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Immune Responses to Infectious Diseases

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ABSTRACT

The immune system is crucial to ensure the survival of vertebrate hosts in a microenvironment surrounded with potentially harmful microbes. Nonetheless, in order to interact successfully with their hosts, infectious disease agents have evolved several mechanisms under strict selective pressure to adapt to the immune system. In this sense, the knowledge of how immune system works as well as the specific strategies used by the pathogens to overcome the immunological responses elicited against the host immunological responses is crucial to better understand disease pathogenesis.

Keywords: Infectious Diseases; Innate Immunity, Adaptative Immunity, Immunoevasion.

INTRODUCTION

The development of an infectious disease in the vertebrates involves complex interactions between the pathogen and the host. The key events during infection include the entry of the infectious agent, invasion and colonization of tissues. Overall the control of infectious pathogens requires different specialized immune responses, depending on the host tissue they replicate and its size. During the development of host protective immunity, the innate and adaptive immune systems cooperate in order to efficiently eliminate the infectious agent [1].

The first line of defense of our body against infectious agents consists of mechanisms that exist before infection, which are capable of rapid responses to microbes and reacting in essentially the same way to repeated infections. This line of defense is made by physical and chemical barriers, such as epithelia and antimicrobial substances produced in the epithelial surfaces [2]. In addition to these barriers, the body has other mechanisms which hinder the entry of the infectious agent, and proliferation within the tissues, such as the production of various antimicrobial agents, acid stomach pH and presence of commensal microbiota [3].

Inside the host tissues, the innate response will continuously fight against the pathogen through the action of phagocytic cells and natural killer cells, blood proteins including members of the complement system and other mediators of inflammation, and proteins called cytokines that regulate and coordinate many of the activities of innate immunity cells [4]. The innate line of defense of the body serves as an efficient barrier for most microorganisms. When they can transpose it, the infection occurs [3].

Extracellular pathogens are spread by the blood and lymphatic systems, and intracellular pathogens multiply by cell-cell interaction, or by direct transmission from a cell to another or for the release of extracellular fluid [5]. Extracellular bacteria are normally susceptible to phagocytosis and some of them develop resistance. This is the case of encapsulated gram-positive bacteria growing in the extracellular space and resistant to phagocytosis by the presence of a polysaccharide capsule [6].

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The extracellular infectious agents are able to replicate outside the host cell, they can replicate in the circulation, into the lumen of the respiratory and intestinal tract as well as in epithelia surface. Some initial barriers are important to limit the pathogen infection, contributing to expulsion pathogens. Among these barriers stand out peristalsis, the mucus secretion gastrointestinal tract, the ciliary movement of the roads air, and a healthy epithelium which acts as a physical barrier between the pathogen and the tissue host [2]. In the case of bacteria that inhabit the system circulatory, the phagocytosis is the main mechanism of innate immunity used to eliminate these infectious pathogens [5].

The most important phagocytic cells are large cells represented by macrophages, neutrophils

and dendritic cells [5]. These cells engulf harmful microorganisms during which recognize pathogen-associated molecular patterns (PAMPs) through its pattern recognition receptors (PRRs) [7]. Once internalized by phagocytosis, the new formed vesicles gives rise the phagosome, which in turn merges into the lysosome originating the phagolysosome [8]. During the maturation of these terminal vesicles, the elimination of infectious agents occurs by the action of enzymes and reactive oxygen intermediates and nitrogen present [9]. While microbicidal mechanisms are constitutively present in phagocytes, these responses can be increased upon activation when the cells are exposed to type II interferon cytokines (IFN-γ), secreted by activated T lymphocytes [10].

The impairment of the phagocytosis is associated with susceptibility to infection in several diseases [11]. The chronic granulomatous disease, for instance, is an inherited disease characterized by an inability of phagocytes to produce hydrogen peroxide and other oxidants needed to eliminate certain infectious agents, a process known as respiratory burst of the ingested pathogens [12]. As a result of this defect, patients become more susceptible to infections caused by bacteria such as *Staphylococcus aureus, Pseudomonas cepacia, Serratia marcescens, Burkholderia cepacia, Escherichia coli, Klebsiella pneumonia, Listeria species and Aspergillus* fungus [13,14]. This disease is also associated with an excessive accumulation of granulomas due to the deficient phagocytosis at the sites of infection, facilitating the growth and spread of the pathogen [14].

However the phagocytic activity is strictly dependent on the size of the pathogens [15]. This is well demonstrated with respect to the host defense against helminths, in which phagocytosis by macrophages or neutrophils are prevented by the parasite size. This restriction demands a different strategy of the innate immune system in an attempt to eliminate the pathogen, in which phagocytes release the contents of their granules abroad by exocytosis [16]. Nonetheless, this is an inefficient mechanism since helminths are resistant to the harmful action of the components present in the granules [17].

The extracellular pathogens are able to activate B lymphocytes to produce specific antibodies which can neutralize the infective agent or its products such as toxins. The humoral immunity induced during the course of adaptive immune responses is the principal mechanism for eliminating extracellular pathogens, as well as for neutralizing their secreted toxins in the organism [5]. The antibody-mediated pathogen recognition promotes the activation of the complement pathway.

The complement system is part of an effective immunity in response to extracellular pathogens [18]. This system can be activated, for instance, by the classical antibody-mediated pathway by several microorganisms, and also pathogens that have mannose in their surface, will trigger this activation via the lectin pathway [19]. The downstream activation of the complement system is responsible to promote innate effector mechanisms characterized by phagocytosis, lysis cell and amplification of the inflammatory process [20].

The antibodies also acts in eliminating large size pathogens such as helminths through a mechanism called cellular cytotoxicity mediated by antibodies known as antibody-dependent cell-

mediated cytotoxicity (ADCC) [21-23]. Chronic helminth are target by specific Th2 cell responses that secrete IL-4 type cytokines which are critical in helping B cell production of IgE and IgA isotype antibodies. These antibody isotypes once recognizing helminthic antigen portions binds though their Fc constant regions to mast cells (IgE) and eosinophil (IgA), promoting activation of these cells and consequent release the content of their granules during the humoral-mediated immunity [24,25].

In the absence of humoral response mediated by B cell lymphocyte, infections with extracellular pathogens can induce host susceptibility. This is the case of the X-linked agammaglobulinemia which is a disease caused by a failure in the precursors of B lymphocytes and their downstream lineage committed differentiated B lymphocytes and plasma cells [26]. Patients with this anomaly tend to develop many infections due to lack of antibodies, showing for instances recurrent bacteria infections with *Haemophilus influenza, Streptococcus pneumoniae, staphylococci* and gastrointestinal infections caused by the parasite *Giardia lamblia* [26,27].

As a collateral effect of the host immunity responses against certain pathogen infections, the humoral immune response may result in cross-reactions against the host autoantigens [28]. This is the case of rheumatic fever, in which antibodies are produced against the M protein of Streptococcus beta-hemolytic and are able to cross-recognize proteins derived from the heart tissues leading to carditis [29-31]. Another deleterious effect of the humoral immune response in chronic persistent infections that induce strong humoral responses is the formation of immune complexes, which may be deposited in the glomeruli, vessels and joints resulting in a range of immune-mediated disorders causing inflammatory damage in these tissues characteristics of auto-immune diseases [28].

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The immune response to intracellular pathogens encompasses a range of effector mechanisms derived from cellular and humoral activities of the host against the invading microorganism. In order to prosper and continuous their lifecycles, the intracellular pathogens must invade the host cells. However, this event triggers several alarms able to recognize not only the microbial components but also the host-derived damage-associated molecular patterns (DAMPs) released from infected tissues [32,33].

Among these signal alarms, are the innate receptors represented by the membrane-associated toll-like receptors (TLR) and the cytosolic nucleotide binding and oligomerization domain (nod) like receptors (NLRs) which are determinant to the inflammatory responses against the pathogens and the outcome of infection [34,35]. The NLRs are part of an intracellular network mechanism that induces the assembly of multiprotein complexes called inflammasomes [36,37]. These receptors once able to sense the microbe components lead to production of proinflammatory cytokines such as interleukin-1 and the induction of inflammatory cell death through the activation of caspase-1 [38,39].

Although the signaling pathways mediated by the innate activate phagocytes and professional antigen processing cells during development of protective immunity, some pathogens such as intracellular bacteria possess the ability to resist phagocytosis and replicate inside the phagocytes, stimulating the production of IL-12. This cytokine activates NK cells to induce the secretion of IFN-γ which in turns increase the synthesis of microbicidal substances inside the phagocytes [40]. The NK cells are also able to directly identify virus-infected cells that have reduced expression of MHC-I molecules. This cellular recognition promotes the destruction of infected cells through the release of cytolytic factors such as perforin and granzyme which are able to target cell apoptosis for clearance of the infectious pathogens [41,42].

The critical role of NK cells in the immunity against virus infection is well demonstrated in patients with deficiency in NK cell activity [43]. These patients display observed recurrent viral infections that are regularly controlled by normal individuals that have NK cell response [44]. Among the recurrent virus in patients with deficiency in NK cell activity are Cytomegalovirus, Herpes Simplex Virus, Papilloma Virus, Varicella Zoster Virus and Epstein Barr Virus [45]. This phenomenon exemplifies the utmost importance of NK cell response in combating virus-infected cells.

Other mechanisms underlying the protective-mediated responses against virus infection depends on the role of type I interferon. During viral infections, this cytokine is produced by the infected cells and its subsequent binding to their specific receptors expressed in uninfected cells surrounding the infection site in certain tissue is able to promote the synthesis of viral proteins that inhibit the viral protein synthesis and activates the degradation of the viral mRNA thus eliminating the virus [46].

Although the cross-talk between the NK cells and phagocytes in the innate system mediates the control of intracellular microorganisms, several pathogens are capable of replicating inside phagocytes. Among these agents are the pathogens represented by the facultative intracellular bacteria such as *Mycobacterium tuberculosis* and *Legionella pneumophila*; and the protozoan parasites such as *Toxoplasma gondii, Trypanosoma cruzi* and *Leishmania* [47-52]. However the phagocytes infected with these pathogens can be destroyed by CD4+ T cells, a major player of the adaptive immune system [53].

The involvement of CD4+ T cells in the protective responses against intracellular pathogens hosted by phagocytes is due to nature of the cellular compartments in which the infectious agents are located. Pathogens present within the vesicular compartment of the cell are able to enter the route of antigen processing and presentation via the MHC class II molecule [54]. The MHC class II-peptide complexes can be recognized by CD4 T cells that once activated can produce IFN-γ. This cytokine increase the microbicidal activity inside the phagocytes [55,56]. However some infectious agents are able to subvert this response thus remaining alive within the phagocytes, leading the formation of granulomas [57]. This structure are mainly constituted by macrophages and T lymphocytes present in the infection site, and works as a tissue barrier to prevent the

spread of the pathogen, but often may result in an intense inflammatory process leading to tissue fibrosis [58].

The pathogens that have the ability to replicate in the cytoplasm of the infected cell such as the viruses, or even infectious agents that escape the phagosome or alternatively prevent the generation of phagolysosomes such as the *Trypanosoma cruzi* and *Listeria monocytogenes* can be eliminated by cytotoxic CD8+ T cells (CTL) [59,60]. Since these pathogens are present in the cytosol, they can be loaded to the processing pathway and presentation via MHC-I molecule. The MHC class I-peptide complexes can be recognized by CD8+ T lymphocytes that once activated produce perforin and granzyme molecules which mediates cellular killing to destroy infected target cells [54].

THE EVASION MECHANISMS OF INFECTIOUS AGENTS

The infectious agents have developed various mechanisms to evade the host immune response (Table 1). Antigenic variation is a common strategy adopted by bacteria, viruses and parasites, and is characterized by genetic mutations that can modify the antigen epitopes that are recognized by T cell receptors and antibodies that ultimately are effective in generating a sterile immune response thereby eliminating the infectious agent from the host. Other avoidance schemes adopted by pathogens are exemplified in protozoan-host interactions [61,62]. The protozoa are the most ancient members of the animal kingdom and they have evolved the intracellular parasitism to ensure the immune evasion strategies for their survival strategies.

Table 1: Immune Evasion Mechanisms by Pathogens.

Immune defense strategie	Immune evasion mechanisms	Pathogen example	References
Recognition of exposed surface molecules	- Mimic of host immune ligands and receptors - Expression of protective surface molecules - Camouflage of the pathogen surface or the infected cell	Virus (e.g. enveloped viruses) Bacteria (e.g. capsule)	(62,80,81)
Innate Immunity – Complement system	- Induction of complement inhibitors	Virus, bacteria, protozoa, fungi	(63,79,82-84)
Innate Immunity – Toll-Like receptors (TLRs)	- Inhibition or change of TLR recognition - TLR suppression	Virus, bacteria, protozoa	(61,85,86)
Phagocytosis	- Impairment of phagocytosis mechanisms - Phagocytes subversion	Virus, bacteria, protozoa, fungi	(62,63,79,84,87)
Cytokines	- Inhibition of ligands/receptors signaling pathway	Virus, bacteria, protozoa, fungi	(61,62,84)
Humoral and cellular responses	- Antigenic variation	Virus, bacteria, protozoa, fungi	(62,88)
Acquired immunity	- Interference with the loading of MHC I and II antigens - Downregulation of MHC I and II - Blockage of antigen presentation	Virus, bacteria, protozoa	(61,62,66,87,89)
T cell responses	- Polarization towards Th2 responses - Induction of T cells with regulatory phenotype	Bacteria, protozoa, helminths	(62,66,79,87,89,90)

Protozoan parasites that infect humans are extremely diverse among eukaryotes with different intermediate vectors of transmission and are responsible for many human diseases such as malaria, Chagas disease amebiasis, toxoplasmosis, leishmaniasis and African sleeping sickness. The virulence of protozoans and its relationship with disease pathology depends on the nature of the transmission vectors and pathogens, number of infecting organisms, the route of infection, the virulence factors associated with the microorganism, and the host defenses. The host-parasite interplay is subject to a constant change due to the strength of the host defenses as the infection proceeds and can lead from sterile elimination of the pathogen to death of the host in the case the pathogen are able to overcome the immune system. These different outcomes of the infection depend on the states of latency and the balance between the parasite colonization and the immune responses achieved along the infection [63].

The specialized virulence factors harbor by different species of parasitic protozoa are able to overcome the host´s immunity in order to promote the parasite survival. These virulence factors act at several different levels of the host immune responses, since the first components of the innate immune response to the ultimate level of the adaptive immunity including the induction and maintenance of adaptive memory responses [64]. Different studies have consistently show that several different protozoan species have acquired subversion strategies of colonization during their evolution with the vertebrate hosts [63].

Among the successful strategies evolved by the protozoan parasites critical for the parasite-host interplay are the modulation and inhibition of the innate host sensors such as pattern recognition receptors (PRRs), thus interfering with the ability of dendritic cells to promote the activation and differentiation of T lymphocyte cell. The protozoan have also evolved strategies to inhibit the complement cascade, phagocyte activation and leukocyte migratory responses [61]. Moreover, it has been in recent studies that the protozoan parasites are able to modulate the regulatory microRNA circuits damping the inflammatory signaling pathways that permit the host to sense and resolve the infection, similar to viruses [65]. These virulence factors are responsible for undermining the immune system thus facilitating the pathogen evasion and its continued persistence in the host leading to a chronic phase of the infectious diseases.

One of the successful adaptation of the protozoa to the humoral response is exemplified by the antigenic variation in African Trypanosomes that cause sleeping sickness in humans [66]. These species of parasites are able to change the antigenic make-up of their variable surface glicoproteins (VSG) therefore escaping for the fixation of antibodies and complement attack from the host [67,68]. The African Trypanosomes or *T. brucei sp.* encodes more than 100 antigenetically different VSGs from about 1000 VSG genes. At a given time a single parasite expresses only one copy of these multiple repertoire genes [69]. However the *T. brucei* parasites switch the VSGs spontaneously during the division so they are able to evade the deadly humoral immune responses promoted by the antibody recognition of the VSG antigens thus causing a chronic infection [70].

Malaria is another infectious disease in which the parasite subversion of host immune response takes a place. The human disease is annually associated with 300 million to 500 million clinical cases worldwide. This statistics yields about 0.5 million to 3 million deaths, mostly among children under the age of 5 years living in sub-Saharan Africa. Human malaria is caused by four species of parasitic protozoa of the genus *Plasmodium: Plasmodium falciparum, P. vivax, P. malariae and P. ovale* [71]. Interestingly, coinfection of more than one species of human malaria parasites is a present in most areas where malaria is endemic, generating multiple arrangement of interspecies interactions [72,73]. The vast diversity of malarial surface antigens is thought to restrict the acquisition protective immunity against the infection. This feature is considered one of main reasons why clinical immunity develops only after repeated infections with the same species [74].

The antigenic diversity in malaria has also a main focus on the parasite cellular level in terms of the repertoire of encoded genes. This feature is created in part by the allelic polymorphism generated by a classical genetic mechanism of nucleotide replacement and recombination. This phenomenon creates genetically stable alternative forms of antigen-coding genes [75]. This antigenic variation can be further elevated in terms of complexity considering that the clonal lineage of parasites can expresses successively alternate forms of an antigen without changes in genotype. This antigenic variation is thought to have a major implications for naturally acquired immunity natural parasite populations [75].

Different immune evasion strategies are utilized by the apicomplexan parasite Toxoplasma gondii to establish the infection and guarantee its dissemination in the host. This obligate intracellular protozoan sequesters cellular functions of the immune system by hijacking of migratory leucocytes to successful modulate the migratory properties of infected cells. Once complete its lifecycle, the parasite rapidly transfer between different leucocyte populations by cytotoxicity-induced egress of the host cells to guarantee its persistence in the host [76]. Other protozoans such as Trypanosoma cruzi parasites also use a different strategy to guarantee a rapid colonization of the host. These parasite species modulate the antigen presenting function of dendritic cells via an action on host sialic acid-binding Ig-like lectin receptors [77]. The activation of these receptors also induce suppression of CD4+ T cells responses, and it is suggested that the sialylation of parasite-derived mucins is required for these inhibitory effects on CD4 T cells [78].

Protozoan parasites also explore multiple adaptations to persist in host cells by evading the host immune system. The obligate intracellular parasite *Leishmania* survive the antimicrobial activities inside their reservoir, the macrophage, where they multiply thus preventing the activation of an effective immune response. This successful strategy is reached by parasite-induced modification of host cell signaling pathways, antigen presentation, nitric oxide and oxygen radical generation, and modulation of cytokine and chemokine production in favor of the parasitism [79]. These different subversion strategies of pathogen escape from the immune system enable us to

understand the molecular basis of chronic persistent infections thus offering promising areas for preclinical and clinical research.

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