MALARIA

Binding of infected red cells

Louis H. Miller

NEARLY a century ago, Bignami and Bastianelli noted that red cells infected with the malaria parasite, *Plasmodium falciparum*, disappear from the peripheral blood. It has since emerged that they are sequestered along the smaller blood vessels, by which means the parasites are protected from the lethal immune activity of the spleen. That same process is responsible for many of the complications of

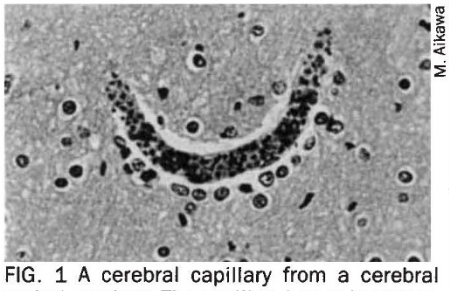

FIG. 1 A cerebral capillary from a cerebral malaria patient. The capillary lumen is obliterated with infected red cells.

severe malaria and for much of its mortality. Thus the placentae of fetuses carried by infected mothers are filled with parasitized red cells, which may contribute to low neonatal weight and to high maternal mortality (especially in a first pregnancy), whereas infected red cells bound to vessels in the brain (Fig. 1) may account for the high death rate in cerebral malaria, which is well in excess of 20 per cent.

These facts give sufficient reason for the exploration of the molecular basis of the cytoadherence of infected red cells, now well under way. Berendt *et al.*, reporting on page 57 of this issue[1], have identified intercellular adhesion molecule-1 (ICAM-1) as a third cell-surface receptor for infected red cells; furthermore, the authors have demonstrated that different parasite clones stick to different receptors — cytoadherence is heterogenous. In due course, that could lead to novel therapies for some of the complications of malaria.

The molecular mechanism by which infected red cells, exploiting knob-like protrusions on their membranes (Fig. 2), bind to the surfaces of venules can be studied because of continuous-culture methods for *P. falciparum*[2] and *in vitro* techniques for the study of cytoadherence[3,4]. Most work in the field has so far relied on human umbilical endothelial cells[3] and a melanoma tumour line[4], but the expression of specific membrane proteins in transfected cells, as with the expression of ICAM-1 in COS cells[1], which transiently express genes at high level, is a more direct route to understanding the details of specific binding.

As yet, there is no direct proof as to which molecules on the red-cell surface mediate attachment to endothelium — one candidate is immunoprecipitated by strain-specific sera[5] that also block cytoadherence in a strain-specific manner[6]. By contrast, the new report brings to three the number of identified host proteins to which infected red cells bind. One is the soluble protein thrombospondin[7], another is CD36 (see refs 8,9) which, like ICAM-1, is a surface membrane protein expressed on specific cells. Binding has been demonstrated either to isolated protein or to cells transfected with the appropriate gene.

Several questions are provoked by this multiplicity of host binding proteins. Are parasitized red cells generally sticky, binding to several proteins? If so, do these proteins have a common group at which binding takes place? Otherwise, what is the physiological significance of the parasitized red cell's capacity to bind to three different host proteins? Which of these, if any, are involved in the sequestration of parasitized red cells to endothelium in uncomplicated malaria, to cerebral vessels in cerebral malaria and to the placenta? Binding to various melanoma-cell lines correlates with the expression of CD36, but that does not define the mechanism of binding in human beings.

The study by Berendt and colleagues[1] marks a start on the unravelling of that problem. Different *P. falciparum* clones, ITO4 and FCR3, are shown to bind to different molecules. But the observation that ITO4 clones bind to COS cells separately transfected with ICAM-1 and CD36, and that FCR3 clones bind only to the latter, in itself suggests that there are least

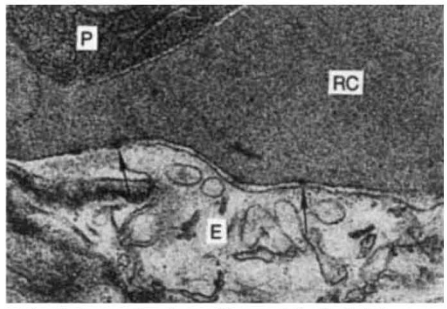

FIG. 2 A cerebral capillary with *P. falciparum* (P)-infected red cell (RC) adherent to the endothelial cell (E) by knobs (arrows). (From ref. 14.)

two distinct binding mechanisms and that red cells, as modified by parasites, do not recognize determinants common to the two host receptors. That is consistent with the absence of homologous regions in the amino-acid sequences of ICAM-1 and CD36. The binding specificity of parasites from patients with cerebral malaria will be awaited with great interest.

The cytoadherence molecules on parasitized red cells would be another part of the story, but perhaps only a part. In animal models, *P. falciparum* sequesters not in cerebral vessels, but in venules elsewhere in the body[10]. Cerebral malaria caused by the rodent parasite *P. berghei* is associated with macrophages and parasitized red cells in the cerebral vessels, and tumour necrosis factor (TNF) has been shown, by antibody blocking experiments, to have a role in the disease[11]. Although macrophages are not found in the cerebral vessels of people with cerebral malaria, seriously ill patients have markedly high levels of TNF (ref. 12).

Given that cultured human endothelial cells express ICAM-1 on the addition of TNF, it is possible that TNF (and other cytokines) may enhance the expression of molecules on the cerebral endothelium to which malarial red cells bind, with the consequence that cerebral vessels are obstructed. That implies that there is now a need to define the putative receptors on human cerebral endothelium when there is, or is not, cerebral sequestration. The outcome might be anti-receptor therapy to reduce the mortality from this dread complication of infection with *P. falciparum*.

The biology of the diversity of mechanisms of cytoadherence is also important. The evolution of cytoadherence, it must be recalled, has been driven not so that parasites can block cerebral blood vessels, but so that they may avoid circulation through the spleen. So why are there several parallel mechanisms? It is a little like the diversity of mechanisms for invasion by parasites, where the pathway used is determined by the characteristics of the red cell and of the parasite clone; *P. falciparum* merozoites may invade red cells by pathways that are dependent on, or independent of, sialic acid, for example[13]. The diversity of receptors both for invasion and cytoadherence may enhance the success of each, thus increasing the chances of survival of parasites living in the blood under continuous immune attack. □

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