Role of Tumour Necrosis Factor (TNF) and Glycosylphosphatidylinositol (GPI) as Important Mediators in the Pathogenesis of Malaria Infection

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ABSTRACT

It has been shown from circumstantial and direct evidence that excess production of Tumour Necrosis Factor (TNF) in response to parasite toxins contribute to severe pathology and death in malaria infection. A study demonstrated that glycosylphosphatidylinositol (GPI) moieties covalently linked to the surface antigens of malaria parasites have the properties of such toxins, as the highly purified GPIs free of associated proteins are able to induce high levels of TNF and IL-1 from macrophages to cause pyrexia and cachexia in vivo. The GPI molecules linked to surface antigens of the parasite glycolipid toxins elicit several pathophysiological responses associated with acute severe malaria. This paper aims to review the effects of GPIs and TNF as mediators of pro-inflammatory and immunological mechanisms in the pathogenesis of malaria.

Key words: Glycosylphosphatidylinositol (GPI), Malaria Infection, Mediators, Pathogenesis, Tumour Necrosis Factor (TNF).

INTRODUCTION

Malaria infection is characterized by periodic fevers. These fevers, in Plasmodium falciparum and Plasmodium malariae (the tertian and quartan malaria respectively), arise through the synchronous release of parasite derived “toxins” during the 48 or 72-hour blood stage development. These in turn cause the release of endogenous pyrogens such as tumour necrosis factor (TNF) and interleukin-1 (IL-1) which mediate the febrile response by acting upon the hypothalamus. There is evidence suggestive of a role for TNF in wider spectrum of malaria associated disease, including severe clinical malaria, various malarial pathologies and even death. A case control study has shown a strong correlation between TNF and IL-1 levels in the sera of malarious individuals and the severity of the disease¹. Circulating TNF can also be detected at high levels in the sera of mice with lethal rodent malaria, the concentration increasing with parasitemia². The administration of recombinant TNF, in experimental models, mimicks a variety of the pathologies often associated with more severe malarial disease. These include anemia, hypertriglyceridemia, hypotension, accumulation of neutrophils in the pulmonary vasculature and diffuse intravascular coagulation³. The GPI molecules linked to surface antigens of the parasite are glycolipid toxins eliciting several pathophysiological responses associated with acute and severe malaria infection, including hypoglycemia and the excess production of TNF with attendant pyrexia and cachexia.
Effects of tumour necrosis factor and glycosylphosphatidylinositol toxin of malaria parasite

TNF contributes to cerebral malaria by upregulating expression of the endothelial cell marker in intracellular adhesion molecule 1, recognized by mature parasites during cerebral sequestration. The administration in vivo of specific neutralizing antibodies against TNF affords some protection to mice infected with lethal malaria. It has been reported that many of the syndromes that occur during the acute disease can also be induced experimentally by the administration of the endogenous pyrogens TNF and IL-1 and high levels of circulating monokines are found in association with the infection. Co-cultivation studies have shown that Plasmodium yoelii and Plasmodium berghei (both are rodent malaria parasites) can induce TNF formation from macrophages. Furthermore, boiled extracts of these parasites are able to induce high levels of TNF in the sera of mice sensitized with bacterial agents.

The GPI moieties are also insulin mimetic regulating glucose metabolism by adipocytes and inducing profound hypoglycemia in vivo. The study proposed that malaria parasite GPI molecules exert a pleiotropic influence on a variety of host cells when released during merogony or cell death; by substituting for the endogenous GPI-based second messenger/signal transduction pathways of the host.

Antigens expressed on the surface of asexual blood stage malaria parasites are major targets of antibodies elicited by exposure to infection. One of the best characterized surface antigens is the merozoite surface protein (MSP-1), a polymorphic protein synthesized during late schizogony. MSP-1\textsubscript{19}, the C-terminal product of secondary enzymatic processing of MSP-1, is the only fragment of this protein that remains anchored to the merozoite surface at the time of the erythrocyte invasion. The C-terminal region of MSP-1 is fairly conserved in both Plasmodium falciparum and Plasmodium vivax, but the sequence divergence between the MSP-1\textsubscript{19} homologs of Plasmodium falciparum and Plasmodium vivax is large enough to prevent significant cross-recognition between species.

MSP-1\textsubscript{19} is a major target of naturally acquired human antibodies that inhibit erythrocyte invasion by merozoites in vitro. Levels of naturally acquired anti-Plasmodium falciparum (PfMSP-1\textsubscript{19}) antibodies measured with conventional enzyme-linked immunosorbent assay (ELISA) have been positively associated with protection from Plasmodium falciparum infections, although not in all African cohorts.

A study showed evidence of an association between levels of antibodies to MSP-1\textsubscript{19} and reduced risk of clinical malaria. A cohort study suggests that the ability of naturally acquired anti-PfMSP-1\textsubscript{19} antibodies to inhibit merozoite invasion in vitro may be a better correlate of clinical immunity to malaria than the mere presence of antibodies measured by conventional ELISA. The prevalence and levels of antibodies to malaria surface antigens such as MSP-1\textsubscript{19} have been used not only as serological correlates of clinical immunity, but also as marker of cumulative exposure to malaria. The study suggests that naturally acquired IgG antibodies to PfMSP-1\textsubscript{19} performed better than those to other surface antigens (MSP-2 and apical membrane antigen 1) as a marker of malaria transmission intensity, but no attempt was made to compare antibody responses to antigens of other human malaria parasites prevalent in the same area.

The genetic polymorphism of merozoite surface protein 2 (MSP-2) of Plasmodium falciparum has been studied due to its applicability as a target for a malaria vaccine development and its putative association with antibody-mediated protection. A study previously identified polymorphic alleles from both MSP-2 families in Plasmodium falciparum isolates. A recent study evaluated the impact of antigenic diversity of repetitive and family dimorphic domains of the merozoite surface protein 2 (MSP-2) on immune response by ELISA using recombinant MSP-2 proteins.

A study sought to determine whether the malarial GPI is insulin mimetic. Mammalian glycosylphosphatidylinositol is proposed to be the second messenger mediating signal transduction in response to insulin. The purified GPI is sufficient to induce a five to six fold increase in both triglyceride lipogenesis and glucose oxidation by...
adipocytes. The sensitivity of mice to the lethal effects of TNF may be markedly increased by exposure to a variety of bacterial agents. This phenomenon has already been used to demonstrate the existence of TNF inducing agents in malarial extracts. The TNF mediated toxicity can be lethal in sensitized individuals. Parasite GPI molecules may also contribute to other forms of cellular dysfunction found in malaria infection such as the polyclonal activation of lymphocytes. The simplest explanation for above observations is that parasite GPI molecules exert an influence on host cells when released during merogony or cell death, by substituting for the endogenous second messenger/signal transduction pathway, which utilizes glycosylphosphatidylinositol and its derivatives to regulate protein kinase C and calcium levels. The demonstration that a single purified GPI species is strongly insulin mimetic substantially validates the proposed role of inositol phosphoglycans in insulin signal transduction. It should be noted, however, that the glycosylphosphatidylinositol of this type differing in polarity and hydrophilicity through the addition of ethanolamine and sugar groups may actually contribute equally or more, than GPI anchored membrane proteins to the pathophysiological response of the host when released during merogony or cell death. It has been postulated that the malaria GPI might also contribute to the polyclonal activation of lymphocytes as a mitogen or comitogen, the existence of which in malaria infections was originally proposed. It has been recently shown that immunization of mice with highly purified malaria GPI prepared from the mature MSP-2 led to a serological anti-GPI response with T-independent features. These anti-GPI sera were able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts. Although it is not possible to exclude the possibility that molecules unrelated to the GPI may also contribute to TNF induction and hypoglycemia in the in vitro response to infection, these data support the view that the GPI may be the dominant pyrogen/toxin of malaria parasites. There is the possibility that antibodies which neutralize the toxic activities of this molecule may be acquired after exposure to parasites and may mediate tolerance or acquired clinical immunity to disease. These antibodies are apparently T independent in nature, hence, any clinical immunity they might provide would wane fast in absence of re-infection, as is thought to be the case with clinical immunity to malaria. The question of the existence of an anti-toxic immunity to malaria has been reviewed. It is further argued, that the identification of the GPI molecule as a parasite toxin and the development of methods to measure an anti-GPI serological response should allow further experimental and epidemiological studies to assess the role of the GPI and anti-GPI antibodies in both the clinical response and clinical immunity to malaria infection. It should be possible, for instance in appropriately defined case-control studies to determine whether the hyperactive malarial splenomegaly and clinically severe or cerebral malaria syndromes are associated with states of physiological hyper-responsiveness to GPI, and correspondingly whether a condition of hypo-responsiveness is associated with the phenomenon of childhood “tolerance” to malaria.

In conclusion, the glycosylphosphatidylinositol (GPI) is a parasite toxin produced by Plasmodium falciparum, inducing the production of TNF and interleukin-1 (IL-1) by host macrophages. Thus, the neutralization of TNF induction and lipogenesis by anti-GPI antibodies may be invaluable in providing a rationale for the development of anti-glycolipid vaccine against malaria.

REFERENCES

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