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Review

Immunoglobulin M: Restrainer of Inflammation and Mediator of Immune Evasion by *Plasmodium falciparum* Malaria

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Immunoglobulin M (IgM) is an ancient antibody class that is found in all vertebrates, with the exception of coelacanths, and is indispensable in both innate and adaptive immunity. The equally ancient human malaria parasite, *Plasmodium falciparum*, formed an intimate relationship with IgM with which it co-evolved. In this article, we discuss the association between IgM and human malaria parasites, building on several recent publications that implicate IgM as a crucial molecule that determines both host and parasite survival. Consequently, a better understanding of this association may lead to the development of improved intervention strategies.

The Antibody Response to Malaria

Antibodies are an important component of protective immunity to *Plasmodium falciparum* malaria [1]. Natural exposure to infection by these parasites drives strong antibody responses to several parasite asexual blood-stage antigens that are responsible for causing clinical disease. This is in contrast to antigens expressed by the pre-erythrocytic and gametocyte stages which do not generally induce protective antibodies following natural exposure to the parasites [2]. The asexual-stage antigens targeted by antibodies include merozoite surface molecules involved in erythrocyte invasion [3], and antigens expressed on the surface of infected erythrocytes (IEs) [4]. The latter antigens, and in particular members of the clonally variant PfEMP1 (*P. falciparum* erythrocyte membrane protein-1) family, mediate IE adhesion to host endothelial receptors and play a key role in parasite evasion of host immune responses [5].

Most studies have focused on how antibodies interfere with erythrocyte invasion or IE sequestration, or how they act as opsonins (see **Opsonization** in the Glossary) for **phagocytosis**, antibody-mediated cellular inhibition, and complement-mediated elimination of *Plasmodium* [6–8]. The great majority of these studies have focused almost exclusively on IgG, despite the fact that **immunoglobulin M** (IgM) is superior at triggering specific effector functions that are required for efficient pathogen elimination. For example, a single molecule of IgM can trigger complement-mediated lysis of an IE, something that would need 1000 IgG molecules [9,10].

We wish to highlight here recent research that is shedding light on the importance of IgM in malaria immunity, and point to outstanding research gaps that ought to be addressed. For a

Trends

IgM is an important class of serum antibody that mediates the clearance of apoptotic and altered cells through complement-dependent and -independent mechanisms.

IgM mediates protection against infection and may play an important role in controlling *Plasmodium falciparum* malaria.

IgM provides new routes to more effective drugs and vaccines.

Fcμ-binding proteins expressed on the surfaces of both infected erythrocytes and merozoites facilitate immune evasion through diverse mechanisms.

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review of the basic biology of IgM, we refer the reader to some of the several excellent reviews available [11–13].

IgM: The Basics

IgM (Box 1) exists as membrane-bound monomeric receptors on B cells and as secreted molecules in plasma at concentrations of 1–2 mg/ml. Secreted IgM molecules are predominantly pentamers and hexamers, which provides soluble IgM with extraordinary functions, including multivalent binding to antigens, receptors, and complement [14,15]. Non-immune

Box 1. The Structure and Function of Human IgM

Human IgM is a pentamer of a basic four-chain structure (monomeric unit) with a mass of ~970 kDa (Figure I), although it can also exist as a hexamer without the J chain with a molecular mass of ~1132 kDa. Hexameric IgM conveys increased avidity for the binding of both antigen and Fc receptors. As with all secreted antibodies, one part of the molecule (the Fab domains) binds to the pathogen, while the other part (the Fc portion) interacts with cells of the immune system via Fc and glycan receptors (see text for detail). A transmembrane monomeric form of IgM is also present as an antigen-specific receptor on mature B cells.

Human IgM is present at ~1–2 mg/ml in blood with a half-life of ~5 days [11]. It has been reported that IgM levels are higher in females than in males [114,115]. Numerous studies have identified a role for immune and non-immune IgM in the protection against numerous viral, bacterial, fungal, and parasitic infections [11].

The Cμ4 domain appears to be particularly important in binding to DBL domains (see text, shown in dark red on the model of IgM in Figure I [14]). In the Cμ4 domain there are three reported allotypes of human IgM (www.imgt.org). Two of these contain the insertion of an extra valine, and the other has an aspartic acid to glutamic acid substitution. Both these variants are found within the critical region proposed for binding to DBL domains [15]. This suggests inter-individual variation in IgM-mediated immune mechanisms against malaria parasites.

The *N*-linked glycans on IgM contribute 12% of the molecular weight (as against 2–3% for IgG) but surprisingly their role in the interaction of IgM with either DBL domains or Fcμ-receptors has not been investigated.

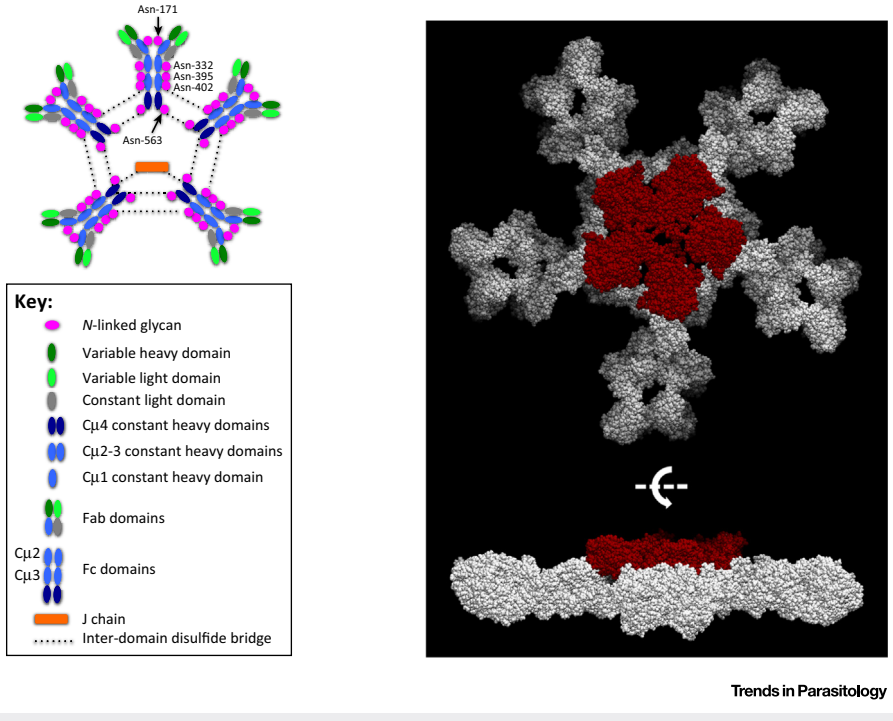

Figure I. Human IgM Structure.

Glossary

Apoptosis: the biochemical process of programmed cell death (PCD) that occurs in multicellular organisms, leading to characteristic cell changes and death. Apoptotic cells are cleared by IgM and complement activation.

Autophagy: a process whereby cells degrade intracellular components to promote their own survival in response to cellular stress.

Complement activation: biochemical pathways that have evolved to label pathogens and/or apoptotic cells for elimination. The classical pathway links to adaptive immune systems through IgM. The alternative and lectin pathways provide antibody-independent 'innate' immunity, and the alternative pathway is linked to and amplifies the classical pathway.

Dendritic cells: leucocytes that sense tissue injury, capture antigens, and present those antigens to T lymphocytes to induce immunity to foreign antigens and enforce tolerance to self-antigens.

Fragment crystalline (Fc) constant region: the portion of an antibody responsible for binding to immunoglobulin receptors on cells and the C1q component of complement.

Fc receptor: a membrane-anchored or soluble glycoprotein that binds to the Fc constant region of antibodies.

Fragment antigen (Fab): the part of an antibody molecule which contains the antigen-combining site, consisting of a light chain and part of the heavy chain; it is produced by enzymatic digestion.

Galactose-α-1,3-galactose (αGal): a carbohydrate found in many organisms. It is not found in primates and humans whose immune systems recognize it as foreign and produce xenoreactive IgM antibodies to it. These can lead to organ rejection after transplantation.

Immunoglobulin M (IgM): the first antibody produced in a primary immune response and that is largely confined to the intravascular pool. It is frequently associated with the immune response to antigenically complex, blood-borne infectious organisms. IgM is the most efficient activator of complement.

Intravenous immunoglobulin (IVIg): a therapeutic preparation containing polyvalent IgG and/or IgM