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Review

Imaging mosquito transmission of *Plasmodium* sporozoites into the mammalian host: Immunological implications

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ABSTRACT

The malaria infection is initiated in mammals by injection of the sporozoite stage of the parasite through the bite of *Plasmodium*-infected, female *Anopheles* mosquitoes. Sporozoites are injected into extravascular portions of the skin while the mosquito is probing for a blood source. Sporozoite gliding motility allows them to locate and penetrate blood vessels of the dermis or subcutaneous tissues; once in the blood, they reach the liver, within which they continue their development. Some of the injected parasites invade dermal lymph vessels and travel to the proximal draining lymphatic node, where they interact with host immunocytes. The host responds to viable or attenuated sporozoites with antibodies directed against the immunodominant circumsporozoite protein (CSP), as well as against other sporozoite proteins. These CSP antibodies can inhibit the numbers of sporozoites injected by mosquitoes and the motility of those injected into the skin. This first phase of the immune response is followed by cell-mediated immunity involving CD8 T-cells directed against the developing liver stage of the parasite. This review discusses the early history of imaging studies, and focuses on the role that imaging has played in enabling a better understanding of both the induction and effector functions of the immune responses against sporozoites.
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1. Introduction: early studies

All science begins with observation of the natural world. The invention of the microscope allowed a magnified visualization of nature long hidden from human eyes. These early observations were made with unstained wet mount preparations. It was such an observation that led Alphonse Laveran [1] to the discovery of the malaria parasite in Algeria. As he wrote, "*On examining a fresh preparation of blood from a soldier suffering from malaria, I observed with astonishment a series of thin and transparent filaments on the periphery of round pigmented bodies. These moved with great agility and their living nature was incontestable. I soon found similar elements in the blood of other patients suffering from malaria and I had no longer any doubt of their parasitic nature.*" This process was later shown to be the exflagellation of *Plasmodium falciparum* microgametocytes. But for almost two decades thereafter there was no clear understanding of how this parasite was transmitted to humans.

The likelihood of mosquito transmission was first revealed to Ronald Ross in 1897 in India during his microscopic examination of the organs of anopheline mosquitoes fed four days earlier on patients infected with

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falciparum malaria. Ross described what he called "*peculiar pigmented cells*" found on the midguts of only those mosquitoes that had fed on malaria-infected patients whose blood contained the crescents characteristic of *falciparum* malaria [2]. On that day in August 1897, which Ross thereafter referred to as "Mosquito Day", he dashed off a poem, "In Exile", which began,

"*This day relenting God*
Hath placed within my hand
A wondrous thing; and God
Be praised. At his command,
Seeking His secret deeds
With tears and toiling breath,
I find thy cunning seeds,
O million-murdering Death".

It would take further studies for Ross to prove that malaria was carried by mosquitoes and to demonstrate the manner of transmission, this time with avian malaria. In 1898 he discovered that these pigmented "cunning seeds" (oocysts) on the midgut surface were packed with structures that he called "germinal threads" or "rods", which eventually reached the mosquito circulation. He was puzzled as to what happened next. As he wrote "*Nature probably makes some extraordinary effort here in order to complete the life cycle. What the dickens she is going to do next I cannot imagine at all.*" He did, however, establish that the rods were more numerous in the head and in the thorax, and there he focused his attention. Further microscopic examinations revealed his crowning conclusion, "*On taking up the thorax… a small round clear mass of tissue fell out and was seen to consist of mostly some wormlike gland with an airtube down the middle. Rods were very numerous here and were seen to be enclosed in numbers in clear cells attached to this gland.*" After some difficulty dissecting out the gland, he wrote, "*the duct led straight into the head piece, probably into the mouth. In other words it is a thousand to one, it is a salivary gland. Malaria is conveyed by a diseased person or bird to a healthy one by the proper species of mosquito, and it is inoculated by its bite. …In all probability it is these glands which secrete the stinging fluid which the mosquito injects into the bite. The germinal rods, lying as they do, in the secreting cells of the gland, pass into the duct when these cells begin to perform their function, and are thus poured out in vast numbers under the skin of the man or bird*" [3].

Ross worked under difficult field conditions in India and had limited equipment and microscopes. Technical improvements on the compound microscope during the last decades of the nineteenth century, coupled with histological staining of thin sections, led to further advances. It was left shortly thereafter to Giovanni Grassi and his Italian colleagues to confirm Ross's avian malaria findings with the human malarias and to publish exquisitely detailed color drawings of sporozoites (spzs) within oocysts and salivary glands [4]. The puzzling and erroneous report by Schaudinn [5] that spzs initiated their further development by directly invading red blood cells confused and held back malaria research for decades. It would take an additional 45 years before it could be established that spzs continue their development in mammals by invading hepatocytes within the liver of their hosts (see Frevert et al., this issue, for studies on the liver). Boyd and Kitchen [6] were able to demonstrate spzs in histological sections of skin of human volunteers bitten by *Plasmodium vivax*-infected mosquitoes. Studies on the fate of spzs injected into the skin by syringe can also be instructive, although syringe injection does not exactly mirror the injection by mosquito bite. Histological studies with *Plasmodium cynomolgi* spzs injected into rhesus monkeys by syringe showed spzs in every one of twelve biopsies taken up to 2 h after injection and in none of seven biopsies taken 4 h and beyond post-injection [7]. In a similar study, Frank Hawking, the father of cosmologist Stephen Hawking, observed spzs remaining in tissues up to 4 1/3 h post-injection [8]. As we shall see, a similar gradual disappearance of spzs from the skin can be observed by fluorescence microscopy after mosquito deposition of spzs into mice; this was accomplished both by microscopic examination of timed biopsy specimens and by intravital microscopy.

Early studies of mosquito probing behavior on living animals were done during microscopic observations of trans-illuminated thin tissues, such as the frog foot web and the mouse ear pinna, while viewing probing by the mosquito proboscis within the skin [9–11]. Two types of probing/feeding behavior were described: a) direct puncture of a dermal blood vessel and b) feeding from a pool of "extravasated" blood from a hematoma formed by blood vessels ruptured during probing. Mosquitoes search for blood by repeatedly thrusting mouthparts into a dermal network of blood vessels until a vessel is pierced [12–14]. Mosquitoes salivate copiously from the distal end of the proboscis into extravascular portions of skin while the proboscis is searching for a blood source within the dermis or subcutaneous tissue. Indeed, malaria can be transmitted by probing mosquitoes even when the mouthparts are withdrawn prior to the initiation of blood ingestion [15,16].

2. Injection of sporozoites into extravascular portions of skin

Evidence suggests that mosquitoes do not commonly inject spzs directly into the blood stream. Electronic recordings of the bite of *Aedes aegypti* showed that salivation occurs only during probing and during withdrawal of mouthparts [17]. Even if some saliva were to be injected during mosquito engorgement, it likely would be re-ingested with the blood back into the midgut. The food canal for ingestion of blood within the proboscis has more than 100 times the cross sectional area of the parallel channel for saliva discharge, and the rate of blood flow into *A. aegypti* is of the order of 10^4–10^5 times the rate of flow of saliva from the mosquito into the bite site [18]. Indeed, spzs are recoverable from mosquito midguts after infected mosquitoes take bloodmeals [19,20] and this backflow has been quantified [21]. Sporozoite infectivity studies with the *Anopheles stephensi*–mouse system showed nonvascular delivery into the skin by allowing infected mosquitoes to probe the mouse ear, after which the bitten portion was extirpated at various times after completion of probing. With control mice, whose fed-upon ear remained intact after a single mosquito bite, more than 80% of the mice developed patent blood infections. When the bite site was extirpated at times up to 5 min after the mosquito bite, only 13% of the mice developed parasitemia. When the bite site was removed at 15 min post-feeding, 53% developed parasitemia. The conclusion was that most if not all spzs are deposited in extravascular portions of the skin tissue and that they tend to take several minutes before reaching and invading a blood vessel [22]. How are these spzs able to reach the blood?

3. In vitro studies with sporozoites

Sporozoite in vitro studies have been aided by a method for initiating and characterizing their motility by exposing them to serum albumin; as low as a 0.5% concentration of bovine serum albumin is effective in strongly initiating motility [23]. Albumin was the first defined molecule shown to be associated with an activating effect on the malaria parasite. Its presence in extracellular components of skin would allow it to function as a physiologically appropriate signal to initiate motility in spzs injected into extravascular portions of the skin. More recently, Perschmann et al. [24] reported that when bound to artificial substrates, the tripeptides RGD and RGE could substitute for albumin as inducers of spz gliding motility. These tripeptides are components of many extracellular matrix complexes and, via the intermediary functioning of integrins, allow focal adhesions on cells such as spzs to anchor the cells to the extracellular matrix. The relationship of these tripeptides to albumin as inducers of motility needs to be further evaluated. However, albumin does seem to be a natural physiological inducer of sporozoite motility and has pleiotropic effects on spzs. It initiates motility and enhances infectivity [23], immunogenicity [25], long-term survival in vitro [23] and secretion of the circumsporozoite protein (CSP); this

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