A Review of Manipulations in Plasmodium – Mosquito Interactions

**Summary**

A key requirement for transmission of malaria parasite is an infected blood meal that initiates parasites transmission cycle. The malaria parasite and its mosquito require differing biting rates of mosquito to ensure parasite transmission success and mosquito reproductive success. The trade-off existing between mosquito biting rate and survival further constrains the attempts by both partners to minimize their successes. This review discusses the attempts by malaria parasites to enhance the transmission and the defense system of its vector to resist infection. This article is a review of several articles obtained from the Internet, www.pubmed.com, medline and several authors via e-mail.

**Key Words:** Malaria Transmission, Plasmodium spp.

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**Introduction**

Malaria, every year, results in 300-500 million clinical cases, one million deaths and is responsible for about 20% of all deaths among children under five years in Africa. Malaria parasites, *Plasmodium* spp, require female anopheline mosquitoes as vectors for sexual development and transmission to vertebrates. These female mosquitoes require a blood meal from a vertebrate host to obtain nutrients to sustain oogenesis and reproduce. *Anopheles gambiae*, a highly anthropophilic mosquito, is the principal vector of human malaria in Africa.

Upon ingestion, parasite gametocytes are rapidly activated to produce gametes in the mid gut of mosquitoes. Fertilization follows, leading to formation of a motile ookinete which penetrates the mid gut. The ookinete ceases its migration upon reaching the basal lamina separating the mid-gut and haemocoel compartments. Here the ookinete undergoes differentiation into the oocyst form. Oocysts grow over a period of days to produce many sporozoites each. These sporozoites are released into the haemolymph to colonize the salivary gland. They reach the salivary duct to be injected into a vertebrate host during mosquito blood feeding.

A long held view among parasitologists is that infection by malaria parasites does not harm their mosquito vectors. Both partners benefit from increased survival and an increased rate of blood feeding – the mosquito to
increase its reproductive success and the parasite to ensure its own transmission. However, mosquitoes face trade-offs during blood feeding. On one hand, fecundity of the mosquito increases with increased rate of blood feeding because of the strong positive correlation that exists between the amounts of blood imbibed by the mosquito and the number of eggs it lays. On the other hand, blood feeding increases the risk of mosquito mortality since mosquitoes are likely to be killed by the irritated vertebrate host while feeding or trying to feed, or by predators due to mosquito’s increased mass. This trade-off constrains the mosquito while the malaria parasite’s attempt to maximize their successes. Coupled to this constraint is the difference in the frequency of blood feeding required by mosquito and malaria parasite to maximize their successes. Koella described a simple model of mosquito reproductive success and Plasmodium transmission success as a function of mosquito biting rate. It was concluded that the parasite’s success is maximal at a biting rate that is higher than required for maximal mosquito’s success, as long as transmission increases more rapidly with fecundity with biting rate.

This article discusses the evolutionary consequences of the differing frequencies of mosquito blood feeding required by mosquito and its malaria parasite.

Manipulation of mosquito by malaria parasite: In Plasmodium-mosquito interactions, it is in the interest of both partners that the mosquito survives for a long time (at least until the infectious sporozoites have developed) and bite frequently. However, since the biting rate that is optimal for the mosquito is not optimal for the malaria parasites; Plasmodium, therefore tries to manipulate several aspects of its mosquito vector’s biting behaviour in a way that should increase its own transmission success. This mode of manipulation is stage specific i.e. it is dependent on the parasite’s developmental stage.

The oocyst is the non-transmissible stage of Plasmodium. It must develop for several days in the mosquito mid-gut wall before it can produce sporozoites, the only stage that can be transmitted to the vertebrate host. The only way to increase overall transmission during this developmental period is to increase its mosquito vector’s survival of which experiments have investigated. The persistence with which Anopheles stephensi mosquitoes attempt to feed on human host is decreased if they are infected with oocytes of the parasite P. yoelii nigeriensis as opposed to a higher persistence in sporozoite – infected mosquitoes. Corroborating this is the finding by Koella and co-workers that oocyst of P. gallinaceum decreased the blood volume that Aedes aegypti takes up for it to be satiated. Plasmodium infected mosquitoes took up less blood than uninfected mosquitoes if they had been starved for 6 days (when parasites would have developed into oocysts) (Fig-1).

The amount of blood is expressed as the residual after controlling; in particular, for the amount of time the mosquitoes were allowed to feed. In infected mosquitoes, the parasites had developed into mature oocysts after 6 days and into sporozoites after 12 days. At the sporozoite stage, the parasite’s interest lies in its mosquito vector’s frequent biting while the mosquito vector is more interested in its own survival. This is because the parasite’s transmission increases more rapidly with biting frequency than mosquito fecundity.

Figure-1: Amount of blood imbibed by Plasmodium-infected mosquitoes 6 or 12 days after the previous engorgement.
So also, transmission of parasite occurs during biting while oviposition occurs days after biting.\(^4\) Behavioural manipulations have been observed in both laboratory and field experiments that malaria parasites manipulated mosquitoes to bite more. Sporozoite infection in mosquitoes caused an increase in the duration of probing and number of probes.\(^11\) Sporozoite infected mosquitoes were also more persistent in biting.\(^9\) Koella and co-workers\(^10\) showed that sporozoites increased the volume of blood required by their mosquito vectors to be satiated and quit host seeking, thereby causing the mosquito vector to bite more.

The gametocyte stage, although a vertebrate stage of *Plasmodium*, has also been implicated in the behavioural manipulation of mosquitoes to aid *Plasmodium* transmission. Lacroix and co-workers\(^8\) investigated this issue and showed in a semi-natural experiment that children infected with gametocyte stages of *Plasmodium* attracted twice as many mosquitoes to themselves as the uninfected children and those harboring asexual stages (Fig-2). However, when infected children were treated, all children had similar attractiveness to mosquitoes. Of all these manipulations, only that of the sporozoite stage has a known mechanism. *Plasmodium* sporozoites reduce the apyrase activity of the mosquito vector thereby causing difficulties in obtaining a full blood meal. The result of this is biting more often.\(^12\)

**Resistant mechanism in mosquito:** The insect innate defense system represents a potentially formidable obstacle to the survival and growth of infecting microorganisms and eukaryotic parasites, in particular those which, like *Plasmodium*, undergo profound developmental changes associated with the invasion of multiple host tissues.\(^13\) The innate immune response of mosquito is activated during mid gut invasion\(^14\) and there is increasing evidence that the mosquito mid gut is an immune-competent organ inducing several immune markers in response to *Plasmodium* infection.\(^15\) Several types of defence mechanisms have been documented in mosquitoes against *Plasmodium*. These are melanotic encapsulation of *Plasmodium* ookinetes at a later stage as they initiate oocyst development,\(^16\) lysis of migrating ookinetes within the mid-gut epithelial cells\(^17\) and destruction of parasites by mosquito immune system peptides. These responses are genetically as well as morphologically distinct,\(^13\) so that one would expect resistance to spread in a mosquito population infected by malaria parasites. However, defence reactions, with melanization being the most studied, are rare in infected field-caught mosquitoes.\(^18,4\) This could be due to the fitness cost of immune response, for instance, defense reactions that result in the melanotic encapsulation of parasites are reproductively costly. Both melanization and egg tanning require tyrosine, so a competition for limited resources ensues ultimately resulting in a reproductive cost (lower fecundity) for the mosquito.\(^19\) Another reason for this lack of immune response in national populations could be down-regulation or evasion of mosquito immune system by *Plasmodium*.\(^19\)

**CONCLUSIONS**

The epidemiological success of *Plasmodium* is partly due to its very high intensity of transmission. This intense transmission is largely due to the parts of *Plasmodium*’s life cycle that takes place within its mosquito vector, particularly the interaction between the lifespan of mosquito, the duration of the parasite’s development and mosquito biting rate.\(^8\) The
knowledge of *Plasmodium*-mosquito interactions is thus of epidemiological importance.

It is also clear that parasite transmission depends on the molecular and cellular interactions acting at different levels of parasite’s lifecycle in vector. Understanding these interactions and identifying the molecules involved will provide valuable information that can be exploited in designing novel transmission blocking strategies for vector borne pathogens.20

REFERENCES