IMMUNE RESPONSE AND THE MANAGEMENT OF MALARIA

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INTRODUCTION

Host immune response plays an important role in the manifestation, progression and resolution of several diseases including parasitic diseases, infections, arthritis, diabetes and allergies. Immune responses have been shown to play an important role in determining susceptibility to malaria attacks and response to treatment with antimalaria drugs. The contribution of host immunity to chemotherapy of malaria is underscored by the detection of sentinel cases of drug resistant infection in children below the age of 4 years and non-immune visitors to malaria endemic areas. Humoral and cellular immune response augment the schizonticidal activity of antimalaria drugs in the indigenous population, consequently, they are able to clear infections associated with parasites of low grades of resistance.

New information available in the last 20 years on immune responses to malaria and identification of several *P. falciparum* antigens has produced a better understanding of the disease, increased the prospects of developing a successful malaria vaccine and enhanced the introduction of new tools for malaria control. Today the contribution of immunology to the management of malaria has expanded to include:

- New perspectives in Malaria diagnosis through the use of rapid diagnostic tests.
- Better understanding of the pathogenesis of malaria and contribution of immune response to the severity of disease.
- Development of vaccines as cost effective tools for malaria control.

The anticipation of an effective malaria vaccine being developed is high especially among health care providers in endemic countries. With the rapid emergence of parasite multiple resistance to drugs, successful vaccine development represents one of the most promising strategies for a cost-effective method of malaria control in the future.

There are however other contributions of knowledge in immunology of malaria to global efforts to control the disease. An overview of these contributions is presented below:

Malaria diagnosis

Prompt and accurate diagnosis of malaria is an essential component of successful management of malaria. Clinical diagnosis based on the presence of clinical symptoms confirmed by the detection of asexual forms of malaria parasites in peripheral blood films is the most rational procedure for malaria diagnosis especially in areas where fever and other symptoms associated with malaria can also be attributed to other viral or bacterial infections. Unfortunately, reliable malaria microscopy is labour intensive, depends absolutely on good techniques, reagents, microscopes and well-trained and well-supervised technicians. These requirements are often difficult to meet in most malaria endemic areas especially at the primary health care level. Consequently, there are often long delays in providing microscopy with the result that decisions on treatment are often taken without the benefit of the laboratory results.

Rapid diagnostic tests based on knowledge of malaria immunity are now available. Improved test kits based on the same principle are at various stages of development and validation in several laboratories in the world including the Malaria Research Laboratory, College of Medicine, University of Ibadan. These tests are based on the detection of *Plasmodium* specific antigens in finger prick blood samples and permit rapid confirmatory diagnosis of malaria at the periphery of the health care system by health workers with minimal training. Antigens derived from malaria parasites in lysed blood are detected using immunochromatographic methods. In most cases, a dipstick or test strip impregnated with monoclonal antibodies directed against the target parasite antigens are used. The currently available tests are based on detection of two parasite antigens. The **Histidine rich protein II (HRP-II)** is a water-soluble protein produced by trophozoites and young (but not mature) gametocytes of *P. falciparum*. The second antigen **parasite lactate dehydrogenase (pLDH)** is produced by asexual and sexual stages of malaria parasites. The test kits currently available detect pLDH from all four *plasmodium* species. The can distinguish between *P. falciparum* species but can not distinguish between *P. vivax, P. ovale* and *P. malariae*. One added advantage of the test is the ability to detect infections normally undetectable by microscopic examination of a peripheral blood film when the parasites are sequestered in deep vascular compartment. Scientists in Cameroon have shown that the test is able to detect circulating HRP-II in women with placental malaria (confirmed by placental smears) even though the blood smears were negative due to sequestration of the parasites in the placenta.

These rapid diagnostic tests are simpler to perform and interpret compared with microscopy. In addition there is no requirement for electricity, special equipment and training as in microscopy. However, there are a number of factors currently limiting routine use of the procedure in endemic areas. For example *P. falciparum* HRP-II is still detectable up to two weeks following chemotherapy and clearance of parasitemia (false positive results). Unlike microscopy, currently available tests are not quantitative and are several times more expensive than microscopy. There are however on going studies to improve on the sensitivity, specificity and application of the technique.

Pathogenesis of malaria

The exact factors responsible for variations in susceptibility to and severity of malaria attacks in different individuals are not yet completely understood. However, there is strong evidence that host immune factors play a critical role in protection against

malaria attacks, resolution of illness and progression to severe and complicated malaria. In the last 10 years, scientific evidence have become available to indicate that cellular immune responses associated with $CD4^+$ cells of the immune system play important roles in the pathophysiology of malaria and protection against infection.

$CD4^+$ cells segregate into two main functional types of T helper cells (Th1 and Th2) producing either pro or anti inflammatory cytokines on stimulation. Cytokine mediated downstream immune responses have in turn been associated with innate resistance to malaria attacks and predisposition to life threatening malaria in man.

T cells mediate cellular immune responses through activation of macrophages (Th 1 response) or promotion of antibody formation (Th2 response). Elevated IgE levels associated with increased Th2 cell population and activity has been detected in cases of severe malaria. Stimulation of Th1 cells in response to malaria antigens result in secretion of interlukin 2 (IL2), interferon gamma (IFNg), tumour necrotic factor alpha (TNFa) and TNFb. These cytokine activate delayed hypersensitivity reactions and have been shown to play a role in pathophysiology of malaria. The deleterious effect of cytokines is however dependent on the concentration, type and relative ratios between the various cytokines produced by T cells in response to malaria infection. For example, increased levels of IFNg) have been associated with enhanced elimination of parasites, protection against reinfection and less severe clinical presentation of the disease. Low blood levels of TNF enhance parasite clearance by the host however in patients suffering from cerebral malaria, high level of TNF has been identified as one of the factors responsible for the pathophysiology of the complication. Elevated IL-10 has also been associated with faster parasite clearance and may prevent the development of severe anaemia by regulating TNF mediated responses.

Although the mechanism of the T cells response in the malaria is still being elucidated, information on this aspect of immunological response to malaria continues to provide new leads on pathophysiology of malaria, development of an effective vaccine and modalities for treating severe and complicated malaria.

Development of vaccines

Studies in experimental animal models and human volunteers have demonstrated that complete protection against malaria is possible through vaccination with attenuated sporozoites. Traditionally, live attenuated pathogens serve as immunogens in the most efficient vaccines; although this may become possible in the future, it is presently not a realistic option for the rapid development of malaria vaccines.

A vaccine is a substance that causes the immune system to develop responses that protect against a specific disease. An ideal vaccine would be:

- *safe;*
- *inexpensive;*
- *easy to administer; and,*
- *When administered in infancy, confer life-long immunity against all forms of the disease.*

This ideal is rarely achieved, and some of the currently available vaccines require booster doses or must be given repeatedly throughout life to maintain immunity (e.g. tetanus toxoid). In practice, most vaccines don't actually prevent infection with a disease organism, but instead enhance the immune system to limit the pathogen's ability to multiply once it invades. The vaccine stimulates antibody and T cell responses that can respond quickly to the infection and get rid of the invader before it causes serious clinical disease.

A successful malaria vaccine would not only block the development of the parasite early in its life cycle, but also provide immunity against the severe clinical consequences of unchecked infection with parasites that might escape this initial immune surveillance. Development of immune responses that limit the ability of the parasite to successfully infect large numbers of red blood cells is considered to be a very important goal for a malaria vaccine. Another approach being explored for the development of a vaccine is the transmission blocking vaccine. Ideally, a vaccine that blocks the transmission of malaria would be of great public benefit. However, there is little industrial support for this type of malaria vaccine simply because its relevance is only to poor countries where malaria is endemic; it does not reduce a person's chances of becoming infected, or reduce the severity of disease - as do the other types of malaria vaccine under development, which do have some industrial support for economic (it will protect tourists and travelers) and political (it will protect peace keeping forces) reasons.

Several antigens and sub units of polypeptides are currently being investigated by scientists world wide including a group in the Department of Zoology, University of Ibadan. One of the leading candidates is the *P. falciparum* Merozoite Surface Protein (MSP). Others include the Circumsporozoite Protein (CSP), Serine Stretch Protein (SERP), Erythrocyte Binding Antigen (EBA), *P. falciparum* Erythrocyte Membrane Protein (PfEMP) and Ring Erythrocyte Surface Antigen (RESA). One of the most difficult challenges facing the development of an effective malaria vaccine is the incredible genetic complexity of the parasite and the capacity to vary antigen expression at the different developmental stages. To surmount this barrier, it is likely that the malaria vaccines will comprise of subunits of various parasite antigens produced by peptide synthesis of recombinant DNA technology

Conclusion

The relevance of immunology to management and control of malaria is not limited to vaccine development alone. Rapid diagnostic tests based on knowledge of malaria immunology will greatly improve the diagnosis and management of the disease at all levels of the health care system. In addition, knowledge of the deleterious effect of host cellular immune response to infection is increasing and is contributing to development of better modalities for managing severe malaria. Critical data suggest that a malaria vaccine is feasible and much of the vaccine research worldwide focus on a safe inexpensive and effective methods for producing immunity against the disease.

Further reading

1. Howard RJ, Uni S, Aikawa M, Aley SB, Leech JH, Lew AM, Wellems TE, Rener J, Taylor DW (1986). Secretion of a malarial histidine-rich protein (Pf HRP II) from Plasmodium falciparum-infected

erythrocytes. J Cell Biol. 1986 Oct;103(4):1269-77.
2. Leke RF, Djokam RR, Mbu R, Leke RJ, Fogako J, Megnekou R, Metenou S, Sama G, Zhou Y, Cadigan T, Parra M, Taylor DW (1999). Detection of the *Plasmodium falciparum* antigen histidine-rich protein 2 in blood of pregnant women: implications for diagnosing placental malaria. J Clin Microbiol. Sep;37(9):2992-6.
3. Makler MT, Hinrichs DJ (1993). Measurement of the lactate dehydrogenase activity of *Plasmodium falciparum* as an assessment of parasitemia. Am J Trop Med Hyg. Feb;48(2):205-10.
4. Nwagwu M, Anumudu CA, Sodeinde O, Ologunde CA, Obi TU, Wirtz RA, Gordon DM, Lyon JA (1998). Identification of a subpopulation of immune Nigerian adult volunteers by antibodies to the circumsporozoite protein of *Plasmodium falciparum*. Am J Trop Med Hyg. May;58(5):684-92.
5. Oduola AM, Omitowoju GO, Sowunmi A, Makler MT, Falade CO, Kyle DE, Fehintola FA, Ogundahunsi OA, Piper RC, Schuster BG, Milhous WK (1997). *Plasmodium falciparum*: evaluation of lactate dehydrogenase in monitoring therapeutic responses to standard antimalarial drugs in Nigeria. Exp Parasitol. Nov;87(3):283-9.
6. Sarthou JL, Angel G, Aribot G, Rogier C, Dieye A, Toure Balde A, Diatta B, Seignot P, Roussilhon C (1997). Prognostic value of anti-*Plasmodium falciparum*-specific immunoglobulin G3, cytokines, and their soluble receptors in West African patients with severe malaria. Infect Immun. Aug;65(8):3271-6.
7. Troye-Blomberg M, Perlmann P, Mincheva Nilsson L, Perlmann H (1999). Immune regulation of protection and pathogenesis in *Plasmodium falciparum* malaria. Parasitologia. Sep;41(1-3):131-8. Review.
8. World Health Organization (2000). Malaria transmission blocking vaccines: An ideal public good. TDR / RBM/ MAL/VAC/2000.1
9. World Health Organization (2000). Malaria diagnosis – New perspectives. WHO/CDS/RBM/2000.14.