The pathological bases of immunomodulatory therapy in malaria

M.I. Muniz-Junqueira, C.E. Tosta

Laboratory of Cellular Immunology, Pathology, Faculty of Medicine, University of Brasilia, 70.910-900, Brasilia, DF, Brazil.
Corresponding: M.I. MUNIZ-JUNQUEIRA, address above.
e-mail: mimjunqueira@unb.br

Abstract/Résumé

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Objectives. The objectives of this review are an attempt to analyse the potential bases for immunomodulary therapy in malaria. Malaria is a major cause of suffering and death and one of the most important problems of public health in vast areas of the world, mainly due to the severe forms of *Plasmodium falciparum* infection.

Epidemiology. According to the World Health Organization, it is currently estimated that a total of 350 to 500 million clinical cases occur annually, which cause something between 1.1 and 1.3 million deaths every year.

Pathogenesis. The hyperactivation of the immune system, with enhanced production of cytokines, mainly TNF, has an important role in the complex pathogenesis of the disease. Enhanced sequestration of parasitized erythrocytes within the small vessels of major organs is a central feature of *P. falciparum* infection. The increased production of pro-inflammatory cytokines and nitric oxide, followed by the up-regulation of endothelial cell adhesion molecules, influences the progression of cerebral lesions.

Immunomodulation. Therefore, different approaches have been attempted to downmodulate the hyperactive immune system in malaria, including the administration of cytokines or anti-cytokine antibodies, antibodies against molecules of adherence, drugs that reduce the excessive synthesis of reactive oxygen species, and drugs with pleiotropic action on the immune system. The impact of these immunomodulatory therapies on the course of malaria has reached variable success.

Application. We submitted this subject to a critical assessment and it was proposed ways to take advantage of immunomodulatory drugs, associated to anti-parasite therapy, to reduce the morbimortality of malaria.

Key words: Immunomodulation, therapy, malaria, cytokines, tumor necrosis factor, cerebral malaria, immunopathogenesis, pentoxifylline, thalidomide, sequestration, nitric oxide, reactive oxygen species.

Les bases pathogéniques pour l'immunothérapie du paludisme

M.I. Muniz-Junqueira, C.E. Tosta

Objectifs. L'objectif de cette étude est d'analyser les bases potentielles de l'immunothérapie du paludisme. Cette maladie est en effet une cause majeure de souffrances et de décès dans le monde, notamment dans les formes sévères dues à *Plasmodium falciparum.*

Épidémiologie. Selon l'Organisation Mondiale de la Santé (OMS), l'estimation du nombre annuel de cas serait de 350 à 500 millions de cas cliniques, avec environ 1,1 à 1,3 millions de morts chaque année. L'hyperactivation du système immun s'accompagne d'une production accrue de cytokines, principalement le TNF, ce qui joue un rôle important dans la pathogénie complexe de cette maladie.

Pathogénie. La séquestration accrue des érythrocytes, parasités à l'intérieur des petits vaisseaux des principaux organes, est le facteur central de l'infection à *P. falciparum*. La production augmentée de cytokines pro-inflammatoires et d'oxide nitrique est suivie de régulation accrue des molécules d'adhésion aux cellules endothéliales ; ce processus influence la progression des lésions cérébrales.

Immunomodulation. Plusieurs approches ont tenté une approche immunomodulatrice en diminuant l'hyperactivité du système immun dans le paludisme : l'administration de cytokines ou d'anticorps anti-cytokines, d'anticorps anti-molécules d'adhérence, de médicaments qui réduisent la synthèse excessive d'oxygène réactif de cette espèce, et enfin des drogues avec une action pléio-

Introduction

The superlative figures concerning the prevalence of malaria in the world pose tremendous challenges related to its treatment and control. How to avoid that 350 to 500 million people, mainly children, fall ill and 1.1 to 1.3 million of them die every year [1] victimized by malaria? Moreover, the widespread and growing problem of antimalarial drug resistance imposes further difficulties: there is a need to adopt a broad therapeutic arsenal to allow drug associations and to cope with the different phases of the vital cycle of malaria parasites.

The present treatment of malaria relies on the association of anti-parasite drugs together with appropriate clinical support. However, mortality rate of those with severe disease remains intolerably high. Although only 1-2% of infected people develop severe malaria, the high prevalence of the infection results in over 3 million cases, and nearly half of them would die [2]. The reasons for this high mortality rate include several factors such as the delay to start treatment, the inadequacy of clinical support, and lack of access to proper therapy [3, 4]. However, death of malaria patients may occur in spite of appropriate anti-parasite therapy and adequate medical support. Why this occurs is not completely understood, but the fact that patients may die even after malaria parasites were cleared from the blood indicates that some other factor is operating. In fact, it is presently recognized that anaemia [5], and the involvement of the brain [6], kidney [7] and lung [8], which characterize severe and complicated malaria, have all some important components of the immune sys-

trope sur le système immunitaire sont les principaux axes de recherche. L'impact de ces thérapeutiques immunomodulatrices au cours du paludisme a atteint des résultats variables.

Applications. Nous avons soumis ces données à une évaluation critique et d'autres voies d'utilisation des moyens de l'immunomodulation associées aux thérapeutiques anti-amariles pourront réduire la morbi-mortalité du paludisme.

Mots-clés : Immunomodulation, thérapeutique, paludisme, cytokines, TNF, malaria cérébrale, immunopathogénèse, pentoxifylline, thalidomide, séquestration, oxide nitrique, oxygène réactif d'espèces.

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tem associated to their pathogenesis [9]. A common feature of the severe complications of malaria is the uncontrolled activation of the immune system. Therefore, the adoption of therapies capable of controlling the untoward immune responses would be beneficial in the sense to reduce the severity of the clinical-pathological manifestations of malaria and improve the prognosis of the patients. Striking improvements in the understanding of the pathogenesis of the disease have prompted to try immunomodulatory therapies. However, although hopeful in a theoretical basis, definite success has not so far been achieved in clinical trials. This review aims at critically analyse the causes of these unsuccessful results, and also to point to some novel features of the immunopathogenesis of malaria capable to improve the approach to the challenge of immunomodulation.

Immunopathogenesis of severe malaria

The clinical patterns of malaria depend markedly on the age and the previous immunological experience of the host.

HYPERACTIVATION OF THE IMMUNE SYSTEM

The hyperactivation of the immune system by parasite components, with overproduction of inflammatory cytokines, is decisive for the pathogenesis of severe malaria [10, 11]. Molecules of *Plasmodium* merozoite surface induce expression of many genes of host cells that are implicated in malaria pathogenesis, as tumour necrosis factor (TNF), interleukin-1 (IL-1), IL-12, inducible nitric oxide synthase, and several adhesion molecules that are expressed on the surface of the vascular endothelium and are recognized by *P. falciparum* EMP1 molecule [12, 13]. The activation of macrophages by interferon-γ (IFN-γ), produced mainly by CD4+ T lymphocytes [14] further increases TNF production by increasing TNF mRNA levels, and upregulates TNF receptors on the target cell surface [15].

Both TNF and IFN-γ have antiplasmodial effects and are associated with the benign forms of malaria. However, if these cytokines are overproduced, or if they act on hyper-reactive endothelial cells, they may play a role in the pathogenesis of severe complications of malaria, as anaemia, lung and cerebral involvement [15, 16].

A central feature of *P. falciparum* infection is the sequestration of parasitized erythrocytes within the small vessels of major organs, mainly brain and lungs. The exacerbated sequestration is a direct consequence of the imbalance of cytokines, mainly overproduction of TNF. This cytokine increases the expression of molecules of adherence in endothelial vessel wall, and consequently enhances the sequestration process and increases the severity of the disease [17].

CEREBRAL MALARIA

This is the consequence of the local patchy involvement of cerebral capillaries and postcapillary venules. The process starts by the adherence of *P. falciparum*-parasitized erythrocytes to endothelial cells and to other erythrocytes. This sequestration may interfere with the local cerebral blood flow and, therefore, facilitates the crowd of leucocytes, which are activated by parasite products released during local multiplication of the parasite [18]. The local production of pro-inflammatory cytokines by activated monocytes and macrophages, particularly TNF, and of nitrogen and oxygen species, leads to activation of the endothelial cells and, eventually, to their own damage and damage of nearby cells [6]. Following activation, endothelial cells increase the production of nitric oxide and the expression of ad-

Glossary

Adhesion molecules
They are cell surface molecules whose function is to promote adhesive interactions with other cells or the extracellular matrix. Leukocytes express various types of adhesion molecules, such as selectins, integrins and members of the Ig superfamily, and these molecules play crucial roles in cell migration and cellular activation in innate and adaptive immune responses.

CBA
It is an inbred mouse strain susceptible to cerebral malaria, when infected with *Plasmodium berghei* ANKA. It is widely used as an experimental model of cerebral malaria.

ICAM-1 (CD54)
It means intercellular adhesion molecule-1. It is an adhesion molecule expressed on endothelial cells, B lymphocytes, and monocytes, usually induced by cytokines. Its major function is to promote cell-cell adhesion. It is the ligand for LFA-1.

Inbred mouse strain
A strain of mice created by repetitive mating of siblings that is characterized by homozigosity at every genetic locus. Every mouse of an inbred strain is genetically identical (syngeneic) to every other mouse of the same strain.

Integrins
They are cell surface proteins whose major function is to mediate the adhesion of leukocytes to other leukocytes, endothelial cells, and extracellular matrix proteins. Integrins are important for T cell interaction with antigen presenting cells and for migration of leukocytes from blood to tissues.

LFA-1(CD 11a plus CD18)
It means leukocyte function-associated antigen-1 and is a β_2-integrin expressed in T lymphocytes and phagocytes.

VCAM-1(CD 106)
It means vascular adhesion molecule-1 and is an adhesion molecule expressed mainly on endothelial cells, macrophages, follicular dendritic cells, and bone marrow stromal cells. It is a receptor for VLA-4 (very late activation protein-4) integrin. Its main role is in lymphocyte trafficking and activation.