cyanate labeling) revealed that the former population is preferentially exported to the periphery. Taken together with other recent data (*7*) indicating that mature NKT cells are ultimately derived from a $CD4^+$ $CD8^+$ thymic subset (which also contains precursors of conventional $CD4^+$ and $CD8^+$ T cells), a plausible model for the intrathymic development and export of NKT cells can now be proposed (see the figure, panel B).

What are the possible implications of this model for the respective parts played by NKRs and TCRs during NKT cell development? In this context, Benlagha *et al.* (*3*) present a key finding: The NKR^- NKT cell intermediate divides rapidly in the thymus, whereas the more mature NKR^+ progeny do not. An interesting interpretation of these data would be that TCR interactions with CD1d on immature NKT lineage cells lead to activation and proliferation of these cells; in contrast, the delayed expression of inhibitory NKRs dampens this proliferative response and prevents potential autoreactivity of mature NKT cells. Intriguingly, engagement of Ly-49 receptors with ligand negatively regulates autoreactivity of NKT cells mediated by TCRs (*8*). Furthermore, enforced ligation of Ly-49 receptors in transgenic mice can interfere with NKT cell development (*9*). Thus, the "T before NK" strategy of receptor expression adopted by developing NKT cells appears to be a way of optimally exploiting the unique properties of each cell lineage.

Benlagha *et al.* (*3*) and Pellicci *et al.* (*4*) also examined the cytokine profile of developing NKT cells. The accepted paradigm (*10*) for conventional $CD4^+$ T cells is that they can be induced to differentiate into either T helper 1 (T_H1) cells, which produce preferentially IFN-γ and related "inflammatory" cytokines, or T_H2 cells, which produce preferentially IL-4 and related "regulatory" cytokines. Mature NKT cells produce large amounts of both IFN-γ and IL-4 and thus do not readily fit the T_H1/T_H2 classification. Surprisingly, it turns out that immature NKR^- NKT cells produce much more IL-4 than IFN-γ, whereas in mature NKR^+ NKT cells this balance reverts in favor of IFN-γ. Because both NKR^- and NKR^+ NKT cells are exported from the thymus to the periphery, it is possible that NKT cells may mediate either T_H1 or T_H2 responses, depending upon which NKT cell subset is preferentially activated.

The work of Benlagha *et al.* (*3*) and Pellicci *et al.* (*4*) has far-reaching implications for understanding NKT cell biology. These studies may define a more general paradigm for the development and selection of lymphocytes of the innate immune system that reaches beyond NKT cells to include NK cells, epidermal γδ T cells, and the B-1 subset of B cells (*11*). In contrast to conventional T and B cells of the adaptive immune system, these innate lymphocytes all express germline–encoded activating receptors of limited (or no) diversity, as well as inhibitory NKRs. Because innate lymphocytes are expanded (rather than eliminated) by strong agonist interactions with conserved self ligands, it is tempting to speculate that delayed expression of inhibitory receptors during development may represent an evolutionarily conserved mechanism to terminate expansion and to control autoreactivity of these cells.

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PERSPECTIVES: PARASITOLOGY

When the Host Is Smarter Than the Parasite

Daniel E. Goldberg

The malaria parasite, *Plasmodium falciparum*, causes millions of deaths each year, mostly among African children (*1*). Drug resistance is rendering the standard affordable agents like chloroquine obsolete. We desperately need new drugs, and toward that end, new drug targets. To the rescue has come the malaria genome-sequencing consortium. The *P. falciparum* genome sequence is nearing completion, and we are sure to turn up new drug targets among the 6000 or so genes of the malaria parasite.

The first place to look is the set of genes (perhaps 60% of the *P. falciparum* genome) that exist in the parasite but not in its human host (*2*, *3*). Most of these will prove to be nonessential—for example, only 14% of yeast genes without mammalian homologs are essential (*4*). Most of the remainder are of unknown function, and it will be a challenge to develop drugs directed against their gene products. Still others may be difficult to express or screen and may not have a potent nontoxic bioavailable inhibitor that can be taken through development. The genome databases have already been exploited to identify good drug targets and inhibitors (*5*, *6*), but the expected drug development riches may amount to a trickle instead of a flood. Soon, we may wish we had more than 6000 genes to work with in the fight against this nefarious parasite. There is another list of genes to consider: Those that are expressed in humans as well as in malaria organisms. Proteins encoded by some of these genes exhibit sufficient differences between man and malaria parasite that they could be exploited as targets for drug development. Many are very similar between the two species, especially in their active sites. Are we to discard these as potential drug targets? According to the study by Zhang and Rathod on page 545 of this issue (*7*), the answer is "not so fast."

Dihydrofolate reductase (DHFR), a key enzyme in the folate metabolic pathway, is an important target for antimicrobial chemotherapeutics such as pyrimethamine, one of the most enduring of antimalarial drugs. Selectivity for pathogen DHFR over the host enzyme is usually the key feature of DHFR inhibitors. Yet, for some agents such as WR92210, the inhibition constants (K_i's) for the human and parasite enzyme differ by a mere order of magnitude; in contrast, cellular toxicity differs by five orders of magnitude. Zhang and Rathod have now explained this discrepancy with a simple but elegant model in which the host, but not the parasite, is able to overcome drug toxicity by making more enzyme (*7*).

There exists in both host and parasite a negative-feedback loop in which mRNA encoding DHFR is bound by its protein, preventing further translation of the mRNA once enough protein has been made. In mammalian cells, when folate substrate levels rise, DHFR mRNA becomes dissociated

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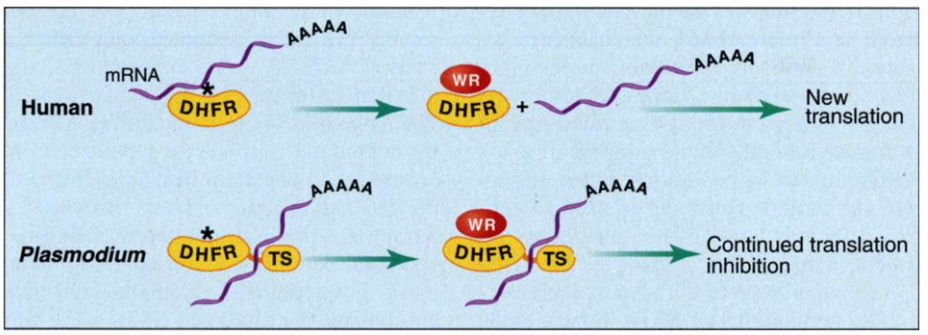

Empowering the host. Response of host and malaria parasite to the antifolate drug WR92210 (WR). Both the human and *Plasmodium* DHFR enzymes are efficiently inhibited by WR. Binding of WR to the human enzyme causes release of DHFR mRNA, leading to new protein synthesis and circumvention of the drug block. *Plasmodium* DHFR is a bifunctional enzyme (composed of DHFR and TS) whose mRNA transcript does not bind to the DHFR catalytic domain, but rather to the linker region that joins DHFR and TS. Therefore, WR binding does not release the mRNA and the parasite cannot respond to drug by making new enzyme. The asterisk denotes active site enzyme.

from its protein and new enzyme is synthesized (*8*, *9*) (see the figure). This allows mammalian cells to respond to substrate levels by translational control of enzyme concentration. DHFR inhibitors work in the same way as folate substrate, stimulating new protein synthesis and thus preventing DHFR blockade by the drug. *Plasmodium*, however, has a bifunctional enzyme composed of DHFR joined to thymidylate synthase (TS). The DHFR-TS mRNA is also bound to its protein, but the interaction appears to be in the linker region joining the DHFR and TS domains. Inhibitor treatment does not cause mRNA liberation, and new enzyme cannot be synthesized. The same mechanism seems to apply to TS: Treatment with a TS inhibitor results in increased enzyme synthesis in mammalian cells (*10*), but such inhibitors do not relieve the mRNA block of TS production in the parasite.

Why is there this difference between man and microbe? By making free DHFR mRNA responsive to substrate concentration, we humans are able to increase metabolic flux with relative ease by boosting translation of the mRNA. The parasite, however, has little need for such regulation. It lives inside an erythrocyte that gives the parasite a relatively constant ionic and nutrient environment. In fact, to date there is no substantive evidence for regulation of any *Plasmodium* gene expression in response to its environment. The parasite, much like a virus, regulates mRNA synthesis through a developmental program of on-off switches (*11*, *12*), but its ability to respond to unexpected changes may be quite limited. By cutting corners with respect to gene regulation, *Plasmodium* is able to streamline its genome. But in this regard, we are more sophisticated than the parasite, and thus we are provided with an opportunity.

No longer should we rely on mere kinetic comparison of host and pathogen enzymes for analysis of inhibitor selectivity. High-throughput enzyme inhibition screens done as simple head-to-head comparisons may miss important lead compounds. The effects on the target must be assessed on a cellular or even organismal level. Screens would even be feasible on a whole-proteome scale. One could look for proteins that were down-regulated in the parasite or up-regulated in the host upon treatment with an inhibitor. In addition to translational regulation, one could also look for differential uptake—for example, toxic L-nucleosides are taken up by *P. falciparum* but not by host erythrocytes (*13*). One could also investigate metabolic differences—for example, phosphorylation of acyclovir by a viral kinase contributes to selectivity of its antiherpesvirus action (*14*). One could exploit different rates of turnover—efluornathine works because, in contrast to the host, African trypanosomes cannot replace inhibited enzyme through new synthesis (*15*). Finally, one could look for differential penetration—ivermectin kills nematodes but not mammals because it cannot get through the blood-brain barrier to affect host neurons (*16*).

Those of us who have studied the biology of clever parasites have developed a profound respect for the ability of these creatures to evade their hosts. Maybe it is time to give a little credit to us hosts, with our extra genomic and cellular complexity. With a little planning we should be able to exploit our mammalian sophistication to develop potent antiparasitic drugs.

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PERSPECTIVES: CLIMATE MODELING

How Accurate Are Climate Simulations?

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It is a fundamental tenet of the scientific method that theories must be consistent with observations. To test our understanding of the climate system, we must evaluate how accurately climate models reproduce not only today's climate (*1*), but also the climate of the past.

Over the past decade, the observed climate record has become more complete, allowing the climatic effects of natural agents and human-related changes in atmospheric composition (collectively referred to as climate forcing) to be estimated. We can now test how well climate models simulate century-scale variations in the observed climate record. There have been numerous intercomparisons of various climate model simulations of 20th-century climate, based on the best available estimates of the climate forcing (*2*).

A standard assumption in these intercomparisons is that the model simulations should reproduce as closely as possible observed climate variability. This assumption must, however, be viewed with caution.

Observational errors, sampling errors, and time-dependent biases degrade the climate record. Considerable effort has been spent at minimizing these biases (*3*, *4*), yet problems remain. Consider for example

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