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Host-Microbial Relationship: Immune Response to Microbial Infections with or without Medication

Faustina Pappoe and Samuel Victor Nuvor

Abstract

Immune responses of the host to any infectious agents vary in controlling the pathogens. The process begins by the entry of microorganisms into the host to initiate host immune response to understand the type of microorganisms and react accordingly for possible elimination of the organisms. In some cases the host co-exists with the pathogens or unable to effectively deal with them leading to disease condition. Thus, the pathogens establish, multiply and cause disease. The review considered the mode of acquisition of infection, pathogenesis and immune responses to microbial infection. Other areas included the enhancement of immune responses to control infection, immune responses of the host under drug treatment and the control of microbial infection. The understanding of the relationship between infectious microbes and the host immune system leading to protective immunity or disease state will give much information about treatment and controlling of microbial infection in our environment.

Keywords: immune response, host-microbial, pathogens, infectious agents, drug treatment

1. Introduction

Several human diseases are caused by pathogenic microorganisms which are diverse and are divided into four major groups namely bacteria, viruses, parasites and fungi [1]. Thus, different pathogens cause varied diseases. Members in each group were classified into subgroups based on unique characteristics they possess [2]. Bacteria were differentiated based on their staining properties due to variation in the cell wall components and those without cell wall, hence there are gram-positive, gram-negative, acid-fast and cell wall defective bacteria. These were subdivided by their shape (spherical and rod-shaped bacteria), growth requirement (e.g. aerobic and anaerobic) among others [3]. Viruses have DNA and RNA with each kind having either single-stranded or double-stranded nucleic acid. These were further classified by the presence or absence of an outer envelope, shape, size and other characteristics [3, 4]. The parasites included protozoa, helminths and arthropods. Unlike helminths and arthropods, which were multicellular, the protozoans were unicellular and conveniently classified by their mode of locomotion.

The protozoans included amoebas, ciliates, flagellates and apicomplexans. The helminths were classified according to their shape: nematodes (roundworms) and platyhelminths (flatworms and tapeworms). The arthropods were also considered as vectors of pathogens mainly viruses and bacteria [3, 4]. Finally, the fungi were made up of unicellular forms (*Saccharomyces cerevisiae*) and multicellular forms (molds). The molds were subdivided into hyphae and conidia forms [3].

Generally, pathogenic microorganisms are either primary/true pathogens or opportunistic pathogens. The primary pathogens were those capable of causing diseases in the host irrespective of the host's immune system. Thus, they cause diseases in immunocompetent and immunocompromised individuals and persons with slight imbalances of the immune system. However, the opportunistic pathogens mostly included the normal flora and only cause diseases in immunocompromised individuals as well as when they occur in parts of the body that were not natural to them [5]. When infection occurs, there is interaction between the host immune system and the pathogens. The outcome involved either immune control towards the infection or disease development with pathological manifestations due to the inability of the host immune responses to effectively deal with the pathogens [5, 6]. Understanding the immune responses to microbial infections with or without medication is necessary in the management, control and prevention of infectious diseases. This chapter focuses on the mode of acquiring infections, pathogenesis and immune responses to microbial infection, enhancement of immune responses to control infection, immune responses of the host under drug treatment and preventing microbial infection.

2. Modes of transmission of infectious diseases

Infection is the multiplication of pathogens in or on the body of the infected host whereas disease is the impairment in the normal function of the host because of damage to the host's cells by the infection [7, 8]. Thus, for infection or disease to occur, the pathogens must attach to or enter the body of the host, multiply, evade the immune responses, cause damage to the host cells and spread to new hosts. In some individuals, the disease is symptomatic while in others, it is asymptomatic. The time interval between infection and appearance of the first clinical sign or symptoms of disease was known as incubation period and this was the time the infection can be spread without the person knowledge [7]. The incubation period is influenced by several factors such as dose of a pathogen, route of inoculation, rate of replication of infectious agent, host susceptibility and immune responses. Hence, incubation period varies among diseases. For instance, non-typhoidal *Salmonella typhi* has incubation period of 10 to 14 days, that of *Bordetella pertussis* is 7 to 10 days, among others [4, 9]. The incubation period is followed by prodromal period whereby microbial agents continuously multiply and the host begins to experience general signs and symptoms of illness which are mostly general to be associated with a particular disease. The signs and symptoms were due to activation of the immune system [5]. After the occurrence of the prodromal period is the period of illness during which individual feels extremely sick and can easily spread the infections followed by the period of decline. The declining period is associated with the controlling of the replication of the pathogens resulting in lessening of the signs and symptoms of the disease. Thus, individuals feel better at this state. This period is followed by the period of convalescence where microbial replication stops, and the person fully recovers from the disease. However, in some cases, individuals who have recovered fully can still spread the infection in the environment [5]. What it means is that the immune responses are strong against the pathogens

to prevent development of clinical manifestations but are unable to destroy the pathogens in the body so the person harbors and spread the infection in the environment. Those individuals are called carriers. A typical example is a person with typhoid fever. The pathogen was continuously shed in the feces to the external environment hence the infection could be acquired through ingestion of fecally contaminated food or drinks [10, 11]. Human immunodeficiency virus (HIV) and hepatitis B and C carriers could spread the infection through blood products and body fluids [12, 13]. Another example was a tuberculosis infected person with mild clinical presentations, but persistent cough could spread the infection through air before the disease was diagnosed [14]. Vertical transmission through transplacental infection was also possible (e.g. *Toxoplasma*, *rubella*, *cytomegalovirus*, *Herpes simplex*, and other organisms including *Treponema pallidum*, HIV, *parvovirus*) [15]. There were other infectious diseases such as anthrax, balantidiasis, toxoplasmosis, taeniasis and rabies that were zoonotic and could be acquired from animals [16, 17]. Insect vectors such as female Anopheles, ticks and sandflies could also help spread the infections including malaria, babesiosis, rickettsiosis and leishmaniasis respectively [18–21]. In summary, infectious diseases can be acquired in several ways including horizontal means such as touching contaminated surfaces, direct skin contact, body fluids, airborne, vector borne, and ingesting raw/undercooked meat. Other mode of transmission includes fecally contaminated food and water and vertical transmission among adult and children.

3. Pathogenicity of microbial infection

The ability of a microbe to cause disease is known as pathogenicity and the degree or extend of the pathogenicity is termed virulence. Virulence varied from mild to severe with varying virulent factors that directly or indirectly play a role in pathogenicity and virulence [22]. Hence, some pathogenic microbes are avirulent causing diseases only occasionally, moderately virulent that cause mild diseases while others are highly virulent causing diseases with severe clinical presentations. For a microbe to cause a disease, the pathogens must attach to and/or enter the host body with the help of virulent factors and colonize [23–25]. The main attachment and entry sites for microorganisms include the skin, conjunctiva, alimentary, respiratory and urinogenital tracts. Some microbes attached to and sometimes penetrate the host body surfaces such as the skin and cells (nucleated and non-nucleated) using adhesins (proteins) located on the surface of the pathogen [26]. The adhesins bind to specific host receptors, which could be transmembrane glycoproteins or extracellular matrix proteins. Others entered directly through open surfaces like skin wounds, through inhalation, a vector such as bites from infected arthropods, mammals like dogs involved in rabies cases and piercing by contaminated devices such as needles [25, 27–30]. The conjunctiva is mostly infected by the fingers, face towels, flies that settle there among others. *Chlamydia trachomatis* and *Neisseria gonorrhoea* were sexually transmitted pathogens that commonly cause conjunctivitis in neonates [31] who acquire the infection from infected cervix during normal birth. Not much about the pathogenesis of *C. trachomatis* is known. However, *C. trachomatis* is an intracellular pathogen and inhibits phagosome and lysosome fusion when it is phagocytosed thereby evading host immune defenses [32]. Mucosal surfaces of the respiratory tracts have immune mechanisms and cells that prevent pathogen attachment and colonization. Hence, some invading pathogens such as *Streptococcus pneumoniae* could attach to epithelial cells only when the mucociliary and other immune mechanisms were defective [33]. However, some pathogens have strong attachment structures. For instance, *Bordetella pertussis* has fimbriae and produces

a kind of protein called filamentous haemagglutinin A (FHA) which enable the pathogen to attach to the epithelial cells of the bronchia and the lungs [34] thereby disrupting the ciliary activity leading to their multiplication, colonization and host tissue damage. *Mycobacteria tuberculosis* is phagocytosed by alveolar macrophages in which most die. However, some survive and continue to replicate until the macrophages die leading to their release, where some reinfect other cells and some enter the blood and lymph circulations; carried to other parts of the body [35]. The pathogens of the gastrointestinal tract cannot be overlooked. *Helicobacter pylori* is an important intestinal pathogen that was associated with chronic gastritis, peptic ulcer and gastric cancers [36]. It possesses flagella and adhesins for attachment to the gastric mucosa. It produces several vital enzymes most notably urease which enable the pathogen to survive in the gastric environment for colonization. Urease acts on urea and degrades it to form ammonia and carbon dioxide. Ammonia neutralizes the acid in the stomach making the environment favorable for its survival. Moreover, *H. pylori* produces toxins such as vacuolating cytotoxin, and cytotoxin-associated gene encoded by the *vacA* and *cagA* genes respectively [37]. These toxins/proteins induce intense inflammatory responses leading to damage to the host tissues. The immune response is unable to eliminate this pathogen hence the use of antibiotics for their eradication. Another example is *Enterohemorrhagic Escherichia coli* (EHEC) serotype O157:H7, which is a true human pathogen and causes bloody diarrhea, hemorrhagic colitis (HC) and life-threatening complication such as the hemolytic-uremic syndrome (HUS). This pathogen is resistant to destruction by the gastric acid and so passes the acidic barrier and get to the recto-anal junction (RAJ) where it attaches tightly and forms attaching and effacing (A/E) lesions on the RAJ mucosal epithelium for colonization [38]. It produces Shiga-like toxins which when enters the circulation leads to HUS. Additionally, *Giardia lamblia*, noninvasive parasite possess sucking disc for attaching tightly to the epithelium surface of the small intestine leading to inflammatory responses as well as malabsorption due to destruction of the villi. The attachment is also aided by lectins, which are found on its surfaces and the flagella aid in motility [4].

Regarding the urinogenital tract, it is mostly sterile as a result of frequent flushing by urine, hence most invaded pathogens are flushed out and do not get access into the system. However, certain pathogens like *Neisseria gonorrhea* when invaded were able to colonize the tract [39]. This results in the infection of mainly the cervix, urethra, and rectum. The mouth, nasopharynx and the eye may also be affected. The virulent factors included pili, which enable it to attach firmly to the epithelial cells of urogenital sites, OPA proteins (adhesives) and IgA proteases [4]. It worth noting that women frequently get urinary tract infection than men because of the difference in the anatomical structure. Thus, men have longer urethra than females.

4. Microbial infections and the corresponding immune response towards their elimination

Infection of the host by the pathogens responses in the host with initial reaction of the innate immune response followed by the adaptive immune responses. Infection involving bacteria is associated with various mechanisms to evade or survive the host immune response. Some of the bacteria form capsules, complex structures which present many diverse antigenic targets to the host body surface [40, 41]. The capsules are effective at hiding many bacterial surfaces and preventing opsonization to enable them circulate systemically within the body. Some of these bacteria involved in capsule formation included *Streptococcus pneumonia*,

Haemophilus influenzae, *Escherichia coli*, and *Neisseria meningitides* which rely extensively on its capsule to prevent antibody and complement deposition on its surface [42] thereby avoiding opsonization and phagocytic clearance.

Viruses also evolve a number of techniques for evading the immune responses by avoiding complement system through rearrangement of epitopes in their surface proteins. The measles virus prevent antibodies binding to haemagglutinin to initiate complement by the classical pathway [43] presumably because the antigenic epitopes were so spaced that effective bridging cannot be obtained between them. Human Immunodeficiency Viruses were able to bind to cells through complement receptors after fixing complement and also Dengue virus which could enter cells through Fc receptors after having bound antibody [44]. Other organisms such as *Herpes virus saimiri*, *Trypanosoma cruzi* and *Schistosoma mansoni* [45], captured complement control proteins to change their function [46]. However, the immune response to microbial pathogens relies on both innate and adaptive components and they work together to eliminate the pathogens. Macrophages and dendritic cells were found in all body tissues, serving as sentinels in wait for pathogens and respond to variety of chemotactic agents that were shed as a result of infection [47]. The cells bind the pathogens via phagocytic receptors that initiated the cytoskeletal rearrangements and membrane trafficking for phagocytosis [48, 49]. Other innate cells like neutrophils, basophils, eosinophils and NK cells contributed together in clearing of the pathogens through phagocytosis, cytotoxicity, and the release of cytokines to enhance their activities in eliminating the pathogens [50]. The adaptive immune cells are made up of B and T lymphocytes, including $\gamma\delta$ T cells, T reg cells and Th17 cells. Microbial antigens are taken up by antigen-presenting cells in the peripheral tissues and delivered to the lymph nodes or spleen through the lymph or blood, respectively. They are therefore recognized by these adaptive cells and differentiate specifically into several types of effector cells, depending on the class of pathogens they recognized. The differentiation of lymphocytes into a particular effector-cell type and their localization to the site of infection were regulated by the innate immune system, generally in the form of cytokines and chemokines [51]. The effector cells therefore exhibit their function through cytotoxicity as well as the release of cytokines which together aid in destroying the pathogens.

5. Enhancement of immune response to control infection

Antigenic features of microbes known as pathogen-associated molecular patterns (PAMPs) are recognized by Pattern Recognition Receptors (PRRs). These involve Toll-like receptors (TLRs), NOD-like receptors (NLRs), AIM2-like receptors (ALRs) and RIG-I-like receptors (RLRs) and stimulation with ligands promptly potentiated the production of proinflammatory cytokines and chemokines [52] which facilitated the clearing of bacterial infections. There was significant reduction in the number of *Haemophilus influenzae* and *Moraxella catarrhalis* bacteria recovered from the nasopharynx through intranasal inoculation of monophosphoryl lipid A in mice [53]. The use of PRR ligands for *Staphylococcus aureus* adjuvants vaccine formulated with a TLR7 agonist and adsorbed onto alum adjuvant (4CT7-Staph) conferred about 80–90% protection against four different *Staphylococcal* strains [54]. NOD-like receptors were also important for clearing a variety of bacterial infections, including *Salmonella Typhimurium*, *S. flexneri*, *Pseudomonas aeruginosa*, and *B. pseudomallei* [55]. Most often, *B. pseudomallei* induces NLRC4-dependent pyroptosis which restricts intracellular bacterial growth. However, the activation of NLRP3, upregulates IL-1 β , promoted the replication of *B. pseudomallei* and recruited excessive neutrophils to the lung leading to tissue damage [56].

Identifying small molecules that selectively activate NLRP3 inflammasome and prevent cytokine secretion may also be promising new therapeutic strategy.

Most bacterial killing are enhanced by autophagy activity in response to cellular stresses, including hypoxia, energy loss, and nutrient deprivation. This process provided a mechanism for the adaptation to starvation and regulated cellular metabolism and homeostasis [57], therefore play a major role in homeostatic maintenance. The use of autophagy as innate immune mechanism for the clearance of intracellular pathogens [58] enhances the efficient immune responses in dealing with pathogens. Alternatively, bacterial clearance could also occur through LC3-associated phagocytosis (LAP), which was mediated through single-membrane phagocytic vesicles that contain engulfed pathogenic bacteria including *Escherichia coli*, *S. Typhimurium*, *Mycobacterium marinum*, and *B. pseudomallei* [59]. These were transiently coated with LC3-II and sirolimus, an mTOR inhibitor, that increased the colocalization of the bacteria with LC3 in phagosomes, thereby augmenting phagosomal maturation and further phagocytosis [60]. Also treatment of macrophages with AMG548, a p38 inhibitor, promoted the clearance of *M. tuberculosis* by inducing autophagy [61]. The host response to hypoxic conditions created by bacterial infections regulated by hypoxia-inducible factor (HIF) which [62] drove the expression of proinflammatory cytokines that mediated macrophage aggregation, invasion, and motility thereby enhancing the intracellular killing of the bacteria during replication [63, 64].

Again, macrophages and neutrophils produced reactive oxygen species (ROS) and reactive nitrogen species (RNS) molecules that acted as a defense mechanism to trigger the clearance of the phagocytosed microorganisms [65]. However, an imbalance in the production and elimination of ROS is associated with human diseases.

6. Drug treatment regime in microbial infection and the interaction with immune response

The treatment of any infections targets the clearing of the pathogens involved and allows the immune system to develop and fully functions. Therapeutic strategies for the treatment of microbial infections have mainly relied on the antibiotics that target pathogenic proteins, DNA, RNA, or cell wall synthesis. In some cases, not all the pathogens are cleared and some may resist clearance. In Tuberculosis (TB) infection, effective drugs have been available for decades, but the disease remained a major infectious disease at global level [66, 67]. This might be due to the emergence of *Mycobacterium tuberculosis* (Mtb) strains showing resistance to some of the most commonly used effective drugs: isoniazid and rifampicin [67]. These multi-drug resistant Mtb strains (MDR-TB) were responsible for 0.49 million cases of tuberculosis, mostly in India, China and the Russian Federation [67]. The interaction between Mtb infection in an immunocompetent host led to latent TB infection, with no signs or symptoms of active disease [68]. This involves the critical role of host innate and adaptive immune responses in the control of Mtb infection. The intrinsic ability of host responses to contain Mtb replication while preventing the development of the typical tissue damage, formed the hallmark of active TB [69]. There was therefore the persistence and a certain degree of replication of Mtb in host tissues in a dynamic equilibrium with the host, which in most cases lasted for lifetime [70, 71]. However, the immune responses that involve phenotype of immune cells with their chemokines and cytokines secretions responsible for the consequences at local level remains to be determined. Eventually, the critical role of the host immune response in the control of Mtb replication, or emergence of active disease instead depend on many factors and

may be assisted by drug therapy or microbial modulation of the immune system. For humans, these interactions could be infection with pathogenic microbes or vaccination [72]. Vaccination with *Bacillus Calmette-Gue'rin* (BCG), an attenuated strain of *Mycobacterium bovis*, protected against tuberculosis (TB), but its effects on the immune system extended far beyond specific protection against TB [73]. BCG vaccination has been shown to afford nonspecific protection against infection by a number of pathogens, including *Schistosoma mansoni* and *Listeria monocytogenes* [73]. The appearance of carbapenem-resistant *Enterobacteriaceae* had also affected the therapeutic benefit of the carbapenem class of antibiotics, which were reserved as a last-line defense [52, 74, 75].

Drug-resistant viral strains has also compromised the effectiveness of treatment, or even lead to its failure. Drug-resistant viruses occurred as a result of mutation at high frequencies of the viral RNA or DNA [76]. Their genotypes could be advantageous in hosts where the drug was present and could become the dominant genotypes in such hosts [77]. Influenza virus also developed resistance to oseltamivir drugs through mutations and there might be possible exchange of genetic information between resistant and susceptible viral strains [78]. The therapeutic options against HIV-1 include more than 20 drugs through their action mechanisms. These targeted to four different points of the viral replication cycle such as the entry of the virus into the cell, inverse transcription, the integration of viral genetic material into the cell nucleus, and maturation of virions [79]. This phenomenon has been associated with the high replicative capacity of the virus and the high error rate in the transcription of its genetic material. These might be due to the presence of specific mutations resulting from pharmacological pressure and suboptimal viral suppression under a treatment scheme [80]. Herpes virus infection depended upon viral inhibition of several cell functions including the turning off of host protein synthesis, inhibition of mRNA splicing, blocking presentation of antigenic peptides on the cell surface and apoptosis [81]. Treatment of HSV-infections with nucleoside analogs was very common but the development of drug-resistant virus from immunosuppress patients with prolonged exposure to the antiviral agent has been established [82–84]. Mutations of the herpes viral Thymidine kinase (TK) and DNA polymerase (DNApol) occurred and involved in mechanisms of resistance to acyclovir and penciclovir [85, 86]. The development of point mutations by the pathogens to survive drugs as well as the host immune response involve various factors associated with the infection. In some cases, less aggressive chemotherapeutic regimens substantially reduce the probability of onward transmission of resistance without significant changes in host pathology [87, 88]. In contrast, high dose aggressive treatment in controlling the resistant populations were effective in *Staphylococcus aureus* infection [89, 90]. There are multitude of results that indicate problem of devising general practices for treatment. There could be the development of conceptual frameworks to follow in administering aggressive and moderate chemotherapy [91], but quantitative systematic analyses are also needed. The challenge was to identify among the diverse potential treatment regimens, that minimized selection for drug-resistance while not compromising patient health [92]. This will go a long way to assist in treating majority of infected people without any side effect.

7. Controlling microbial infection: The best way

Currently, the phenomenon of multi-drug resistance due to indiscriminate administration of high-doses of antibiotics has been the bane of controlling microbial infection. The indiscriminate and inappropriate use of drug in treating

infection has also led to significant toxicity in the infected patients, which present other challenges to tackle. The environment plays a major role in facilitating transmission of several important health care-associated pathogens. These included vancomycin-resistant *enterococci* (VRE), *Clostridium difficile*, *Acinetobacter spp.*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *norovirus* [93–95]. These pathogens are frequently shed into the environment to contaminate, water and surfaces of any objects for days and increase the risk of infection of humans. In addition, infection occur through vectors of many pathogens, which spread quickly and affect human population.

Together in the environment, microorganisms form complex communities that play critical roles in either maintaining the well-being of their hosts or destroying the host. In order not to allow their survival to the detriment of the existence of the host, they have to be cleared in both the host and the environment. Therefore, several treatment means have been developed to control microbial infections and these have led to the development of antimicrobial drug resistance pathogens. Addressing this challenge, appropriate use of antimicrobials in human medicine is needed. There should be a means of ensuring timely production and communication of critical diagnostic results and standardized drug susceptibility testing reports in accordance with local treatment guidelines [96, 97]. Also, there should be provision of facility-specific cumulative susceptibility reports for bacterial pathogens against antibiotics, daily counseling to clinicians on etiological infection diagnoses and management, and interpretation of test results. Targeted therapy of difficult-to-treat resistant pathogens and complicated infections are very important guidelines in successful treatment of patients. However, some treatment regimens have been developed to be very useful to avoid the development of microbial resistance. These included the use of nanoparticles to destroy the biofilms and also lessen the doses of antibiotics required in treating patients [98]. The development of a recombinant lysis-deficient *Staphylococcus aureus* phage P954, to kill the target cells but not destroy the host cells would alleviate the concern about the use of bacteriophages for therapeutic purposes [99]. These damping the potential immune response, rapid toxin release by the lytic action of phages, and in dose determination difficulty in clinical situations. Phage therapy was currently practiced routinely and successfully in countries such as Poland and Russia [100] and could be developed rapidly to combat the emergence of antibiotic-resistant pathogenic bacteria [101, 102].

Mast cells (MCs) have also been shown to contribute to host–defense responses in certain bacterial infections. Treatment with recombinant IL-6 from engrafted mast cells enhances bacterial killing and resulted in the control of wound infection and normal wound healing [103]. Taken together, host innate immune response will be a potential means in boosting the clearing of microbial organisms.

Generally, public health strategies in controlling infectious diseases needed proper coordination, planning of infection control activities, post-prescription review, and feedback [93, 104, 105]. There should be a team of Clinical Microbiologist and well equipped laboratories with experience staff, working together to inform and improve individual patient care, contribute to outbreak management of infection and provide accurate surveillance data on infectious diseases. This information could be subsequently used in the review of local treatment guidelines, the design and evaluation of national health policies [106].

8. Conclusion

The microbial infection involved the use of many strategies by the pathogens to survive in the host. These have resulted in the development of drug resistance

strains in many pathogens, which persist and continue to be harmful to the host. Many treatment strategies have been failing and making it difficult in controlling diseases. This requires the development of revised scientific means to successfully control infections. Therefore, successful treatment of infections including bacterial and viral infections is the enhancement in both the use of antibiotics (for bacterial infections), antiviral (viral infections) and the host's immune defenses. As a result of the development of drug resistant strains in many treatment cases the enhancement of mostly innate immune response together with the adaptive immune response will go a long way in treating patients without difficulty.

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