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(REVIEW ARTICLE)

Role of antibody diversity in the management of malaria parasite invasion

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Abstract

The widespread incidence of malaria infection which result in breakdown of immunity and consequently death in the absence of effective health care measures such administration of appropriate drugs is as a result of failure of the immune system in combating the pathogenic *Plasmodium* species responsible for malaria infection. This review focuses on the role of antibodies in immune response to malaria and the role of antibody variation in the management of malaria.

Keywords: Malaria; Antibody; Plasmodium; Immune response

1. Introduction

Malaria is caused by *Plasmodium*, a genus of parasitic protozoans of the sporozoan subclass Coccidia. *Plasmodium* infects red blood cells in mammals (including humans), birds, and reptiles worldwide, especially in tropical and temperate zones. The organism is transmitted by the bite of the female Anopheles mosquito [1]

Malaria in humans is caused by five species; *P. vivax* (producing the most widespread form), *P. ovale* (relatively uncommon), *P. falciparum* (producing the most severe symptoms), *P. malariae*, and *P. knowlesi*. *P. knowlesi* is a specie mostly associated with animals but also found in human malaria cases. *P. reichenowi, P. falciparum* and *P. gaboni are* responsible for malaria in chimpanzees, *P. mexicanum* and *P. floridense* are found in reptiles, while *P. relictum* and *P. juxtanucleare* can be isolated from birds [2]

Malaria occurrence worldwide has been estimated to infect approximately 600 million people, resulting in the death of an estimated one to three million people each year, with majority of patients being five years or younger [3]**.** Studies have shown that those mostly at risk of severe malaria infection are; young children, pregnant women, immunosuppressed individuals and elderly travellers. *P. falciparum* induced malaria in non-immune pregnant travellers increases the risk of maternal death, miscarriage, stillbirth and neonatal death and may be fatal if treatment is delayed beyond 24 hours after the onset of clinical symptoms irrespective of age group. Unlike *P. falciparum* malaria, malaria caused by other species of *Plasmodium* cause significant morbidity but rarely result in the death of infected individuals [4]

Studies have associated the virulence of *P. falciparum* to its ability to escape the human and vector immune system by different mechanisms [5-6]. The response of the immune system to *Plasmodium* parasites is complex and targets different stages of its life cycle. Immune attack involvement is high in the erythrocytic stage in contrast to pre-

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erythrocytic stage, and major immune players in the pre erythrocytic and erythrocytic stages are CD8+ T cells and antibodies, respectively [7].

2. Antibody diversity

The human body can produce an antibody repertoire which can recognize almost every possible antigenic structure, but this cannot be achieved by encoding the antigen-receptor specificity directly in the genome sequence [18].

Antibody diversity has been explained with three theories. These theories present the possible ways which allow B cells to generate an antibody repertoire capable of reacting with a wide range of antigens:

(1) The germ-line theory postulates that separate genes exist for each antibody molecule and that the antibody repertoire is largely inherited.

(2) The deoxyribonucleic acid (DNA) rearrangement theory proposes that a limited number of genes undergo genetic rearrangements to create antibody populations.

(3) The somatic mutation theory proposes that a limited number of inherited genes undergo mutations to generate antibody repertoires.

The DNA rearrangement theory and the somatic mutation theory provide more plausible explanations supported by in vivo and in vitro studies [19].

Antibodies are "Y" shaped glycoproteins comprising of two light chains on both sides of an heavy chain. Both the light chain and heavy chain are divided into variable, constant and joining regions. These regions are encoded by different germ-line genetic loci. Variable (V) region, joining (J) region, and constant (C) region gene products are assembled into a functional antibody. Variable portion genes (V) code for amino acids that constitute the framework regions of the variable region, and three hypervariable complementarity-determining regions (CDR1, CDR2, and CDR3) [20]. The hypervariable regions form the three-dimensional antigen-binding pocket. Antibody specificity is determined by the specific amino acid sequences in CDR3. The joining (J) segment is, in reality, part of the V region and provides some of the framework for the antigen binding pocket. Only heavy chains have an additional diversity (D) gene. The large number of V, J, D, and C genes available for recombination result in antibody diversity [19].

3. Immune systems and response to infection

Immune response involves the recognition and attack with the purpose of destruction or suppression of pathogens. This is achieved through the innate and adaptive immune systems. Innate immunity is immunity inherited by offspring from parents. It is the first line of defense when pathogens gain entrance into the body system. It is nonspecific and uses general pathogen recognition mechanisms, through pathogen-associated molecular patterns (PAMPs) recognized by cell surface or intracellular pattern recognition receptors (PRRs), such as toll-like receptors or NOD-like receptors (NLRs) and RIG-like receptors (RLRs) (Kawai and Akira, 2009). Cell of the innate immube system include; monocytes/macrophages, dendritic cells, mast cells, natural killer cells, granulocytes, B1 cells, and innate lymphoid cells (ILCs). Despite lacking specificity, it reacts immediately on the invasion by pathogens and activates the adaptive immune system by presentation of the foreign antigen peptides [8].

Due to the need for activation, the adaptive immune system requires activation by the antigen hence it acts at a slower pace when the body is invaded by pathogens. It comprises of two main cell types, the B cell and the T cell which express specific receptors on their cell surface for pathogen recognition [9].

On activation, B cells of the adaptive immune system, mature into plasma cells which produce antibodies. Antibodies (Ab), also known as immunoglobulins (Ig), are large Y-shaped glycoproteins which function in the immune system by neutralizing pathogens such as pathogenic bacteria and viruses [10]. Antibodies are specific hence can recognize a unique molecule of the pathogen, called an antigen, with the aid of their fragment antigen-binding (Fab) variable region [11]. Antibodies protect the body from pathogens by binding to the antigens on the surface of the pathogens, preventing the pathogens from entering the host cell, causing the pathogens to clump together after which the clumped pathogens are engulfed by phagocytes or activating the complement system which then acts to burst the pathogen. One prominent pathogen which antibodies have the responsibility of combating is *Plasmodium* species which cause a disease condition known as malaria [12].

4. Role of antibodies in the management of malaria parasites invasion

The transmission of *Plasmodium* from the vector (e.g Anopheles mosquito) via the skin, makes the skin the first physical barrier and first line of defense against many pathogens including *P. falciparum* malaria parasites [13]. After inoculation, sporozoites stay in the skin for several hours and are activated into a state of readiness for the hepatic stages. Antibodies found in the skin tissues also inhibit sporozoite motility in the dermis [14]. Approximately 50% of the sporozoites do not leave the inoculation site. As a result, this early stage could play a key role in vaccine design [15].

In the erythrocytic stage of malaria, antibodies can opsonise merozoites for uptake or to inhibit invasion of red blood cells. Antibody mediates cellular killing, blocks adhesion of infected red blood cells to endothelium, and neutralizes parasite toxins to prevent the induction of excessive inflammation. It also marks merozoites for lysis by complement. This stage is also known by proinflammatory cytokine response that activates macrophages [16].

In the gametocytic stage, antibodies kill gametocyte through complement-mediated lysis and prevent sequestration and maturation of gametocytes in the host. Antibodies derived from host during blood meal are also highly responsible for complement-mediated killing of gametocytes and prevent gamete fusion in mosquito. Nitric oxide produced by macrophages is also important to kill gametocytes [17].

Studies have shown that the surface antigens of malaria parasites and the parasite proteins inserted into the plasma membrane of the infected red blood cell exhibit clonal antigenic variation. For this cause, management of malaria requires the development of a diverse repertoire of antibodies capable of blocking parasite invasion and tissue adhesion in order to attain effective antiparasite immunity [21]. The expression of antigenic variants by *Plasmodium* of the same and different species that is not recognized by the existing antibody repertoire may lead to uncontrolled parasite replication and therefore pathology. The gradual acquisition of clinical immunity after repeated infection is a result of the development of a diverse antibody repertoire [22].

5. Conclusion

In conclusion, the antigenic variation of *Plasmodium* species can only be combated by the generation of a broader range of antibody diversity in response to antigenic variants. Antibody diversity therefore is key factor in maintaining acquired immunity to malaria.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest Exist.

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