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Host Immune Response To Malaria

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ABSTRACT

Malaria is still a health threat, especially for children and pregnant women in endemic areas. The World Health Organization (WHO) reports 228 million cases of malaria occur worldwide and an estimated 405,000 deaths from malaria globally in 2018. A series of malaria control efforts according to WHO recommendations have been carried out widely. However, these programs face obstacles. Therefore, the existence of an effective malaria vaccine is absolutely necessary in a series of malaria control strategies. Development of a malaria vaccine requires a basic concept regarding the host's immune response to malaria. Unfortunately, only a few in Indonesia have reviewed how the immune response is. This article will present an understanding of how the human immune system responds to *Plasmodium falciparum.*

Introduction

Until now, malaria is still a health problem, especially for children and pregnant women in endemic areas. The World Health Organization (WHO, 2019) reports 228 million cases of malaria occur worldwide and an estimated 405,000 deaths from malaria globally in 2018. Most malaria deaths occur in children younger than five years in Africa and accounted for 67% (272,000) of all deaths from malaria worldwide. Malaria is an endemic disease in several countries in the world including Indonesia.

In 2018 there were 28 high endemic districts / cities from 4 provinces, namely Papua, West Papua, NTT and East Kalimantan (Kemenkes, 2018). According to Riskesdas in 2010, malaria caused by *Plasmodium falciparum* had a prevalence of 86.4% and was the highest prevalence in among all types of malaria (Kemenkes, 2011).

In addition to having a high mortality and prevalence rate, falciparum malaria also has a high rate of morbidity and progression. A series of malaria control efforts according to WHO recommendations have been carried out extensively, including prevention with Long-Lasting Insecticidal Nets (LLIN), vector control with Indoor Residual Spraying (IRS), and treatment with Artemisinin-based Combination Therapy (ACT). However, these programs face obstacles, including the spread and increase in the number of parasites that are resistant to antimalarial drugs and vectors that are resistant to insecticides. Therefore, the existence of an effective malaria vaccine is absolutely necessary in a series of malaria control

strategies, in addition to existing effort (Nindela, 2015).

Development of malaria vaccines has been ongoing for more than six decades, but until now there has been no vaccine that has been licensed. The main challenge in developing an effective malaria vaccine is the ability to provide protection against various forms of malaria parasites. caused by complex life cycles with various antigens expressed at each stage. Another major challenge is understanding minimal interactions between parasites and human immune mechanisms (Hill, 2011).

Because malaria parasites are very complex, the direction of vaccine development is carried out with several different approaches. Early in the development of the vaccine, efforts were made to focus on the pre-erythrocyte phase, namely the parasitic period in the form of sporozoites that enter the blood vessels and into the liver, which then progresses to maturity and begins the multiplication process (Douradinha, 2011). The following review will discuss the life cycle malaria parasites and immune response mechanisms against malaria infections.

Malaria

Malaria is a disease caused by intracellular obligate parasitic infection (protozoa) of the genus plasmodium which can be transmitted by the bite of an infected female Anopheles mosquito parasite (vector borne disease). This disease is usually characterized by fever, anemia, and hepatosplenomegaly. Malaria can attack anyone, especially residents who live in areas where the place is a place that suits the needs of mosquitoes to develop (Arsunan, 2012).

There are five species of plasmodium that can cause malaria in humans, namely *Plasmodium falciparum (P. falciparum), Plasmodium vivax (P. vivax), Plasmodium ovale (P. ovale), Plasmodium malariae (P. malariae),* and *Plasmodium knowlesi (P. knowlesi)*. But according to WHO, species that are often found and become a global focus are *P. falciparum and P. vivax*. In 2018, *P. falciparum* accounted for 99.7% of malaria cases in Africa, 50% of cases in Southeast Asia, 71% of cases in the Eastern Mediterranean, and 65% in the Western Pacific. Whereas *P. vivax* is the main parasite in the American region as much as 75% (WHO, 2019).

For survival, all species of malaria parasites basically require two types of life cycles, namely the sexual / sporogony cycle, the cycle in the mosquito body and the asexual / schizogony cycle, the cycle in the human body. Each stage of parasitic development is characterized by differences in antigen expression. Therefore understanding the life cycle of the malaria parasite is the basis for efforts to develop a malaria vaccine. The development of parasites as well as the interactions of parasites and their hosts determine the severity and pathogenesis of the disease clinically (Ballou, 2005).

Asexual Cycle (Schizogony)

When female Anopheles mosquitoes are infective inhaling human blood, sporozoites in the salivary glands will enter the bloodstream for about half an hour. After that, sporozoites will enter the liver cells and develop into liver schizons consisting of 10,000-30,000 liver merozoites (depending on the species). This cycle is called the eco-erythrocyte cycle which lasts for approximately 2 weeks. In *P. vivax and P. ovale*, after

sporozoites enter they do not develop directly into schizons, but some form dormant forms called hypnozoites. The hypnozoites can stay in the liver cells for months to years. At some point when the body's immunity decreases, it will become active so that it can cause a recurrence or recurrence (long term relapse) (CDC, 2019).

Merozoites originating from broken liver schizons will enter the bloodstream and infect red blood cells. In red blood cells, the parasite develops from the trophozoite stage to schizon (8-30 merozoites, depending on the species). Furthermore, infected erythrocytes (skizons) rupture and merozoites that come out will infect other red blood cells. This cycle is called the erythrocyte cycle. Each broken erythrocyte schizon will produce 6 - 32 merozoites which will infect new erythrocytes and start the cycle again. The number of erythrocytes lysis is one of the causes of anemia. After several generations of merozoites are formed, some of them grow into sexual forms that are gametocytes (gamete stem cells). The shape of gametocytes varies in each species of malaria parasite (Krattigen, 2006).

Sexual Cycle (Sporogony)

Mosquitoes will be infected with malaria when sucking the blood of patients who contain gametocytes. When mosquitoes suck the blood of patients, gametocytes carried in the blood will then undergo the process of maturation into male and female gametes in the gut of mosquitoes. Both types of gametes then unite to produce ookinet, ookinet moves to penetrate into the outer intestinal wall and experience maturation into oocysts. Furthermore oocysts will undergo meiotic division into sporocysts that contain thousands of sporozoites. These sporozoites are infective and are ready to be transmitted to humans. Based on the parasite life cycle there are 3 fundamental targets for developing a malaria vaccine, namely; pre-erythrocytic phase (sporozoit, liver stage), asexual erythrocytic and sexual phase (Targett, 2005).

Host Immune Response To Malaria

Immune responses to parasitic life cycle stages (stage specific), are divided into 3 namely:

Immune response at the Eksoeritrositer Stadium

The immune response at this stage is the immune response to the sporozoite and intrahepatic stages. The immune response at the sporozoite stage is antibodies that inhibit the entry of sporozoites into the hepatocytes. Sporozoites stimulate B cells to produce antibodies through Th2 cell intermediaries. Th2 cells will produce IL-4 and IL-5 which stimulate the formation of antibodies by B cells. The reaction of antibodies with this stage causes neutralization and opsonization occurs in phagocytic cells such as macrophages. Stimulated macrophages trigger the release of IL-12 which then activates Th1 cells. Th1 cells produce pro-inflammatory cytokines such as IL-2, IFN-gamma, and TNF a which can stimulate macrophages and other phagocytic cells.14,15 The immune response at the intrahepatic stage is mainly caused by CDC Tc cells. Sporozoites associated with dendritic cells activate Th cells which then produce IFN-gamma and activate Tc cells to destroy infected hepatocytes directly or indirectly

through IFNgamma secretion and NO (Hidayati, 2003).

Immune Response in Erythrocyte Stadium

The immune response at this stage is in the form of antibodies and phagocyte activation by Th cells. These antibodies function to agglutinate merozoites, block the entry of merozoites into erythrocytes, and kill infected erythrocytes (Riley, 2019). Infected erythrocytes will be captured by dendritic cells or macrophages which then release IL-12 will activate naive T cells into Th1 and then produce IFN- gamma. In addition, Th 1 produces IL-2 to stimulate NK cells which in turn will produce gamma IFN. The gamma IFN will then stimulate the action of cell dendritic and macrophages. On the other hand Th1 will help B cells to form antibodies. These antibodies will bind to parasites that come out of the blood and carry out opsonization (Stevenson, 2007).

Immune Response to the Sexual Stadium

The immune response at this stage is in the form of antibodies that inhibit the development of gametocytes in humans and inhibit the fertilization of gametes in mosquito vectors, inhibiting zygote transformation into the next stage before being smoked by mosquito vectors. Antibodies cause opsonization of macrophage cells (Draper, 2018).

Conclusion

Malaria is a disease caused by intracellular obligate parasitic (protozoa) infections of the genus plasmodium that can be transmitted by the bite of an infected female Anopheles mosquito parasite (vector borne disease). The Plasmodium life cycle consists of asexual (schizogoni) and sexual cycles (sporogoni). The immune response to the stage of the parasitic life cycle (stage specific) depends on the stage of eksoeritrositer, erythrocytes, and sexual stage). After understanding the basic immunology of the host response to malaria, it is hoped that vaccine development will be better.

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