People with malaria have a reduced immune response not only to the malaria parasite, but also to other organisms and antigens (foreign proteins), including vaccines^{5,6}, possibly because antigens of the malaria parasites are very similar to those of other microorganisms⁷. To impede the immune response strongly, the parasite must target it at an early stage. Several studies have hinted that immune responses in malaria might be impaired because fewer macrophages are generated in the bone marrow, and because these smaller populations process antigen ineffectively^{8,9}. Macrophages, along with other 'antigen-presenting cells', can start or re-boot the immune response by processing and then presenting fragments of antigens to the T cells, of which there are two types. The 'effector' T cells kill the microbe directly, whereas the 'helper' T cells enable B cells to make antibody against it (Fig. 1).

The most potent antigen-presenting cells are the so-called dendritic cells¹⁰. Found in all tissues, dendritic cells have the unique ability not only to assist in boosting or amplifying an immune response on subsequent exposure to an organism, but also to initiate a response against a new microbe. Clearly, any suppression of these cells would result in something akin to an orchestra attempting to learn a new symphony when their conductor's arms were tied. Yet this is what Urban and colleagues⁴ now show that *P. falciparum* does.

The authors have found that *P. falciparum* prevents the maturation of dendritic cells. As a result, functional activity of the dendritic cells is impeded — Urban *et al.* measured dramatic reductions in T-cell proliferative responsiveness to the malaria parasite and other antigens. The authors show that binding of infected intact red blood cells to the surface of the dendritic cells is critical for impairing the activity of dendritic cells. We already know that the ability of malaria-infected red cells to stick to the endothelium of blood vessels in the brain and other tissues (such as the placenta¹¹) is related to disease pathogenesis. Indeed, some of the parasite proteins involved in adhesion have been defined, including an antigen known as PfEMP1. Molecules that bind to this antigen in endothelial cells have also been identified, and include CD36 and thrombospondin.

Urban and colleagues suggest that the PfEMP1 antigen may be responsible for binding to dendritic cells. Two parasite lines that adhere to CD36 and thrombospondin also stick to dendritic cells and inhibit their maturation. But a line that does not bind to CD36 and thrombospondin does not bind dendritic cells and does not affect their function. Their data do not, however, exclude the possibility that other antigens from the parasite bind to other ligands on the dendritic

cells. Blocking studies with antibodies may identify the critical interactions. Moreover, although vascular adhesion is a well-known property of *P. falciparum*-infected red blood cells, it has not been seen with another strain of malaria parasite, *P. vivax* — yet immunosuppression has been described in both types of infection^{2,3}.

Urban and co-workers think that adhesion of infected red blood cells to dendritic cells is not a chance event. Instead, they say, it results from a selective advantage to the parasite, such that it is not destroyed by the immune response. But because the immune response is affected at such a critical, central place, it is not surprising that it has been difficult to fine-tune immune suppression to the combined advantage of both the parasite and the host. It is estimated that *P. falciparum* kills between 1.5 and 2.7 million children per year¹². Without drug intervention, of course, the death rate would be considerably higher — to neither the host's nor the parasite's advantage.

Although PfEMP1 is a variant antigen (that is, several different forms may be expressed over the course of a single infection), we could, perhaps, find conserved domains that would be the basis of a vaccine. But antibodies induced by specific vaccination should block adherence of the parasite, not only to blood vessels but also to dendritic cells. The result may be potent anti-parasite immune responses that clear the infection.

Clearly, other molecular pathways may be involved in malaria-induced immunosuppression, apart from those suggested by Urban and colleagues. Nevertheless, the authors do give us an insight into the immunoregulatory pathway(s) that the malaria parasite has adopted to survive. From these findings we can design strategies to stimulate immune responses to a variety of infectious organisms, or to dampen immune responses to self-antigens in the context of autoimmunity. □

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Daedalus

Virtual overpopulation

Animal reproduction is a strategic process. Creatures such as fish, whose eggs are metabolically cheap, can spawn them in thousands in the hope that a few will survive. Those with costlier offspring must be more prudent. Birds, for example, have to build a nest, lay eggs, incubate them and feed the hatched chicks for some time. If the parents produce too many eggs, they will be unable to find enough food to support themselves and all the chicks over that time. Some chicks will die, wasting scarce resources. Conversely, too few eggs represent a lost reproductive opportunity.

The birds can, presumably, assess the food resources of their environment fairly well. But how do they judge the number of rivals competing for those resources? One solution is 'mustering'. Starlings, ducks, and many other species, gather together in the breeding season into vast flocks. Each bird makes the most conspicuous display and loudest noise it can manage, to show its rivals the reproductive competition they must face. All the birds gain some sense of their population density, and can judge the most cost-effective number of eggs to lay.

The mustering of urban birds, especially starlings, is a great nuisance in many big cities. Numerous attempts to poison or discourage these pests have failed. Daedalus now plans to subvert their mustering. He will place sets of huge parallel mirrors across the most popular mustering sites. The birds will see their numbers reflected repeatedly to infinity, and will decide that they are vastly overpopulated. Concave mirrors could magnify the more distant images, making them ever larger and more intimidating. The cowed birds will therefore lay very few eggs, and the urban nuisance will steadily abate.

The strategy can clearly be elaborated. Amplifiers (with time-delay to avoid feedback howl) could exaggerate the birds' cries. The surveillance cameras in many cities could portray the birds to themselves on vast numbers of TV screens around their sites. But Daedalus now wonders if cities themselves represent an instinctive human mustering. The steady flood of people into huge, crowded, noisy cities, especially in the developing world, may subconsciously impress all their inhabitants with the intensity of the reproductive competition. With luck, the resulting instinctive response will defuse the population explosion without anyone having to make hard policy decisions.

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