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Perspective

Malaria Disease Perspective and an Opinion: Should Malaria Treatment Target the Parasite or the Malarial Pathophysiology Generated by the Parasite or Both?

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Introduction

The malaria disease is caused by primarily four protozoan microorganisms of the *Plasmodium* genus transmitted by the female Anopheles mosquito namely: *P. falciparum, P. vivax, P. Malariae, P. ovalae*. A fourth one, *P. knowlesi* is known natural pathogen of the marquis but can also infect human. With its ability to infect both mature and immature red blood cells (RBC's), multiply rapidly, cause severe malaria anaemia (SMA), adhere to blood vessels endothelium, cause cerebral malaria, *P. falciparum* causes the most complications of the disease with high fatality rates. The most prevalent human malaria parasite is *P. vivax* with a propensity to relapse when dormant liver stages (hypnozoites) are activate to reinvade RBC's many months to years after the initial malarial infection. The other parasites cause varying disease manifestation with less fatalities.

Malaria Disease

The malaria disease progression follows more or less the same pathophysiological pattern regardless of the aetiological agent although the severity might differ in different age groups, immunological status, physiological states and disease phenotypic presentation. Malarial disease causing apicomplexan parasite of the five main *Plasmodium* species seem to have acquired a genotypic adaptation to be able to: i. selectively invades humans, ii. selectively infect the female species of the Anopheles mosquito, iii. be an obligate intracellular microorganism, iv. complete a life cycle resident in two diametrically different hosts, v. survives and thrives in two immunologically hostile environments (the human and the mosquito) from time immemorial, and vi. remain a pathogenic agent when other microorganisms that colonize the gut, the skin and other body cavities have adapted to be commensals. These parasitic traits allow the parasites to nature a non-fatal infection until the next generation progeny has been transmitted successfully from the human host to the vector and from the vector back to the human being. Both the substantive or definitive (main) host and the intermediate (vector) host provide an enabling environment for the parasite to orchestrate all it developmental stages such that specific parasite growth and development only are found in a particular host and not the other. Such a synchronized development denotes an evolutionarily coordinated genetic system which, of necessity, requires a symbiotic corporation from the entities that formulate its living environment, otherwise there is no reason why both the human being and the mosquito have been forced to be passive recipients of the parasitic aggression. Or is there an unrelenting coercion by the parasite that evades the immunological surveillance of both the human being and the mosquito? But to what end? Does the *Plasmodium* parasite serve any gainful advantage to both the mosquito's and human being's existence which both may exploit for their survival which has possibly been lost during evolutionary translations and transitions?

Malaria disease and human genetics: *P. vivax* and Duffy Blood Group

Certain blood group antigens and red blood cell (RBC) morphological and biochemical characteristics have been known to protect as well as predispose to malarial infection which could be genetic modifications and evolutionary selection pressure of the gene pool able to rebut the malarial onslaught. The Duffy (FY) glycoprotein is such a receptor for inflammatory biomarkers (chemokines) [1,2] and also for *P. vivax* parasites red blood cell invasion such that individuals that do not have the antigen Fy (a-b-) tend to be resistant to *P. knowlesi* and *P. vivax* infection since the invasion process requires at least one of the P. vivax Duffy Binding Protein (PvDBP) to be present [3]. The evolutionary selective pressure, therefore, will result in high populations numbers of Fy (a-/b-) null in areas of higher *P. vivax* prevalence. The ultimate scenario is that, the parasite with the widest geographical distribution in the world [4], presents a non-lethal infection at the expense of eradicating the human race [5-7]. Whether it is the parasite's acquired evolutionary to produce a non-fit strain that does not kill the host and commit self-parasiticidal action in the process or it is the host's ability to induce hypnozoites formation at the point that the parasitaemia may have reached peri-lethal levels is not very clear. What reactivates the hypnozoites to induce malaria again is not clear as well What is evident though is that there is a continuous and persistent malaria. Some have hypothesized that it is the host's production of certain proteins that reactivates the liver dormant stages [8] leaving the question what causes the body of the host to produce such proteins? It is suggested that the hypnozoite activates when it recognizes the same *Anopheles* specific protein, which it had previously recognized as a sporozoite to invade the salivary gland in the vector. In the same vein, it is also suggested that the deposition of certain proteins that are associated with the initial infecting sporozoites, by the vector, are recognized by the hypnozoites reactivating them into action [9], meaning that new bites from uninfected mosquitos signals a chance for transmission of the parasite. Another line of thought is that a febrile illness by the parasites or other associated disease my provide the trigger for relapses in *P. vivax* infection [10]. Also recently suggested is that *P. vivax* relapses are a result of the geographical setting directing their frequency with fast-relapses and slow-relapses in the tropics and temperate regions, respectively [11]. Some are also of the opinion that it is not the hypnozoites that cause relapse of *P. vivax* malaria but that they just facilitates ongoing infection [12] which really had not stopped but may have been contained due to establishment of a "war-free-zone" within the body. Overall, there seems to be some cross-talk that occurs between the parasite dormant forms, the geographical environment and the host that perpetuates the infectious cycle with an obvious advantage to the parasite survival [13] and some quite obscure benefits from infection to the human host. The possibility of the human host playing an innocent victim to the malaria infection, that has been the core of attention, seem not to sound true looking at the fact that the common pathophysiology that is perpetrated by parasite is usually in collaboration with host. However, treatment of malaria, first and foremost, has been targeted at the eradication or elimination of the parasite. Amelioration of the pathophysiology is usually taken as a secondary aspect of malaria complications.

Malaria Pathophysiology Maps out Malaria Disease

In general terms, a balance between the malaria parasite continuous life cycle execution and the human host's ability to contain and maintain a non-lethal infection, may formulate the bedrock of treatment and management of malaria by any parasitic agent. Regardless of the cause of the infection, there are common disease manifestations elicited by the infection to which there seems to be no evolutionary adaptations. Red blood cell invasion, invariable will result in RBC's haemolysis subsequently leading to severe malaria anaemia (SMA) with an accompanying erythrodysgenesis (reduced erythroid progenitors) with low reticulocytes counts and myeloid cells proliferation. Accompanying the parasitized RBC's (pRBC's) destruction is the 8-fold destruction of non-parasitized RBC's (npRBC's) that worsen anaemia. SMA sequelae manifests as reduced oxygen supply to vital organs, breathlessness, increased cardiac output leading to pulmonary hypertension and other complications. Malarial infection also tends to result in reduction in blood glucose levels (hypoglycaemia) and development of non-respiratory acidosis with hyperlactaemia. Aberrant inflammatory cascades are some of the underlining drivers of the disease, amplifying the infection periodicity-severity with each new and subsequent blood stage (merozoites) invasion.

Pathophysiology Removal Panacea for Malaria Disease?

Critical to these developments is the rollercoaster chain reaction of events, which, even in low or absent parasitaemia states, seem to unravel disease manifestations typical of malarial disease as long as there has been an activation of hypnozoites or infection. Therefore, would it be plausible to focus more on the elimination of the pathophysiology of the malarial infection, together with it attending presentations, than on the parasite per se as is common practice? By proscribing malaria pathophysiology, the parasitic activity on malarial disease may be of little effect. In malaria holoendemic areas, semi immunity is achieved after several mosquito bites even in people who have positive peripheral parasitaemia showing the possibility of living with the parasite and be malarial disease free. Inadvertently, a parasite infected environment with a disease-free establishment is displayed and could this be the naturally intended scenario gone afield? The Duffy (Fy a-/b-) null cited above does not preclude infection by the *P. vivax* parasite but forefends and protects against malarial disease development. This may show that, possibly the development of malaria disease is an unintentional occurrence resultant from some expunged human-malarial parasite symbiosis.

And the big question is can the purging of the malaria disease aspect from this eternal relationship restore the commensalism of the malarial parasite, if ever it existed before? The intestinal flora has a tendency towards pathogenicity when the gut environment is distressed. And does the malarial disease indicates an upset systemic milieu? Very much possibly so as certain external and internal changes and influences are thought to trigger relapses of malaria and that semi-immune status is possible.

If it is a given that there is a natural set-point where malarial parasites do not result in incipient malarial pathophysiology even in the presence of the parasite, how and why will the human body tolerate this setup? Research is emerging on the possibility of the malarial parasite playing sentinel overtures to the development of certain noncommunicable diseases like diabetes mellitus (DM). Malaria has been reported to induce hypoglycaemia in individuals with DM type 2 [14] suggesting a possible protective role of the infection to the calamitous new world disease. The malarial parasite has no capacity to utilize other carbohydrate sources of glucose like glycogen or starch and rely on the exogenous glucose supply through an exhibition of substantial increase in pRBC's membrane's permeability to glucose and utilization at 75 times more than the npRBC's [15]. The merozoite surface membrane protein, glycosylphosphatidylinositols (GPI), induces synthesis and expression of GLUT 1 transporters ubiquitously on many cell types increasing the uptake of glucose by several margins which results in reduced glucose and also mimics insulin signalling [16,17], which may be beneficial for the DM 2 patient if the exposure time can be managed. In a DM 2 individual, this may lower blood glucose levels drastically. Patients with DM 2 have also been shown to be more susceptible to *P. falciparum* infection [18] that may be explained by the readily available high plasm concentrations of glucose that allows for a rapid parasite population increase. However, the infection took longer to develop into a symptomatic malaria disease. Insulin resistance has been shown to be increased by malaria infection [19] showing possibly influence of the parasite, through inflammation induction, to increase reserve glucose for parasitic utilization. Malaria also has been reported to improve glucose homeostasis in humans [20].

Malaria and Diabetes Mellitus Type 2

The above shows that possibly the malaria parasite played a natural role in the development or control DM 2. The resultant fight against malaria, population movements and gene dilutions may have perturbed this natural phenomenon resulting in increased cases of DM 2 seen currently around the world. Malaria incidences are on the wane while DM 2 incidences are increasing. There is a possibility that malaria infection has a protective capacity in DM 2 through its propensity for blood glucose reduction. This may mean that treatment of malaria aimed at solving the pathophysiology of malaria, which is the main problem, may be an elixir to the disease than eradicating the parasite. If the parasite is prevented from causing malaria disease, which is possible and has been shown in malaria endemic areas, then living with the parasite may be beneficial. There seems to be little information on prevalence and on the influence of *P. vivax* malaria on

glucose homeostasis in DM 2. A low prevalence may mean that *P. vivax* infection may be protective against the DM 2. Where this assumption is true, treatment of the malaria pathophysiology may be the aim of current antimalaria treatment seeing that the malaria parasite rides on the ensuing disease to increase its chances of survival. The argument is that, without the malaria pathophysiology elicitation, there will not be malaria disease to talk about and the parasite's presence in the body may go unnoticed as happens with other commensals.

There have been some modicum indications that both the parasite and its ensuing pathophysiology may be terminated in animal models of malaria.

Anti-Malarial Disease Pentacyclic Triterpenes

A new paradigm on phytochemical pentacyclic triterpenes as antimalarial has been fostered as breaking new ground on the malaria pathophysiology eradication. A study by Mavondo., *et al*. (2016) showed that Asiatic acid, a pentacyclic triterpene from *Centella asiatica* displayed a strong prophylactic, suppressive and curative effect against malaria in Sprague Dawley rats [21,22]. The report indicated that a pre-infection asiatic acid administration of retarded parasitaemia induction, averted severe malaria development, reduced inflammation, avoided anaemia and maintained weight at a dose three times lower that commercial drug, chloroquine [21]. These studies have indicated that the removal of malarial pathophysiology resulted in the amelioration of the disease in an animal model confirming earlier reports anecdotal reports of the anti-*plasmodium* reports of triterpenes from different plant species. The glucose preservation of Asiatic acid in murine malaria has also been reported with subsequent food and water intake improvements [23] increasing the fact that forbidding of malaria pathophysiology results in highly susceptibility of malarial parasites to eradication. However, the actual mode of action of the triterpene is a subject of future research but sufficient grounds to assume the earlier stated facts and their association with eradication of malaria when the pathophysiological effect of the disease is compelling enough to assert the association.

The antidiabetic, anti-inflammatory and effect for pentacyclic triterpenes was also confirmed in China [24-26]. The pentacyclic triterpenes effects on metabolic disease and anti-parasitic activity makes a compelling synergism in the eradication of the pathophysiology of malaria creating an anti-disease approach to malaria which is poignantly set to provide a lasting panacea to the disease. One facet of the two-edged sword approach to malaria management, without the other, may compromise efficacy of the regimen. This has been experienced with other drugs like chloroquine (CHQ) which, while they eradicate the parasite, also induce side effects (e.g. hypoglycaemia) that compromises the body's ability to fight infection and invariably resulting in drug resistance. Removal of the pathophysiology (anti-disease aspect) while eradicating the parasite (anti-parasitic aspect) has the dual effect that allows the body to combat and protect against infection at the same time increasing the chances for successful malarial disease management. Ultimately, where the parasite may not be eradicated, abrogation of the malaria pathophysiology may still achieve the same results where the parasite is emasculated and rendered ineffective to commandeer and orchestrate a disease phenotype while resident in the human host. Continuation of its life cycle without causing disease in man, seems like the most balanced approach to combating this seemingly eternal disease agent as complete removal of the parasite from certain natural environment seem to through a natural coexistence of the parasite, the mosquito and the human being off balance which as has been seen with DM 2 rising incidences, may be catastrophic in the future generations.

Conclusion

While it may still be a long way to go, anti-disease approaches that target the pathophysiology of malaria, seem to offer the most effective way towards malaria disease eradication and elimination. Note, the target need be the eradication of the disease and not the parasite. Conversion of the parasite into a normal flora or commensal of the systemic circulation in the ambit of disease elimination proposes a safer approach than total elimination of the *Plasmodium* species as drug resistances by the parasite threatens the whole human population at present.

Just a thought!

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Conflict of Interest

The authors declare no conflict of interest in this work.

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