Mast cells promote malaria infection?

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ABSTRACT

Purpose: Malaria remains the most deadly human parasitic disease, mostly because of the mosquito-born protozoan parasite *Plasmodium falciparum* with ~627,000 deaths reported in 2012. Unfortunately, there is resistance to most drugs, and successful vaccines are still not developed. The role of the immune system is critical but poorly understood.

Methods: One specific publication that reported a new way through which the immune system may promote malaria pathogenesis is discussed.

Findings: Kenyan children with mild and severe malaria had increased plasma levels of the Flt3 ligand, a soluble cytokine released from the surface of mast cells (MCs). A positive correlation was found between disease severity and frequencies of circulating BD $CA3^+$ dendritic cells. These human equivalents of the rodent $CD8^+$ T cells migrate to tissues with a heavy parasite load and cause damage primarily through cytolysis.

Implications: Malaria parasites may promote malaria pathogenesis by triggering MCs, which expand a unique class of dendritic cells with the subsequent activation of pathogenic $CD8^+$ T cells. However, MCs may have additional regulatory functions. Selective inhibition of MC activation may serve as an adjuvant treatment. (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮) © 2015 Published by Elsevier HS Journals, Inc.

Key words: Flt3l, immunity, infection, malaria, mast cells, T cells.

INTRODUCTION

Malaria remains the most deadly human parasitic disease mostly because of the mosquito-born protozoan parasite *Plasmodium falciparum*. The World Health Organization[1] estimates that ~627,000 people died of malaria worldwide in 2012, of whom 482,000 were children, or one child dying every minute mostly from severe anemia or brain disease. The role of the immune system in the pathogenesis of malaria is critical, but poorly understood. Both allergic and nonallergic immune responses may regulate malaria pathogenesis.[2,3]

DISCUSSION

Guermonprez et al used mice infected with the rodent *Plasmodium chabaudi chabaudi* clone AS a model of nonlethal infection that develop antiparasitic T cells, and mice infected with *Plasmodium berghei* ANKA then developed a lethal infection that involves immune-mediated pathology through $CD8^+$ T cells. The investigators reported that malaria parasites may affect pathogenesis of the disease by triggering mast cells (MCs), which expand a unique class of dendritic cells (DCs) with the subsequent activation of pathogenic $CD8^+$ T cells.[4] These DCs, which in mice express the membrane receptors CD8α and in humans the BDCA-3, are expanded by Flt3 ligand (Flt3l), a soluble cytokine released from the surface of MCs. Apparently, antigen-presenting cells recognize *Plasmodium* DNA–hemozoin complexes and release type I interferon, which increases production of xanthine dehydrogenase mostly by endothelial cells in parasite-infected tissues such as the lung. This enzyme then acts on xanthine and hypoxanthine, generated and secreted from ruptured infected erythrocytes, to convert them into uric acid crystals, which stimulate MCs

Accepted for publication March 10, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.03.014
0149-2918/$ - see front matter

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to release Flt3l through activation of the surface high-affinity immunoglobulin E (IgE) receptor.[4]

Interestingly, in the case of *P chabaudi* AS non-lethal infection, the $CD8^+$ T cells decreased parasite growth, whereas in the case of the lethal *P berghei* ANKA infection, which reflects some aspects of severe human malaria, these $CD8^+$ T cells promoted disease.[4]

Guermonprez et al[4] also examined Kenyan children with mild and severe malaria and found a positive correlation between plasma levels ofFlt3 and disease severity and frequencies of circulating $BDCA3^+$ DCs. These human equivalents of the rodent $CD8^+$ T cells migrate to tissues with a heavy parasite load and cause tissue damage primarily through cytolysis.[4]

Mosquito saliva can trigger dermal MCs,[5] but this action led to secretion of MC-derived macrophage inflammatory protein 2 and increased interleukin (IL)-10 expression in the lymph nodes, leading to downregulation of the immune response.[6] Genetic polymorphism to these saliva components, as found in Ethiopian versus Tanzanian children, further make definitive conclusions difficult.[2] Nevertheless, MCs may also have a protective role against parasitic infections.[7–9] In particular, malarial peroxiredoxin triggers tumor necrosis factor (TNF) release from MCs through a non-IgE mechanism and decreases parasitemia in mice.[10] Remarkably, MCs are the only cell type that stores preformed TNF in their secretory granules, and once released it can activate T cells.[11,12]

Cerebral malaria involves trapping of infected erythrocytes in the brain microvasculature; it was therefore of interest that vascular endothelial growth factor (VEGF) was increased in patients with cerebral malaria compared with healthy adults, and it was found that malarial parasite antigens induced VEGF secretion from human MCs.[13] Treatment of human brain microvascular endothelial cells with serum from patients with severe falciparum malaria greatly increased the expression of substance P mRNA.[14] These findings may be important because IL-33 was also significantly elevated in infants infected by *P falciparum* compared with infection-free controls,[15] and IL-33 was

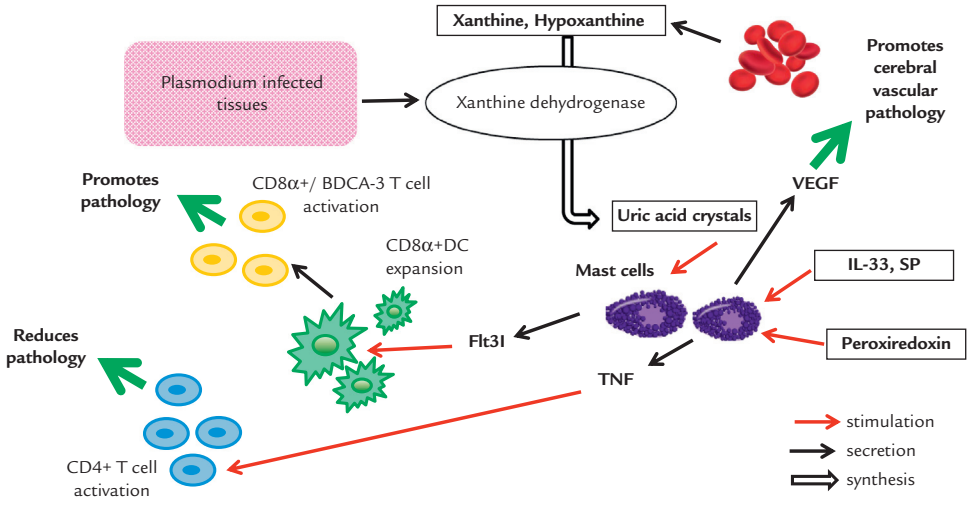

Figure. Diagrammatic representation of the potential role of MCs in malarial infection. Uric acid crystals trigger release of surface Flt3l from MCs, expanding $CD8\alpha^+/BDCA3^+$ DCs, which promote the development of pathogenic $CD8^+$ T cells. In contrast, stimulation of MCs by IL-33 and SP triggers release of VEGF which promotes cerebral pathology. MC stimulation by other triggers such as peroxiredoxin lead to release of TNF, which can stimulate $CD4^+$ T cells and reduce infection. DC = dendritic cell; Flt3l = Flt3 ligand; IL = interleukin; MC = mast cell; SP = substance P; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

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