Quantifying Malaria Dynamics Within the Host

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Science **333**, 943 (2011);
DOI: 10.1126/science.1210775

These new results have important implications for understanding the genetics of human cancers (see the figure). Aneuploidy, or even copy number changes in key regions of chromosomes, can cause a modest mutator phenotype and may promote the accumulation of mutations in some cancers even in the absence of initiating mutations (i.e., aneuploidy as an initiator event). One such example is the mosaic variegated aneuploidy cancer predisposition syndrome, a rare condition in which different chromosomes and body tissues can be affected in the same individual and the proportion of aneuploid cells is usually more than 25% (*13*, *14*). Aneuploidy may also be caused by mutations accumulated during cancer progression (i.e., aneuploidy as a later event), as suggested by the acquisition of somatic *STAG2* mutations observed by Solomon *et al*. Furthermore, that aneuploidy can result in increased mutation rates could explain how low levels of aneuploidy that result from reduced levels of components involved in chromosome segregation can drive tumorigenesis, whereas even higher rates of aneuploidy can suppress it by causing slow growth or cell death (*1*). Similarly, defects in STAG2, which likely result in mildly increased aneuploidy, would be predicted to drive tumorigenesis through induction of a mutator phenotype. The broader implication is that mutator phenotypes in cancer could result from deregulation of genes that do not obviously prevent mutations. It remains to be seen whether aneuploidy can also drive the accumulation of genome rearrangements, including translocations and copy number changes that contribute to tumorigenesis.

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10.1126/science.1211154

MICROBIOLOGY

Quantifying Malaria Dynamics Within the Host

A statistical method reveals the roles of the immune system and cell availability in regulating parasitemia.

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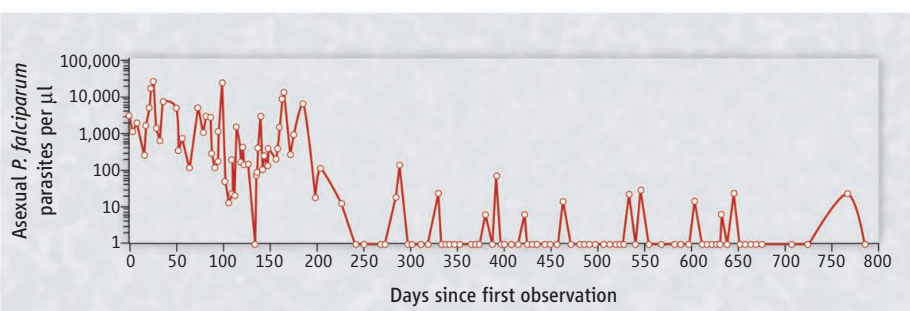
Generations of malariologists have been intrigued by the mechanisms that control the number of malaria parasites living in the bloodstream (i.e., the extent of parasitemia) in an infected human host. Past studies have shown that parasite numbers rise and fall during infection (see the figure) (*1*) and that parasitemia is regulated by an array of forces, including human immune defenses, interactions among the parasites themselves, and the availability of resources, such as the red blood cells that the parasites invade. On page 984 of this issue, Metcalf *et al*. (*2*) take an important step toward better understanding of these controls. Drawing on data from mice, they present a new statistical approach to analyzing how parasitemia changes over time and to quantifying and comparing the roles played by the immune system and the availability of red blood cells in regulating parasite numbers.

Within a host, the dynamics of malaria parasitemia are complex. Past studies have demonstrated relationships between levels of parasitemia and the onset of fever, disease severity, and the transmission of parasites to mosquitoes, which act as a vector. Researchers have also explored the role of human genetic variation in regulating parasitemia, identifying traits that influence infection load. Genetic analyses of malaria parasites have shown that humans living in areas where malaria is endemic can be simultaneously infected with different *Plasmodium* species and genotypes, and that the parasites actively contribute to regulating their densities by sensing their environment (*3*, *4*). As a result, we now understand that innate and adaptive immune mechanisms, as well as the parasite population itself, define the host's carrying capacity for *Plasmodium* (*3*, *5*).

To develop their approach, Metcalf *et al*. borrowed concepts from population ecology. Their statistical model, for instance, views cell-to-cell transmission of malaria as analogous to host-to-host transmission of a pathogen. This model enabled the researchers to compare "bottom-up" controls on parasitemia (such as the availability of red blood cells) to "top-down" controls (analogous to an organism's control by natural enemies; in this case, the "enemy" is the immune system). In particular, the researchers used what is known about how malaria parasites infect cells and spread to define an "effective propa-



An infection's rise and fall. Parasite numbers in the bloodstream of a child infected with the malaria parasite *P. falciparum* follow a pattern of recurrent peaks that decline in amplitude over time. The parasitemia in this child lasted nearly 800 days (*1*).

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gation number" (P_e) of infection; this allowed them to calculate the number of new infected cells to arise in a susceptible (R_0) or immune (R_e) host, and to evaluate the overall survival of the parasite population within the host.

To evaluate their model, Metcalf *et al*. used extensive time-series data available from mice infected with *P. chabaudi*—which has similar within-host dynamics to human malaria parasites. The results elegantly illustrate the power of using this approach to dissect a range of scenarios in this mouse model by analyzing the dynamics of both parasite counts and total red blood cell numbers; it is the most rigorous quantitative analysis of immune regulatory data we have seen.

One result has noteworthy implications for our understanding and interpretation of protective immunity to *Plasmodium* parasites. Metcalf *et al*. report that high inoculating doses can overwhelm the early innate immune mechanisms that clear the parasites from the bloodstream. Supporting this conclusion, data from induced infection in humans, as well as vaccine trial data from mice and humans, show that time to patency (infection) and fever—both indirect measures of parasite numbers—are sensitive to a high inoculating dose of parasites [e.g., (*6*)]. Metcalf *et al*.'s analysis provides evidence to support a low-dose blood-stage vaccine approach that induces a robust protective innate T cell response (*7*). Although past models could accurately incorporate early immune responses, Metcalf *et al*.'s model revealed complex time dependence in the efficacy of the adaptive immunity. Longer-term studies are needed to validate this approach to predicting longevity of vaccine efficacy to regulate parasitemia in clinical trials.

Metcalf *et al*.'s observation that a reduced availability of susceptible red blood cells has an antiparasite effect is particularly relevant to understanding human malaria pathogenesis. We and others have shown dramatic reductions in red blood cell numbers in acute and severe malarial infection in humans (*8*–*10*). Given Metcalf *et al*.'s observations, we propose that these declines in red blood cell numbers, as a result of their destruction and decreased production, should lead to reduced P_e. This antiparasite effect of red blood cell resource depletion is supported by recent papers on the hematological analysis of thalassemias and malaria disease severity (*9*, *10*). Using detailed data on total infected and uninfected red blood cell counts, those papers showed that the dramatic declines in red blood cell numbers in acute malaria do not lead to increases in the proportion of infected red blood cells. In addition, the increased red blood cell counts associated with microcytic anemia in various inherited blood diseases, including α-thalassemia, would cause P_e to be reduced by increasing the population of uninfected red blood cells. Further investigation of this intriguing interplay among variations in erythrocyte numbers caused by thalassemia, other host red blood cell polymorphisms, and effective propagation numbers in time-series analyses of disease progression is merited with this ecological approach.

Malaria parasites infect a wide range of hosts, including lizards, birds, rodents, and gorillas and other primates, and Metcalf *et al*.'s statistical approach promises to have numerous applications in malaria population biology. In particular, it could help to inform and evaluate malaria interventions and to answer questions about basic biological mechanisms.

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10.1126/science.1210775

IMMUNOLOGY

The Adjuvant Effects of Antibodies

The positive aspects of a negative immune receptor provide a new understanding of immune-boosting antibodies.

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Monoclonal antibodies (mAbs) are perhaps the most exciting, specific, and flexible vehicle for treating cancer. Major leaps in the engineering of mAbs over the past three decades have improved their effectiveness against target antigens. CD40, a member of the tumor necrosis factor receptor (TNFR) superfamily expressed on antigen-presenting cells, is one such target, but so far the clinical efficacy of a mAb against this molecule in cancer patients has been limited. On page 1030 of this issue, Li and Ravetch (*1*) demonstrate that a mAb to CD40, with enhanced binding to another protein on antigen-presenting cells, increases activation of the antigen-presenting cells and thereby promotes an adaptive immune response. This has implications for the design of other therapeutic mAbs.

Li and Ravetch investigated the ability of antibodies against CD40 to boost immunity (driven primarily by T cells) against ovalbumin and other antigens expressed by tumor cells in mice. They targeted ovalbumin by coupling it to a mAb specific for DEC205, a protein expressed on the surface of dendritic cells (a type of antigen-presenting cell). The idea was to boost presentation of ovalbumin to T cells, thereby activating them. By itself, this ovalbumin-DEC205 conjugate generated little immunity toward ovalbumin. However, when a mAb specific for CD40 was added to the immunization strategy, a dramatic increase in the generation of ovalbumin-specific T cells was observed. The CD40-specific antibody therefore acted as an adjuvant, improving the immune system's response to an agent (ovalbumin) that had little effect itself.

Stimulating CD40, an activating receptor expressed on antigen-presenting cells, has been shown to enhance the immune functions of these cells (*2*). However, Li and Ravetch show that the nature of the invariable Fc portion of the CD40 mAb is crucial to its adjuvant effect. In addition to binding the CD40 molecule through its variable domain, the Fc portion of the mAb also must bind to an Fc receptor (called FcγRIIB). This is surprising because FcγRIIB is considered an inhibitory receptor that suppresses immunity (*3*). The other members of the Fc receptor family are all activating receptors, but a role for these receptors was discounted because the effect of the CD40 mAb was not

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