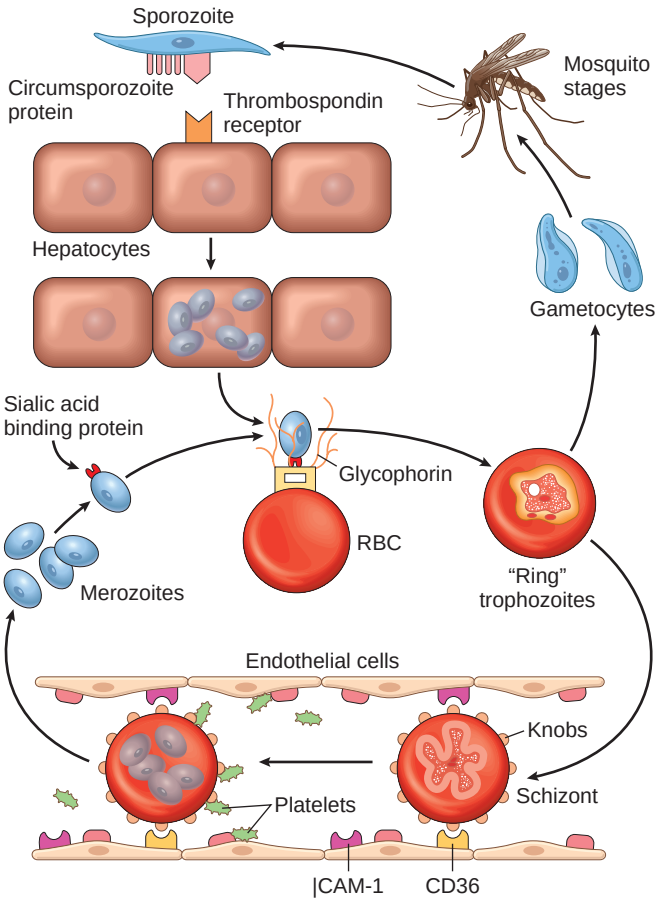

Figure 8-46 Life cycle of *Plasmodium falciparum*. Both exoerythocytic and erythrocytic stages are depicted. ICAM-1, Intercellular adhesion molecule 1; RBC, red blood cell. (Drawn by Dr. Jeffrey Joseph, Beth Israel-Deaconess Hospital, Boston, MA.)

the species of the malarial parasite. Although most malaria parasites within the red cells develop into merozoites, some parasites develop, under specific conditions, into sexual forms called *gametocytes* that infect the mosquito when it takes its blood meal.

Plasmodium falciparum causes more severe disease than the other *Plasmodium* species do. Several features of *P. falciparum* account for its greater pathogenicity:

- *P. falciparum* is able to infect red blood cells of any age, whereas other species infect only young or old red cells, which are a smaller fraction of the red cell pool.
- *P. falciparum* causes infected red cells to clump together (rosette) and to stick to endothelial cells lining small blood vessels (sequestration), which blocks blood flow. Several proteins, including *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), associate and form knobs on the surface of red cells (Fig. 8-46). PfEMP1 binds to ligands on endothelial cells, including CD36, thrombospondin, VCAM-1, ICAM-1, and E-selectin. Red cell sequestration decreases tissue perfusion and leads to ischemia, which is responsible for the manifestations of cerebral malaria, the major cause of death in children with malaria.
- In *P. falciparum* infection, GPI-linked proteins, including merozoite surface antigens, are released from infected red cells and induce cytokine production by host cells. These cytokines, including TNF, IFN-γ, and IL-1, suppress production of red blood cells, increase fever, stimulate the production of reactive nitrogen species (leading to tissue damage), and induce expression of endothelial receptors for PfEMP1 (increasing sequestration).

Host resistance to *Plasmodium* can be intrinsic or acquired. Intrinsic resistance stems from inherited alterations that reduce the susceptibility of red cells to productive *Plasmodium* infections. Resistance may also be acquired following repeated or prolonged exposure to *Plasmodium* species, which stimulates a partially protective immune response.

Several types of mutations affecting red cells are highly prevalent in parts of the world where malaria is endemic and are absent in other parts of the world. Most of these mutations are deleterious in homozygous form, suggesting that they are maintained in populations due to a selective advantage for heterozygous carriers against malaria. The mutations fall into four broad classes.

- Point mutations in globin genes—sickle cell disease (HbS), HbC disease (hemoglobinopathies)
- Mutations leading to globin deficiencies—α- and β-thalassemia
- Mutations affecting red cell enzymes—glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Mutations causing red cell membrane defects—absence of DARC (Duffy surface blood group), band 3, spectrin

P. vivax enters red cells by binding to the Duffy blood group antigen, and most of the population of West Africa is not susceptible to infection by *P. vivax* because they do not have the Duffy antigen. The mechanisms of the protective effects of the other three types of mutations are less well understood, but likely involve a favorable shift in the balance between the growth of intraerythrocytic parasites and their clearance by host phagocytes.

Individuals living where *Plasmodium* is endemic often gain partial immune-mediated resistance to malaria, evidenced by reduced illness despite infection. Antibodies and T lymphocytes specific for *Plasmodium* reduce disease manifestations, although the parasite has developed strategies to evade the host immune response. *P. falciparum* uses antigenic variation to escape from antibody responses to PfEMP1. Each haploid *P. falciparum* genome has about 50 *var* genes, each encoding a variant of PfEMP1. The mechanism of *var* regulation is not known, but at least 2% of the parasites switch PfEMP1 genes each generation. Cytotoxic T cells may also be important in resistance to *P. falciparum*. Current vaccine trials have demonstrated decreases in severe disease but only modest efficacy against clinical infection.

MORPHOLOGY

The diagnostic test for malaria infection is examination of a Giemsa-stained peripheral blood smear, which permits the asexual stages of the parasite to be identified within infected red cells. Insertion of parasite proteins into the red cell membrane leads to recognition by macrophages,