Article

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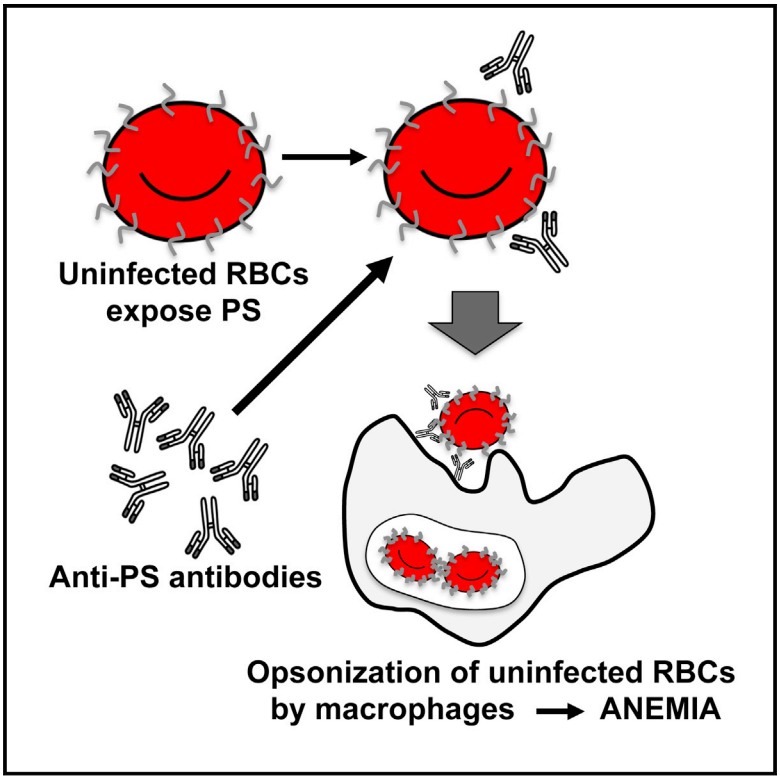
Anti-Self Phosphatidylserine Antibodies Recognize Uninfected Erythrocytes Promoting Malarial Anemia

Graphical Abstract



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In Brief

Fernandez-Arias et al. demonstrate that anti-self antibodies recognizing phosphatidylserine are generated during malaria and bind to noninfected erythrocytes in mice. Anti-phosphatidylserine antibodies facilitate clearance of noninfected erythrocytes and contribute to anemia. These antibodies are also found in human malaria patients and correlate with the peak of postmalarial anemia.

Highlights

- During mouse malaria, anti-phosphatidylserine antibodies bind to uninfected erythrocytes
- Anti-phosphatidylserine antibodies mediate phagocytosis of uninfected erythrocytes
- *P. falciparum*-infected humans with late anemia have anti-phosphatidylserine antibodies
- Anti-phosphatidylserine antibodies contribute to anemia in mice

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Anti-Self Phosphatidylserine Antibodies Recognize Uninfected Erythrocytes Promoting Malarial Anemia

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SUMMARY

***Plasmodium* species, the parasitic agents of malaria, invade erythrocytes to reproduce, resulting in erythrocyte loss. However, a greater loss is caused by the elimination of uninfected erythrocytes, sometimes long after infection has been cleared. Using a mouse model, we found that *Plasmodium* infection induces the generation of anti-self antibodies that bind to the surface of uninfected erythrocytes from infected, but not uninfected, mice. These antibodies recognize phosphatidylserine, which is exposed on the surface of a fraction of uninfected erythrocytes during malaria. We find that phosphatidylserine-exposing erythrocytes are reticulocytes expressing high levels of CD47, a "do-not-eat-me" signal, but the binding of anti-phosphatidylserine antibodies mediates their phagocytosis, contributing to anemia. In human patients with late postmalarial anemia, we found a strong inverse correlation between the levels of anti-phosphatidylserine antibodies and plasma hemoglobin, suggesting a similar role in humans. Inhibition of this pathway may be exploited for treating malarial anemia.**

INTRODUCTION

Malaria-induced anemia involves both decreased erythropoiesis and increased removal of red blood cells (RBCs) (Haldar and Mohandas, 2009). For each RBC lysed directly due to *Plasmodium* infection, about eight uninfected RBCs are killed in *P. falciparum* (Jakeman et al., 1999; Price et al., 2001) and 34 in *P. vivax* (Collins et al., 2003) infections. The removal of uninfected RBCs during infection may be a result of direct oxidative damage and/or transfer of oxidized lipids from infected to uninfected RBCs (Uyoga et al., 2012), which are recognized by macrophages and removed from the circulation (Arese et al., 2005). Additionally, loss of complement regulatory proteins coupled with increased levels of immune complexes in malaria would render RBCs more susceptible to complement-mediated lysis (Stoute et al., 2003). However, a puzzling prolonged RBC loss is frequently observed in patients after successful antiparasite treatment (Biemba et al., 1998; Price et al., 2001; Ritter et al., 1993; Woodruff et al., 1979), despite the levels of oxidative stress (Das and Nanda, 1999; Kulkarni et al., 2003) and complement regulatory proteins (Stoute et al., 2003) returning to normal levels after parasite clearance.

Malaria, like other infectious diseases that can lead to anemia (Toplak and Avcin, 2009; Vergani and Mieli-Vergani, 2013; von Landenberg et al., 2007), induces the generation of anti-self antibodies against a variety of antigens, such as RBC cytoskeletal (Berzins et al., 1983; Ternynck et al., 1991) and membrane (Arese et al., 2005; Zouali et al., 1986) proteins, enzymes (Ritter et al., 1993), sugar moieties (Ravindran et al., 1988; Satapathy et al., 1993), DNA (Adu et al., 1982; Daniel Ribeiro et al., 1984; Zouali et al., 1986), and phospholipids (Consigny et al., 2002; Facer and Agiostratidou, 1994; Jakobsen et al., 1993).

Using a mouse model of malaria, we show here that anti-self antibodies generated during malaria recognize phosphatidylserine (PS), which is exposed in both infected and uninfected RBCs. Uninfected RBCs exposing PS are young RBCs expressing high levels of CD47, a molecule that inhibits phagocytosis (Sosale et al., 2015), yet in the presence of anti-PS antibodies macrophages efficiently phagocytize these cells. Transfer of affinity-purified anti-PS antibodies from *Plasmodium*-infected mice into other infected mice prolonged anemia after parasites had been cleared. Conversely, blocking of PS in infected mice resulted in faster recovery from anemia. These findings indicate that autoimmune anti-PS antibodies induced by malaria specifically bind to the surface of uninfected RBCs and mediate their clearance, contributing to anemia in mice. The analysis of the sera of human *P. falciparum* patients show that late postmalarial anemia correlates with high levels of anti-PS antibodies during the days of most pronounced anemia. Taken together, these results implicate anti-PS antibodies as mediators of postmalarial anemia.

RESULTS

Anti-Self Antibodies Recognize Uninfected RBCs during Malaria

As a model to study malarial anemia, we have used mice infected with *Plasmodium yoelii* 17XNL, a well-characterized nonlethal infection that induces strong anemia in mice with relatively low parasitemia (Figure 1A). In the sera of *P. yoelii*-infected mice,