Naturally Acquired Antibodies against Malaria

Subjects: Infectious Diseases

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Here, we discuss naturally acquired antibodies in malaria, and the potentially harmful or beneficial effects of them.Most studies have focused on the inhibitory effect of antibodies, but we review both the beneficial as well as the potentially harmful roles of naturally acquired antibodies, as well as autoantibodies formed in malaria. We discuss different studies that have sought to understand acquired antibody responses against P. falciparum antigens, and potential problems when different antibodies are combined such as in naturally acquired immunity.

Keywords: malaria ; Plasmodium falciparum ; immunity ; antibodies

1. Introduction

Antibodies are important for naturally acquired immunity against malaria. These antibodies can exert their effector functions by simple binding (steric hindrance), complement activation, cellular cytotoxicity, and opsonophagocytosis. Plasmodium falciparum elicits antibody responses against many of its protein components, but there is also formation of antibodies against different parts of the red blood cells, in which the parasites spend most of their time. Despite the fact that the malaria parasite presents a number of antigens to the immune system, which has the ability to generate a substantial variability in the production of antibodies, most people living in endemic regions are still not able to maintain high levels of effective antibodies for a long period of time unless repeatedly exposed to the parasites. The presence of atypical memory B cells could be one of the reasons for the immune inefficiency.

2. Examples of issues when measuring antibodies at merozoite stage

Merozoite surface protein 1 (MSP1) is the most abundant protein on the merozoites and plays an important role in erythrocyte binding and invasion. Some studies have found correlations between anti-MSP1 antibodies and protection against clinical symptoms, while others have not. Anti-MSP1 antibodies have been shown to inhibit erythrocyte invasion, enhance monocyte-mediated phagocytosis of parasites, and aid in complement fixation [1][2][3]. MSP1 is produced as a 196-kDa precursor that undergoes a two-step proteolytic processing essential for both egress and invasion. There is evidence for the existence of naturally acquired antibodies that block this important proteolytic processing of MSP1 [4], called processing inhibitory antibodies, but it is interesting to note that the same study also found antibodies that could interrupt the binding of the processing inhibitory antibodies. Thus, any protective advantage that may be associated with interrupting the MSP1 proteolytic process could also be abrogated by these blocking antibodies, because they target the same epitope. This is one of the few studies that have elegantly shown that antibodies can be beneficial not only for the human, but also for the parasite. Binding of blocking antibodies to the epitope in the presence of processing inhibitory antibodies would ensure the parasite full proteolytic processing of MSP1 and thus a proper invasion of RBCs. Most studies in the field of malaria have focused on finding the antibodies that inhibit the parasites, since these antigens could be potential vaccine targets, but we should probably put more emphasis on showing those results that could also be beneficial for the parasites. Having antibodies that can be both good and bad could be one of the explanations for why no malaria vaccine has yet proven to be fully successful. We have ourselves, for example, shown that inhibitory results can be severely affected depending on which parasite line of *P. falciparum* is used for the experiments [5]. When purified plasma samples (containing mostly antibodies) from endemic areas of Tanzania were used in growth inhibitory assays, parasite-specific antibodies in most samples inhibited the growth of 3D7 and K1 *P. falciparum* lines, but when W2mef was used, the growth was actually enhanced, sometimes as much as 25–50%. It is well established that in endemic areas, many different parasites circulate and if antibodies are produced naturally that can enhance the growth of parasites, this is an efficient way for parasites to avoid getting cleared by the human immune system and this should be studied more in detail. It is also known that parasites can vary their invasion pathways to evade inhibitory antibodies [6] and there is evidence that an increase in the growth of parasites can be obtained when naturally acquired antibodies from some individuals are added to *P. falciparum* parasites in vitro [7]. For other pathogens such as the parasite *Leishmania* or viruses like Zika and Dengue, it has been shown that antibody-mediated responses involving the complement or FcR

pathways do not always lead to protection or reduced infection, but can sometimes be exploited by these pathogens for enhanced invasion of host cells [8]. This phenomenon is known as antibody-dependent enhancement (ADE) and it is not clear whether *P. falciparum* could also use this mechanism to enhance hepatocyte or erythrocyte invasion. A study suggested that this could definitely be possible, since a monoclonal antibody obtained from $MSP1_{42}$ vaccines enhanced parasite invasion and polyclonal IgG enhanced invasion in a complement-dependent manner [9].

3. Examples of Autoantibodies at the blood stage

Autoantibodies targeting different human cellular components have been associated with P. falciparum infections in endemic areas. Autoantibodies can be directed against membrane phospholipids [10][11][12], erythrocyte membrane proteins [13][14], or DNA [14]. During an acute episode of malaria, it is quite common to become DAT (Direct Antiglobulin Test)-positive, a sign that there are autoantibodies bound to RBC. This can later disappear, even though studies have found around 5% of an apparently healthy adult population in Kenya and Thailand to be DAT-positive [15][16]. Another study has shown a relationship between DAT-positivity and acquired protective immune responses against malaria [17], indicating that these antibodies could have a protective effect.

Not much is known about the mechanisms through which autoantibodies are generated in malaria infection, but it has been suggested that the expression of parasite proteins such as PfEMP1 on erythrocyte membranes could be an initiation step. For instance, a genome-wide study [18] found that PfEMP1 shares a 14-amino acid motif with a human serum protein, vitronectin. This creates a molecular mimicry pathway for autoantibody generation during a normal immune response directed against PfEMP1.

Autoantibodies could also be generated against components such as phosphatidylserine (PS), which is a membrane phospholipid not normally exposed, since it is a resident of the plasma membrane inner leaflet, but it is exposed when the erythrocyte ruptures. Autoantibodies targeting DNA and other cytoplasmic components could be a form of homeostatic response to mop up cellular fragments, or debris produced during erythrocyte rupture that accompany blood-stage infection, or are generated by oxidative damage associated with antimalarial drug use [19]. If this is the case, then these antibodies will not have any protective effect against future P. falciparum infections. On the contrary, they could instead do more harm than good. Autoantibodies have been shown to aggravate malaria pathology by inducing cell lysis, microthrombosis, and inflammation [20]. A recent study demonstrated a clear correlation between kidney injury and autoantibodies against DNA and PS in Ugandan children with severe P. falciparum malaria [21]. Anemia, a major symptom of malaria, has also been shown to be associated with anti-PS antibodies [11][21][22]. However, there are also autoantibodies that could be associated with protection against malaria, as found in a Liberian population where antibodies targeting Band 3 neoantigens were found [23], and sera obtained from autoimmune patients could have similar effects [24]. Anti-Band 3 (neoantigen) antibodies correlated with lower parasite density and higher hematocrit [23][25], suggesting a possible role in protection against malaria, even though the correlation could also just be a result of exposure, since the neoantigens are not naturally exposed when there is no malaria. However, it is interesting to note that during the recent years, it has been speculated that having malaria is protective against certain autoimmune diseases such as systemic lupus erythematosus (SLE), and sera of patients with SLE has been shown to inhibit in vitro the growth of P. falciparum [26].

4. Conclusion

The ability of malaria parasites to complete their life cycle despite the abundance of antibody attacks is probably a high level of evolutionary success with a win–win situation between the human host and the parasites. Antibody responses are able to protect the host enough for the host to survive, but not enough to kill the parasites; thus, parasites can survive in low numbers and be transmitted to a new host. The field of malaria research where combinations of antibodies with different specificities are used together needs more focus in future studies to elucidate what happens in real life in a human being during the development of natural immunity against malaria.

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