



## Interaction between parasite and vector for Malaria disease transmission-a review on Malaria

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### Abstract

The parasite, Plasmodium needs an insect vector (mosquito) and a vertebrate host (human) to successful malaria transmission. The parasite use the vertebrate hosts for their asexual reproduction and insect host for sexual multiplication. In order to know the mechanism of disease transmission, knowledge about the possible interactions causes by the three components, vector, parasite and host is important. The mosquito feeding behaviour greatly contributes in the rate of malaria transmission. To assist the rate of transmission of malaria, the parasite, Plasmodium completes a complex developmental stage in the mosquito. In the mosquito the parasite, passes complex developmental stages and ensuing changes into three important forms of their life cycle: ookinete, oocyst and sporozoites. This review study concludes that, the interactions among vector, parasite and host in terms of reproductive behaviour and blood-feeding behaviour helps in transmitting malaria to the vertebrate hosts mainly, human being.

**Key words:** Malaria transmission, plasmodium life cycle, mosquito life cycle, insect vector, vertebrate host

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### Introduction

Malaria is a mosquito-borne disease caused by the parasitic protozoan belonging to the genus, *Plasmodium*. The disease causes yellow skin, seizures and finally coma or death (Caraballo and King, 2014). Approximately 198 million cases of malaria were found throughout the world in 2013, and an estimated amount of deaths were 584 000. Among them 90% of all malaria deaths occur in Africa (WHO, 2014).

The disease is transmitted by the infected female Anopheles mosquito with Plasmodium parasites that feeds on human blood to get nutrients for survival and reproduction (Warrell and Gilles, 2002). The mode of transmission is through the bite of infected female Anopheles mosquito that introduces the parasites, Plasmodium from the mosquito into human blood (Mury and Kumar, 2005). The disease causes symptoms that typically include fever, headaches,

vomiting and fatigue. Once a human becomes infected with malaria, the symptoms usually begin 10-15 days after being bitten (Warrell and Gilles, 2002).

In humans, malaria is caused by *P. falciparum*, *P. vivax*, *P. knowles*, *P. ovale* and *P. malariae*. These species has the same life cycle with only slightly differences from each other. In general, Plasmodium needs a vertebrate host (human) and as well as an insect vector (mosquito) to successful complete their life cycle (Simonetti, 1996). During feeding by an infected mosquito, the parasite, Plasmodium takes the chance for its successful transmission from vertebrate host to insect vector. In the life cycle of Plasmodium, the sporozoites (an infective motile form) are inoculated by mosquito (the primary host) into the human (the secondary host) during feeding blood (Capone et al., 2013). The circulatory system

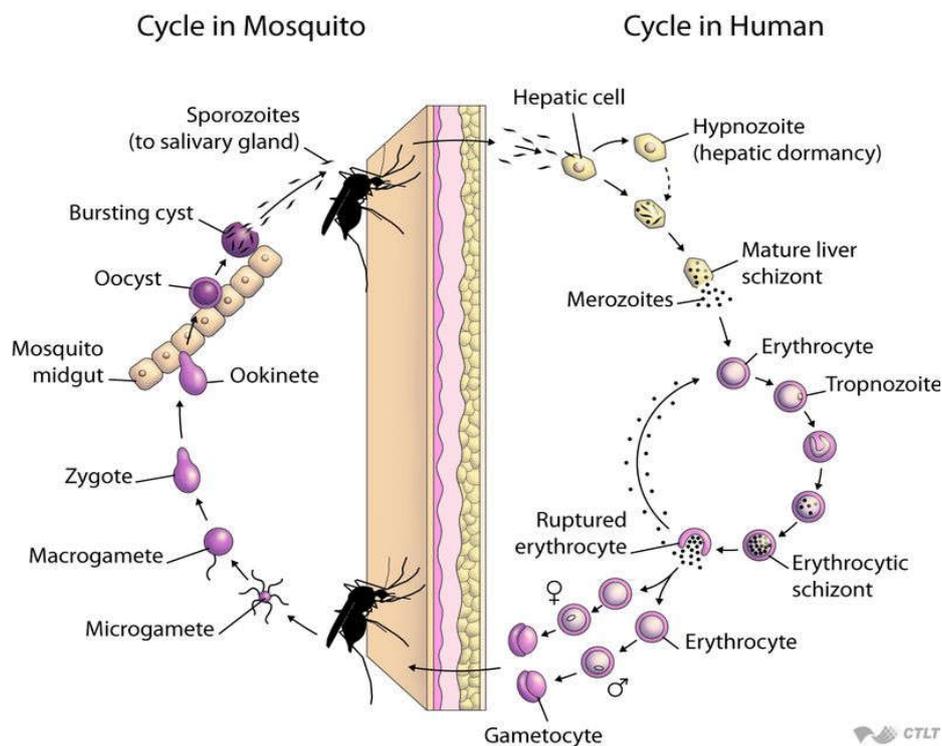
acts as a carrier for sporozoites to the liver cells (hepatocytes), where it reproduces asexually (tissue schizogony or exoerythrocytic schizogony) and producing thousands of merozoites which later are released into bloodstream (Capone et al., 2013).

Although the disease-causing forms of Plasmodium parasite only exist in human blood stages, the female Anopheles mosquito is the obligatory vector for disease transmission. This vector has 4 main life stages: egg, larvae, pupa and adult. The essentiality of this vector in response to parasite is that they facilitate transmission of disease to the host because their saliva carry parasite. Here, I want to focus on the different stages of parasite life cycle in mosquito, from gametocytes (preliminary uptake by mosquito) to sporozoites (start infection of a human body) (Smith and Lorena, 2013). The Plasmodium must

conquer many barriers and roadblocks during their complex developmental progression to ensure transmission. So, an interesting research questions for this kind of research topic is that, how the Plasmodium-mosquito interactions contributes to successful parasite transmission to the vertebrate host.

**Life cycle of Plasmodium**

The life cycle of a Plasmodium is very important to understand the possible interactions that are mention in this essay. Normally the parasite, Plasmodium enters as sporozoites through infected female mosquitoes during biting a host. Multiplication of the Plasmodium starts in the hepatic cells of liver of the vertebrate host.



**Figure1.** Life cycle stages of a Plasmodium

After that they attack the RBC (red blood cell) which leads to ensuing rupturing of the RBC. The sporozoites are formed and stored in the salivary glands of mosquito. These sporozoites are

transforming into a host when mosquito bite them. Generally, the parasite requires two hosts to carry out its life cycle: an insect vector (mosquito) and a vertebrate host (human). The life cycle consists of 3 stages: (1) infection of a human with sporozoites, (2)

asexual reproduction and (3) sexual reproduction. The 1st and 2nd phases are take place inside the human body, though the third one starts in the human body but completed into the mosquito host (Simonetti, 1996) (Figure1).

The first life stage of Plasmodium, stage of infection starts when infected female mosquitoes anopheles bite a host and injects saliva infected with sporozoites into the blood circulatory system of human host (Smith and Lorena, 2013). The next stage, the asexual reproduction known as exoerythrocytic schizogony takes place within the hepatic cell of liver. Within 30-60 minutes after inoculation, the sporozoites enter in to the liver cells and start dividing to schizonts (exoerythrocytic schizogony) (Simonetti, 1996). Each schizont gives birth to thousands of merozoites that are then released into the bloodstream marking the end of the exoerythrocytic phase of the asexual reproductive stage (Muryand Kumar, 2005).

Merozoites then released into the blood stream and invade the red blood cells (RBCs) and start the erythrocytic phase. A ring stage is the first stage after invasion that evolves into a trophozoite (Simonetti, 1996). The next stage is the erythrocytic schizogony that initially produces immature schizont and then mature schizont. Each mature schizont gives birth to new generation merozoites are released in the blood stream after rupturing RBCs (Simonetti, 1996). Sexual reproductive cycle is the last stage of a plasmodium life cycle, which is also occur into the RBCs. The parasite can differentiate into male and female gametocytes that are a non pathogenic form of the parasite. During biting an infected person, the female anopheles mosquito takes up these gametocytes with the blood meal. After that the gametocytes become mature and form microgametes (male) and macrogametes (female) during a process known gametogenesis (Muryand Kumar, 2005). In the mosquito gut, the nucleus of microgamete is divided and produces eight nuclei; each nucleus fertilizes a macrogamete leading to a zygote (Simonetti, 1996). Then the zygote develops into a motile ookinete that penetrates the epithelial cells of midgut and develops into an oocyst. The oocyst undergoes several rounds of asexual

replication resulting in the production of thousands of sporozoites (sporogony). That is the end of the sexual reproduction stage or sporogony (Simonetti, 1996).

After rupture the mature oocyst, the sporozoites are releases into the hemocoel (body cavity of mosquito) and invade the salivary glands, thus completing the life cycle. A new cycle will start when the above mentioned infected mosquito takes a blood meal from the next victim.

The primary host Anopheles mosquitoes are vital vectors of this malaria disease. The life cycle of an Anopheles mosquito possess four separate stages: egg, larvae, pupa and adult (Figure 2). In general, female mosquitoes mate once during their entire life time and lay eggs at intermissions throughout their whole life time. The male mosquito rather feeds on plant juices and do not suck blood. For egg laying the female mosquitoes have to a blood meal (Smith and Lorena, 2013). So, after the taking of blood meal, the mosquito hunts for suitable location to lay their eggs. It takes normally 2-3 days to get digest the blood meal and eggs development in tropical areas and can be delayed depending on temperate climates (Sreenivasamurthy et al., 2013). The mosquito prefers to lay their eggs normally in a pool, slow running water and in rice field. Actually, eggs are laid on water surface followed by hatching process. Hatching take place in 2-3 days, the larvae feed on small organic particles after hatching. The developmental period of a mosquito counts normally 11-13 days from eggs to adult (Sreenivasamurthy et al., 2013). This cycle is continued until the female mosquito dies.

#### **Plasmodium-mosquito interactions**

Current understanding is that there is critical interactions take place between the parasite, Plasmodium and mosquito. These interactions are starting from eggs production by the mosquitoes that require blood meals to start the process of laying eggs. During the time female mosquitoes are trying to feed on blood from the host, the parasite takes this chance of feeding behaviour of mosquito for its transmission from one host to another (Smith and Lorena, 2013).

### Life cycle of Anopheles mosquito

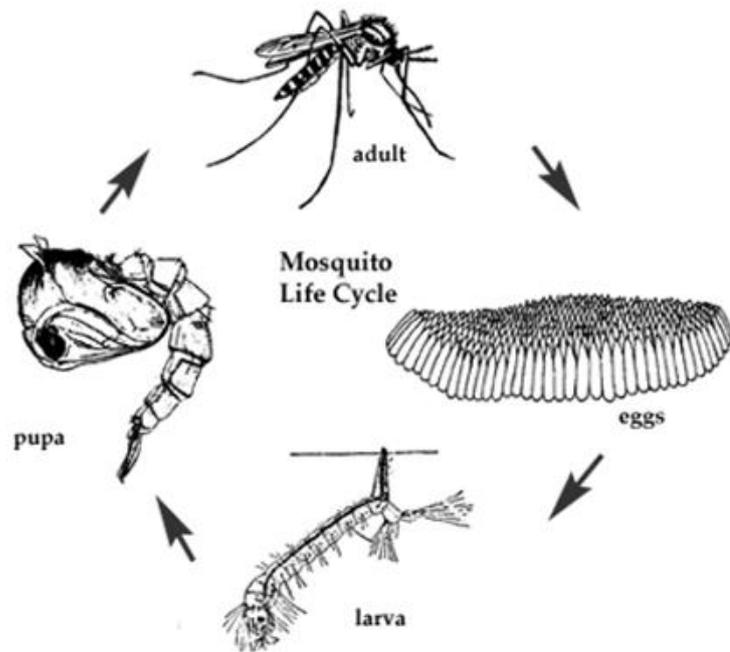


Figure 2. Life cycle stages of an Anopheles mosquito

The parasite, try to manipulate life history and feeding behaviour of the mosquito to increase its rate of transmission (Schwartz and Koella, 2001). The situations start the possible interactions among the mosquito-parasite and host (Smith and Lorena, 2013).

The parasite, Plasmodium undergoes a complex life cycle and fulfils their short sexual life cycle in the insect host. To complete the life cycle, Plasmodium needs to survive in the insect host, cross several physical barriers (midgut epithelium, salivary gland), and try to avoid damage by the immune system of mosquito (Muryand Kumar, 2005). The developmental period and transit in the mosquito is a complicated and unsafe journey for the parasite, Plasmodium because considerable parasites are losses during this period (Muryand Kumar, 2005).

Generally, merozoites of parasite, Plasmodium are mainly found in an infected host (human), but they have no impact in the transmission of malaria disease and immediately die after ingestion by mosquito (Muryand Kumar, 2005). In fact it is believed that,

few of these parasites can go into terminal alteration pathway and normally ends with female and male gametocytes production. These sexual form are required for initiating a new the life cycle of a parasite, Plasmodium in an insect vector that enhance the spread of disease development in to the host (Smith and Lorena, 2013).

In mosquito after blood meal consumption the ingested gametocytes moves to the midgut. Usually, gametogenesis takes place inside mosquito midgut. Immediately after the gametogenesis, the newly developed exflagellating motile male gametes are interacting with sialic acid found on the erythrocyte layer (Smith and Lorena, 2013).

In the midgut of mosquito, the ookinetes that are formed have to cross some barriers, like the epithelial cells after that they reached in the basal lamina of midgut. Several complex interactions take place when they come in the direct contact with immune system of mosquito (Muryand Kumar, 2005). In *Plasmodium berghei*, for every thousand ingested gametocytes, merely two active ookinetes are

generated. Only 2–20% of them can effectively march into the midgut and form mature oocysts (Mury and Kumar, 2005). However, the parasite can bear the huge losses, because the population of parasite will be re-expanded in the oocyst stage (Mury and Kumar, 2005). Within a 2-week period the ookinetes that are changed into oocysts can produce 1000 sporozoites (Muryand Kumar, 2005). After that the mature sporozoites are invade the mosquito salivary gland and finally reached in the salivary duct and ready to inject in new vertebrate host during blood feeding. Most of the released sporozoites are degenerated and only 20% of the sporozoites can arrive at the lumen of salivary gland (Smith and Lorena, 2013). In this stage the immune system of mosquito inhibits the sporozoites to bind and cross of the mosquito salivary gland (Muryand Kumar, 2005).

In Plasmodium life cycle an insect vector is one of the most vital parts that make possible transmission of disease (Smith and Lorena, 2013). There has been huge pressure on the Plasmodium to defeat the immune defences express by a mosquito. The interactions between Plasmodium-mosquito are versatile, in the sense that a minute number of Plasmodium decreases the strength of mosquito, whereas the immune system of mosquito beside the parasite has the equal effect in dropping the fitness (Mury and Kumar, 2005). Naturally, single oocyst of Plasmodium can produce enough sporozoites to decrease mosquito virulent. Also a mosquito has to tolerance the parasite because she needs to pay high cost for delivery immune responses against Plasmodium (Muryand Kumar, 2005). Generally, when the rate of disease transmission is high, Plasmodium occurrence is low. This ultimately leads to the mosquito infected with Plasmodium carry low numbers of the parasite (Anderson et al., 1999).

### Discussion

The mosquito is an absolute requirement for transmission and survival of the parasite, Plasmodium in nature. The review was carried out to study the possible interactions between Plasmodium and insect vector contributing to malaria transmissions.

The interaction between mosquito and Plasmodium was observed in the midgut of mosquito when ookinete develop and midgut invasion occur. The peritrophic matrix (PM) of mosquito midgut composed of proteins, chitin, proteoglycans and glycoproteins, and make physical barrier for ookinete (Smith and Lorena, 2013). The ookinete are secretes enzyme that disrupt the PM. The *P. gallinaceum* secretes chitinase in the midgut of mosquito for own development (Smith and Lorena, 2013).

Next to PM, the ookinete of Plasmodium invade the midgut epithelium. Here the ookinetes first interact with glycoproteins of midgut for invasion. Carbohydrate may play a role in binding ookinete to the midgut. An antibody (MG96) blocked Plasmodium development that is the evidence of interaction between parasite and mosquito (Smith and Lorena, 2013). It seems that ookinete needs to interact with different types of sugar, protein and lipid of the midgut epithelium for invasion. In *A. aegypti* ATPase of *P. gallinaceum* can help in midgut invasion (Smith and Lorena, 2013).

Similar to Plasmodium invasion of midgut, some residue of carbohydrate play a role in invasion of the salivary glands by sporozoites of Plasmodium. The invasion of sporozoites is blocked by specific lectins that completely bind sporozoites on the salivary glands (Smith and Lorena, 2013). For example, *P. falciparum* and *P. berghei*, saglin inhibit sporozoites to invasion the salivary glands (Smith and Lorena, 2013). In every feeding cycle, a few of sporozoites enter into the salivary gland and causes some damage to the plasma membrane during invasion.

In addition to these physical barriers the immune system of mosquito interacts with Plasmodium. During invasion of the midgut and the salivary gland the discharge of mosquito the immune factors from their haemocytes and fat body (Smith and Lorena, 2013). Some protective genes play a major in the immune system of mosquito. For example, APL1C gives protection to mosquito against *P. berghei*, while APL1A protect *P. falciparum* (Smith and Lorena, 2013). Although the mainstreams of immunity responses are found during midgut invasion but there is some successful defensive

response was found when sporozoites attack the salivary glands. Within minutes the released sporozoites into the haemolymph are degraded (Smith and Lorena, 2013).

Regarding to the possible transmission of Plasmodium the saliva of mosquitoes is a mediator source that creates interaction between vector and parasite. Because saliva of mosquitoes contain parasite (Plasmodium) that causes malaria (Rivero et al., 2003). The sporozoites that present in the saliva of mosquito can manipulate the behaviour of their insect vector by increasing the biting rate (Schwartz and Koella, 2001). For example, in infected *Anopheles gambiae* with *P. falciparum* sporozoites not only increase the duration of biting but also the rate of biting (Schwartz and Koella, 2001).

On the other hand, oocysts decrease the chance of mosquito biting and fecundity. In the oocyst stage, the parasite only shows their interest of mosquito's survival (Schwartz and Koella, 2001). However, blood feeding, increases the mortality risk of mosquito. Because, feeding act as a risk, due to the defensive behavior of host and also, blood-fed mosquito looks are clumsy, obvious and nutritious prey, and killed by predators (Schwartz and Koella, 2001).

However, the parasite gives more importance on biting, while the mosquito is concerned with their survival (Schwartz and Koella, 2001). Generally, the transmission of parasite is likely to rise more rapidly with the frequency of biting than fecundity of mosquito. Because of every bite have a probability in parasite transmission. Another reason is, transmission starts during biting, but oviposition starts few days after biting (Schwartz and Koella, 2001). So the mosquito gives more importance on survival than Plasmodium. For example, *An. stephensi* infected with sporozoites show more persistent than uninfected mosquitoes (Schwartz and Koella, 2001).

Vector-borne parasite can change the biting behaviour of mosquitoes for their successful transmission. The rate of biting is one of the cores entomological issues for transmission of malaria and increased several feeding by infected insect vectors

has extremely suggestions for malaria epidemiology (Schwartz and Koella, 2001).

## Conclusion

Now a day, the malaria parasite is the most extensively studied parasites that infect human being. This review mainly focuses on the probable interactions takes place between the vector-parasite for transmission of malaria diseases. The complex interactions between life-history traits and the effects of parasite infection (and many other traits) contribute in the evolutionary pressures on hosts and parasites and thus, ultimately on the epidemiology of malaria. The parasite and vector genomes significantly involved in the interactions between parasite and vector. However, further studies are needed to express the effect of the vector parasite and host mediating interactions.

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