

New target, old drug for malaria

β -blockers—drugs commonly used to treat hypertension—should be investigated for the treatment of malaria, say Kasturi Haldar and Jon Lomasney (Northwestern University, Chicago, IL, USA). According to the researchers, signalling through the host β -adrenergic receptor and the heterotrimeric guanine nucleotide binding protein Gas is involved in the entry of the malaria parasite *Plasmodium falciparum* into erythrocytes. Reporting in *Science* (2003; **301**: 1734–36), Haldar, Lomasney, and colleagues show that β -blockers inhibit infection of human erythrocytes in vitro by *P falciparum* and reduce parasitaemia in mice infected with *Plasmodium berghei*.

The blood-stage cycle of the malaria parasite is initiated when merozoites invade erythrocytes. During this multistep process, the erythrocyte membrane undergoes considerable changes and the parasite becomes surrounded by a parasitophorous vacuole. After replicating within the vacuole, the parasite lyses

the erythrocyte and a new batch of merozoites is released to restart the cycle, which is responsible for malarial pathology.

In her studies of erythrocyte invasion, Haldar has been investigating which host-cell proteins are incorporated into the parasitophorous vacuole. “The only erythrocyte proteins recruited into the vacuole are a subset of proteins associated with erythrocyte rafts”, cholesterol-rich domains of the cell membrane, she explains. “Among these proteins are Gas, a protein involved in signal transduction, and the Gas-coupled β -adrenergic receptor, so we asked whether Gas has a specific function in parasite invasion.”

The researchers discovered that a peptide consisting of the last 11 aminoacids of Gas, which blocks its interaction with the β -adrenergic receptor, inhibited *P falciparum* infection of erythrocytes in vitro. “Peptides are not very deliverable to patients”, explains Lomasney, “so we

also investigated the effect of agonists and antagonists of the β -adrenergic receptor. Agonist treatment increased malarial infection and antagonists blocked the infection. Our working hypothesis is that when infected erythrocytes lyse, antigen release causes an increase in circulating catecholamines and these act through the β -adrenergic receptor to make uninfected erythrocytes more susceptible to attack by merozoites”.

“This original work is consistent with what we know about erythrocyte invasion”, comments Phil Rosenthal (University of California, San Francisco, CA, USA), “and the interesting insight is that host signalling mechanisms are apparently usurped by the parasite to facilitate invasion. It is hard to predict, however, whether β -blockers will be a useful therapy for malaria. They are well tolerated but they have some side-effects so they will need to be antiparasitic at doses well below those that cause toxicity”.

Jane Bradbury

Daptomycin approved for skin and skin-structure infections

The US Food and Drug Administration (FDA) has approved a novel antibiotic, daptomycin, for parenteral treatment of major abscesses and other skin and skin-structure infections. The approval “is very good news”, says Robert Moellering, physician-in-chief and chairman of the department of medicine at Beth Israel Deaconess Medical Center (Boston, MA, USA).

“It sends a message that the FDA is willing to give expedited approval to new antibacterial agents that fulfil a need—in this case, by having activity against multiresistant Gram-positive bacteria”, including *Staphylococcus aureus*, *Streptococcus pyogenes*, and vancomycin-susceptible strains of *Enterococcus faecalis*. The FDA based its decision to approve the drug on a review of studies involving 1409 adults (<http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01252.html>).

Daptomycin is the first approved

product in a new class of antibiotics, the cyclic lipopeptides, which act directly on the bacterial cell membrane. “Known peptide antimicrobials act on

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Staphylococcal skin infection

the cell membrane, but they usually do so in a pretty gross fashion—punching holes in it and letting the internal contents leak out, which may damage mammalian cells and cause toxicity”, explains Moellering. “But this drug has a lipid tail that inserts itself into the membrane without rupturing it,

creating channels that allow ions to leak out. The membrane is depolarised, so it can no longer carry out its transport processes. This kills the bacteria, but they’re not lysed, which is probably why the drug isn’t more toxic.”

Because daptomycin has a novel mechanism of action, “there is much less chance of cross-resistance with currently available antimicrobials”, notes Moellering. And although it is currently approved for a single indication, he adds, “a lot of physicians are anxiously awaiting the results of current phase III trials of daptomycin for the treatment of bacteraemic disease and endocarditis due to staphylococci, enterococci, and other organisms. If the results of those trials are positive, then this drug will prove to be a valuable addition to the armamentarium and could open the door for the development of other lipopeptides”.

Marilynn Larkin