COVID-19 and innate immunity

Teimuraz Tavkhelidze

Teaching University Geomedi, Tbilisi, 0114, Georgia
Email: teimuraz.tavkhelidze@geomedi.edu.ge
DOI: 10.56580/GEOMEDI0004

Abstract

The human body fights many pathogens in the environment with different methods. One of them is immunity. There are innate and acquired immunities. The purpose of innate immunity is to maintain the body's own and biological individuality, to identify and destroy foreign substances and cells, including pathogenic bacteria and viruses, as well as tumor cells that have grown in the body. The innate immune response accomplishes this by means of myeloid lineage cells that have no strict specificity for antigens, do not elicit a clonal response, and have no memory for primary contact with a foreign agent. Acquired immunity has the ability to recognize and respond to individual antigens, characterized by a clonal response in which lymphoid cells are also involved. He has an immunological memory. The body responds to COVID-19 invasion with both innate and acquired immunity. This article reviews the innate immune response to the invasion of COVID-19 in the body.

Keywords

COVID-19, interferon, cytokines, coronavirus, immunity, RNA, PAMP, DAMP

Introduction

The immune system is responsible for the implementation of immunity in the body, which exists in vertebrates and combines the organs and tissues that protect the body from disease, identifies and destroys pathogens (from viruses to parasitic worms), as well as tumor cells. However, sometimes the identification of pathogens is complicated due to their adaptation and evolutionary development in the host organism.

There are many ways to detect and eliminate foreign agents by the immune system in developed organisms. This process is called the immune response. All forms of immune response can be divided into congenital and acquired responses. The purpose of innate

immunity is to maintain the body's own and biological individuality, to identify and destroy foreign substances and cells, including pathogenic bacteria and viruses, as well as tumor cells that have grown in the body. The organism accomplishes this by means of myeloid lineage cells that do not have strict specificity for antigens, do not elicit a clonal response, and have no memory for primary contact with a foreign agent. Acquired immunity even has the ability to recognize and respond to individual antigens, characterized by a clonal response in which lymphoid cells are also involved. It is characterized by immunological memory. The main difference between them is that the acquired immunity is highly specific to a particular type of antigen and has the ability to destroy them quickly and efficiently upon repeated encounters.

Antigen

An immune response is triggered by a substance called an antigen. For example, people who have been exposed to chickenpox, measles, diphtheria, have lifelong immunity to these diseases. This is accomplished through immune antibodies and lymphocytes, their interaction with the antigen, its subsequent inactivation, and its elimination.

Antigens are divided into exogenous and endogenous based on their origin:

The exogenous antigens that make up most of the antigens are antigens of infectious-parasitic origin (viruses, rickettsiae, bacteria, parasites) and of non-infectious origin (proteins of foreign origin and protein-containing compounds, haptens, which are in the composition of dust, food, flower dust, some medicinal substances).

Endogenous antigens are Infectious and/or parasitic antigens (protein components of microbes "settled" in the tonsils, intestines, oral mucosa, and respiratory tract) and non-infectious antigens, which are produced when the body's own proteins are damaged as well as tumors.

Congenital immune system

In vertebrates (e.g., humans) the immune system is made up of many types of proteins, cells, organs, and tissues, the relationship between which is complex and dynamic. Because of such a sophisticated immune response, the vertebrate immune system adapts over time, creating immunological memory and allowing the body to effectively defend itself against specific foreign substances or cells. The basis of vaccination is based on this principle.

The innate immune system is evolutionarily much older than the acquired immune system and is present in all species of plants and animals [1]. Compared to an acquired immune system,

the innate immune system is activated more rapidly at the first appearance of a pathogen but detects the pathogen with less accuracy. It responds not to specific antigens, but to certain classes of pathogenic antigens that characterize pathogenic organisms (bacterial cell wall polysaccharides, double-stranded RNA of some viruses, etc.).

Congenital immunity has cellular (natural killers, phagocytes, granulocytes, minor subpopulations of T and B lymphocytes) and humoral (lysozyme, interferons, complement system, inflammatory mediators) components. The local nonspecific immune response is otherwise called inflammation.

The main functions of the innate immune response in vertebrates are: Attraction of immune system cells to the site of pathogen penetration by the production of chemical factors, including specific chemical mediators, and cytokines; Activate the components of the complement system; Detection and destruction of foreign bodies in organs and tissues by leukocytes; Activation of the acquired immune system during the antigen presentation process.

The immune system of humans and other vertebrates is a complex of organs and cells that can perform immunological functions. First of all, the immune response is carried out by leukocytes. Most of the cells of the immune system originate in hematopoietic tissues. In adults, the development of most of these cells begins in the bone marrow. Only T-lymphocytes differentiate into the thymus (mammary gland). Mature cells accumulate in lymphoid organs and near the borders of the body's environment, near the skin or mucous membranes.

The immune system protects the body from infection on several levels, with the specificity of protection increased with each level. These levels are:

- Level 1 - Physical barriers that prevent infections (bacteria and viruses) from entering the body. If the pathogen crosses these barriers, then the next level will try to protect the organism;
- Level 2 is the innate immune system. It is found in all plants and animals. When pathogens override innate immune mechanisms as well, the next level of protection will be involved in vertebrates;
- Level 3 is the acquired immune system. This part of the immune system adapts its response to the infectious process to improve the detection of foreign biological material. Such an improved response is maintained in the form of immunological memory even after pathogen destruction. This allows the acquired immune

mechanisms to respond more quickly and vigorously with each subsequent appearance of the same pathogen.

The complement system plays an important role in the immune response. It is a biochemical cascade that attacks the membrane of cells of foreign origin. The complement system contains more than 20 different proteins. This is the main component of humorous innate immune response. There are many types of complement systems, including in invertebrates.

In humans, this mechanism is activated by binding to complement proteins on carbohydrates on the surface of microbial cells or on antibodies attached to these microbes (the second case illustrates the relationship between the mechanisms of innate and acquired immunity). The signal from the complement attached to the cell membrane elicits rapid reactions aimed at destroying that cell. The rate of such reactions is due to the sequential proteolytic enhancement of complement molecules, which in themselves are proteases (proteolytic enzymes of the hydrolase class). Once complement proteins attach to the microorganism, their proteolytic action is released, which in turn activates other proteases in the complement system, and so on. Thus, a cascading reaction is generated that amplifies the initial signal. The cascade produces peptides that attract immune cells, enhance vascular ionization, and opsonize the cell surface (adsorbable antibodies and complement factor), which are labeled for destruction.

Blood-forming elements play an important role in the immune system.

Leukocytes are the main cells in both innate (granulocytes and macrophages) and acquired (primarily lymphocytes) immunity. In addition, their actions are closely related to each other.

Natural killers are large lymphocytes that have cytotoxicity to tumor and viral cells. Today these cells are considered as a separate group of lymphocytes. They are formed as a result of the differentiation of lymphoblasts in the bone marrow. They are transformed into killers in different tissues and organs (lymph nodes, spleen, liver, intestines, thymus, uterus, etc.), where they turn into natural killers of different variants. Natural killers are so-called because they, unlike T-lymphocyte killers, are ready to kill without examining a foreign cell, immediately. The mechanism of action of natural killers is the same as that of T-killers: both killers carry in their heads the same granules in which the toxic substance is placed. The NK-cell closely contacts the sacrificial cell and releases a toxic substance into it that kills it. Natural killers are protected from this poison.

Congenital immune response phagocytes (macrophages, neutrophils, dendritic cells), proliferative cells, basophils, eosinophils, and natural killers detect and destroy foreign

particles through phagocytosis (absorption and intracellular digestion). Congenital immune cells are important mediators in the activation of acquired immune mechanisms.

COVID-19

Coronaviruses have become relevant today. They are difficult to fight because they change and become quite virulent when they enter the host. Some strains of coronavirus of zoonotic origin, such as coronavirus associated with severe acute respiratory syndrome (SARS-CoV), coronavirus of the Middle East Respiratory Syndrome (MERS-CoV) and New Coronavirus (SARS-CoV-2), pose a high risk to human health. The first SARS-CoV explosion occurred in 2003 [2].

Coronavirus disease-2019 (Corvavirus disease-2019 - COVID-19) is a highly contagious serious respiratory disease caused by SARS-CoV-2 and first detected in Wuhan, China in December 2019. SARS-CoV-2 spread rapidly around the world, and the World Health Organization declared a pandemic of SARS-CoV-2 on March 11, 2020 [3]. The COVID-19 pandemic has dramatically changed people's lifestyles, put great pressure on the existing medical care system, and has become a huge social and economic burden. The presence of multiple coronaviruses in bats, including SARS-associated CoVs, and the sporadic crossing of coronaviruses on the human species barrier, suggests that cases of zoonotic transmission may occur in the future. Therefore, it is urgent to find a solution to control the COVID-19 pandemic, as well as potential similar pandemics in the future, especially for the prevention of viral spread and treatment of viral diseases. Understanding the mechanisms of interaction with the coronavirus host is crucial for the development of effective vaccines and therapies [2]. Coronaviruses belong to the Orthocoronavirins subfamily of the coronavirins family. Orthocoronavirins subtype viruses can be divided into four genera: alpha-coronavirus, beta-coronavirus, gamma-coronavirus, and delta-coronavirus [3]. Among these viruses, four of the seven strains of alpha- and beta-coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1) are known to cause mild upper respiratory symptoms in humans, commonly recognized as seasonal colds [3]. In contrast, the other three strains (SARS-CoV, MERS-CoV, and SARS-CoV-2) transmitted by zoonotic transmission can cause severe respiratory symptoms with unique pathogenesis, including severe lymphopenia and extensive pneumonia caused by antiviral reactions [4].

Coronaviruses are RNA-membrane viruses that have the largest viral RNA. Upon infection with the coronavirus, the virus's life cycle begins by binding to the virus spike protein S at the target cell surface receptors, causing the virus to fuse with the target cell [5]. During the intracellular viral life cycle, the genomic RNA of the coronavirus is not coated with the

nucleocapsid (N) protein, causing the translation of two open reading frames. Open reading frames (ORFs) produce two major polyproteins, pp1a and pp1ab, which are then cleaved by viral proteases encoded by nonstructural protein 3 (Nsp3), a papain-like protease, and Nsp5 (3C Protease-like) genes to produce functional non-structural proteins (Nsp1-Nsp16) [6]. The viral replication and transcription complex (RTC) generated by Nsp2-Nsp16 additionally promotes viral genomic RNA replication and subgenomic mRNA transcription. Among these proteins, Nsp3, Nsp4, and Nsp6 are involved in the formation of double-membrane vesicles (DMVs), along with two other replications of viral organs, namely convoluted membranes (CMs) and small open double membranes (DMS). Which provide replication of viral genomic RNA and subgenomic RNA of the protective microenvironment [7]. Nsp7 and Nsp8 are two RNA-dependent RNA polymerase (RdRp) cofactors that are present with RNA-modified enzymes in Nsp12 [8] and Nsp13-Nsp16 to facilitate viral RNA synthesis and modification. [9]. It is noteworthy that the 3 ′ –5 ′ exonucleases present in Nsp14 performs the function of RNA testing during RNA synthesis [10]. In the viral life cycle, the RNA defense mechanism is formed by Nsp10 (cofactor), Nsp13 (RNA 5 ′ triphosphatase activity), Nsp14 (N7-methyltransferase activity), and Nsp16 (2′-O-methyltransferase activity). However, their mechanism is still unclear [11,12,13].

Immediate cellular response to the invasion of pathogens is crucial to maintain cell homeostasis and survival of the living organism. Host responses are turned on by embryonic line-derived cellular receptors known as Pattern Recognition Receptors (PRRs), which detect specific samples of "non-self" and "foreign" molecules called Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns" (DAMPs). In mammals, activation of PRRs by activation of PAMPs or DAMPs activates innate immune responses and generates multiple IFNs and pre-inflammatory cytokines. Various PRRs have emerged in recent decades, such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD) receptors (NLRs), and C-type lectin (CLRs), AIM2-like receptors (ALR), cyclic GMP-AMP synthesis (cGAS), and retinoic acid-induced gene I (RIG-I) -like receptors (RLRs) [14,15,16,17,18]. Among these receptors, TLR and RLR are the two major receptors responsible for detecting RNA virus infection and launching interferon antiviral programs [1].

Detection of viruses by the host's innate immune system rapidly initiates the production of interferon, which leads to the expression of hundreds of immune serum globulin (ISG) and subsequent antiviral responses. Subsequently, the produced interferons and cytokines coordinate timely and balanced early immune responses, further provoking the host's immune

responses, which in addition trigger host antiviral defense programs by locating several types of immune cells at the sites of viral infection [19].

Interferon-induced transmembrane (IFITM) proteins have been reported to block the fusion of virus membranes with cell membranes [20] or inhibit intracellular transport of virus-containing particles [21, 22].

Conclusions

The coronavirus pandemic is very important. These coronaviruses have distinct characteristics related to their virulence and pathogenicity. First, all three highly pathogenic coronaviruses are zoonotic and originate from bats or lizards [23]. Thus, our immune system is "naive" and not prepared for a "never seen" occupant. Secondly, as we have discussed, coronaviruses have many mechanisms that target a variety of innate immune responses to avoid host antivirus defense programs. Untimely and inadequate congenital immunity activation can lead to the multiplication of viruses, which is directly related to the severity of the disease and mortality. Finally, coronaviruses can cause elevated levels of circulating inflammation prior to cytokines and chemokines by the host's uncontrolled immune responses - "Cytokine Storm" [1].

Coronavirus 2 (SARS-CoV-2) is characterized by severe respiratory syndrome caused by a significant effective immune response of the host organism and a devastating effect on immune dysregulation. The term "cytokine release syndrome" was coined. Cytokine Storm and Cytokine Release Syndrome are life-threatening systemic inflammatory syndromes involving elevated levels of cytokines and hyperactivity of immune cells, which can be caused by a variety of treatments, pathogens, tumors, autoimmune and monogenic conditions.

The cytokine storm was formerly called the flu-like syndrome that develops after systemic infections such as sepsis, as well as after immunotherapy that forces alveolar macrophages to produce excessive amounts of cytokines, resulting in a cytokine storm. It is thought that the increased immune response led to increased lethality during the 1918-1919 pandemic.

One of the earliest targeted methods of treating cytokine storms is the use of a monoclonal antibody against interleukin-6 tocilizumab receptors developed in the 1990s to treat idiopathic multicenter castleman disease. Many other disorders (sepsis, primary and secondary hemophagocytic lymphohistocytosis, autoimmune disorders, and Covid-19) have been reported, which are the cause of cytokine storm and whose treatment requires the use of immune therapy [24].

References

1. Charles Janeway et al. Immunobiology; Fifth Edition (неопр.). — New York and London: Garland Science (англ.). 2001. — ISBN 0-8153-4101-6.
2. Yusuke Kasuga et al. Innate immune sensing of coronavirus and viral evasion strategies. Experimental & Molecular Medicine 53, pages 723–736 (2021).
3. Fung, T. S. & Liu, D. X. Human coronavirus: host-pathogen interaction. *Annu. Rev. Microbiol.* **73**, 529–557 (2019).
4. Tse, L. V., Meganck, R. M., Graham, R. L. & Baric, R. S. The current and future state of vaccines, antivirals and gene therapies against emerging coronaviruses. *Front. Microbiol.* **11**, 658 (2020).
5. Li, F. Structure, function, and evolution of coronavirus spike proteins. *Annu. Rev. Virol.* **3**, 237–261 (2016).
6. Thiel, V. et al. Mechanisms and enzymes involved in SARS coronavirus genome expression. *J. Gen. Virol.* 84, 2305–2315 (2003).
7. Angelini, M. M., Akhlaghpour, M., Neuman, B. W. & Buchmeier, M. J. Severe acute respiratory syndrome coronavirus nonstructural proteins 3, 4, and 6 induce double-membrane vesicles. *mBio* https://doi.org/10.1128/mBio.00524-13 (2013).
8. Subissi, L. et al. One severe acute respiratory syndrome coronavirus protein complex integrates processive RNA polymerase and exonuclease activities. *Proc. Natl Acad. Sci. USA* 111, E3900–E3909 (2014).
9. Snijder, E. J., Decroly, E. & Ziebuhr, J. The nonstructural proteins directing coronavirus rna synthesis and processing. *Adv. Virus Res.* 96, 59–126 (2016).
10. Eckerle, L. D., Lu, X., Sperry, S. M., Choi, L. & Denison, M. R. High fidelity of murine hepatitis virus replication is decreased in Nsp14 exoribonuclease mutants. *J. Virol.* 81, 12135–12144 (2007).
11. Ivanov, K. A. & Ziebuhr, J. Human coronavirus 229E nonstructural protein 13: characterization of duplex-unwinding, nucleoside triphosphatase, and RNA 5'-triphosphatase activities. *J. Virol.* 78, 7833–7838 (2004).
12. Chen, Y. et al. Biochemical and structural insights into the mechanisms of SARS coronavirus RNA ribose 2'-O-methylation by Nsp16/Nsp10 protein complex. *PLoS Pathog.* **7**, e1002294 (2011).
13. Chen, Y. et al. Functional screen reveals SARS coronavirus nonstructural protein Nsp14 as a novel cap N7 methyltransferase. *Proc. Natl Acad. Sci. USA* 106, 3484–3489 (2009).
14. Takeuchi, O. & Akira, S. Pattern recognition receptors and inflammation. *Cell* 140, 805–820 (2010).

15. Krieg, A. M. AIMing 2 defend against intracellular pathogens. *Nat. Immunol.* 11, 367–369 (2010).
16. Sun, L., Wu, J., Du, F., Chen, X. & Chen, Z. J. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. *Science* 339, 786–791 (2013).
17. Yoneyama, M. et al. The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. *Nat. Immunol.* **5**, 730–737 (2004).
18. Geijtenbeek, T. B. & Gringhuis, S. I. Signalling through C-type lectin receptors: shaping immune responses. *Nat. Rev. Immunol.* 9, 465–479 (2009).
19. Iwasaki, A. & Medzhitov, R. Control of adaptive immunity by the innate immune system. *Nat. Immunol.* 16, 343–353 (2015).
20. Li, K. et al. IFITM proteins restrict viral membrane hemifusion. *PLoS Pathog.* **9**, e1003124 (2013).
21. 21.Thiel, V. et al. Mechanisms and enzymes involved in SARS coronavirus genome expression. *J. Gen. Virol.* 84, 2305–2315 (2003).
22. Spence, J. S. et al. IFITM3 directly engages and shuttles incoming virus particles to lysosomes. *Nat. Chem. Biol.* 15, 259–268 (2019).
23. Andersen, K. G., Rambaut, A., Lipkin, W. I., Holmes, E. C. & Garry, R. F. The proximal origin of SARS-CoV-2. *Nat. Med.* 26, 450–452 (2020).
24. Fajgenbaum, D. C. & June, C. H. Cytokine storm. *N. Engl. J. Med.* 383, 2255–2273 (2020).