The presentation of antigens against the background of the lack of arginase exit from neutrophils creates the conditions for the activation of adaptive immunity.

Conclusion

The analysis of the experimental data makes to highlight the stages of acute inflammation, describing the interaction of innate and adaptive immunity. In the initial stage of acute infectious inflammation develops the activation of neutrophils induced by the pathogen. At this stage, the neutrophils synthesize and secrete IFN-γ and activate the synthesis of NADPH oxidase, myeloperoxidase, arginase. This will start the activation of innate immunity, consisting in the involvement of cytotoxic T-lymphocytes and NK cells to the inflammation site. Achieving a certain high level of activation of NADPH oxidase triggers the formation of neutrophil extracellular traps that bind, inactivate or damage the pathogens through the action of active forms of oxygen and nitrogen. At the stage of disclosure of traps in the extracellular environment, receives arginase, there is a local reduction of arginine concentration, which entails a weakening of the functional activity of T-lymphocytes. At this stage is the inhibition of adaptive immunity. The next stage of acute infectious inflammation due to reduced expression of innate immunity receptors (TLR), under the influence of toll-interacting protein, the reactivity of the innate immune system is reduced. Disclosure of neutrophil extracellular traps is limited.

Antigens presentation of in the absence of the release of arginase from neutrophils creates the conditions for the subsequent activation of adaptive immunity.

Source of Financing

The authors declare a lack of funding for the study.

Acknowledgment

The authors of this study show appreciation all the employees of the Department of Pathophysiology and Clinical Pathophysiology for splendid support in the preparation of this manuscript.

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