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Modelling the Effects of Malaria on Red Blood Cell Surface Binding at the Vascular Interface

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Malaria is one of the largest diseases affecting tropical and subtropical regions, with more than 200 million cases and between 400,000 and 500,000 deaths annually, disproportionately afflicting the young, elderly or immune-compromised (1)(2). Infamously spread by infected mosquitoes, the disease is caused by several parasitic species of plasmodium (*P. falciparum*, *P. malariae*, *P. vivax*, *P. ovale* and *P. knowlesi*). Symptoms of the disease can include chills, fever, nausea, anaemia and vomiting and flu-like symptoms such as body aches and malaise, in extreme cases it causes seizures, coma and death. The progress of the disease is directly linked to the life cycle of the parasite. After infection from a mosquito bite the plasmodium enters the liver where it undergoes asexual reproduction. The parasite then enters the blood stream where it infects the red blood cells (erythrocytes) and again undergo asexual reproduction multiple times which eventually results in the bursting (lysis) of the infected cell, release of the plasmodium back into the blood serum enabling new erythrocyte infections. It is during this stage that male or female forms of the plasmodia can develop which renew the plasmodium life cycle if ingested by a female mosquito. It is also during this blood stage of the disease that the most symptoms are seen due to the combined effects of the blood cell lysis, the by-products of plasmodium reproduction and the accumulation of plasmodium infected red blood cells in capillaries.

Regions infected with malaria show a tendency to have a much higher prevalence of the sickle cell trait in the population. The carriers of this trait have inherited one gene which encodes for normal haemoglobin and one which encodes a version with a single point mutation. If an individual inherits the sickle cell trait from both parents they will have sickle cell disease, named due to the shape of the red blood cells formed, which causes a number of health complications. If only one copy of the gene is present the blood cells have a normal appearance at rest but can become sickle shaped under stress conditions. Individuals with the sickle cell gene are more resistant to malaria, meaning this trait confers a genetic advantage. The reason for this resistance is only partly understood.

Plasmodium falciparum is responsible for ~50% of malaria cases and causes the most malaria related deaths. During the blood stage *P.falciparum* infected erythrocytes bind to the blood vessel walls (composed of endothelial cells), with the accumulation of infected erythrocytes causing restrictions in blood flow in microvascular tissues such as capillaries, causing local inflammation and preventing the removal of the infected blood cells in the spleen. The sequestration of infected erythrocytes in the brain it is associated with the severest forms of the disease. *P. falciparum* infected erythrocytes bind to endothelial cell surfaces due to the manipulation of erythrocyte membrane composition by the parasite. Inside the erythrocyte the plasmodium produces a protein (*P. falciparum* erythrocyte membrane protein 1 (PfEMP1)) which makes its way to the red blood cell membrane surface where it is localized in parasite induced knoblike protrusions on the erythrocyte surface. From here PfEMP1 can interact with several proteins found in the endothelial cell membranes, anchoring the infected erythrocyte to this.

In this issue of biophysical journal, Fröhlich *et al* have developed planar endothelial membrane models on solid support materials containing the eukaryotic membrane proteins ICAM-1 (Intercellular Adhesion Molecule 1) and CD36 (cluster of differentiation 36), both of which PfEMP1 can utilize as adhesion receptors to bind the infected erythrocytes to the vascular lining (3). The interaction of *P. falciparum* infected red blood cells with this model vascular surface was measured as a function of endothelial receptor density in the supported lipid bilayer and shear flow, mimicking the pumping of blood. Results showed a direct correlation between the density of CD36 and ICAM-1 in the membrane models and the strength of infected erythrocyte surface binding. The model vascular surface bound plasmodium infected blood cells changed morphology under flow increasing the surface-to-surface contact between the erythrocyte and the endothelial membrane. The investigation also showed how red blood cells from donors with the sickle cell trait showed weaker binding than those without, revealing a link between the strength of infected erythrocytes endothelial adhesion and malarial resistance, in agreement with previous studies (4)(5)(6).

This study builds work using similar membrane models where the interaction of the infected erythrocyte with cell surface receptors in models of the placenta was examined (7) and complements a recent study examining plasmodium infected erythrocyte accumulation in synthetic models of human capillary's (8).

This new type of advanced biophysical assay system accurately models the intrinsic strength of cell/host receptor interactions providing a valuable tool to precisely and quantitatively investigate receptor driven cell adhesion in the vascular system.

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