velopmental Biology, Elena Pasquale of the La Jolla Cancer Research Foundation in California and her colleagues report finding Cek5, an Eph-family receptor that has a transmembrane-type ligand, arranged in a top-to-bottom concentration gradient in the retina, at right angles to the nasal-temporal Mek4 gradient. To try to complete the picture, Pasquale has begun looking to see whether Cek5's ligand is arranged in a gradient along the dorsal-ventral axis of the tectum.

The story of the Eph receptors goes beyond the optic tectum; family members are popping up throughout the nervous system, and in non-neuronal tissues as well. What they are doing there is unknown, but some researchers are finding evidence of a common theme. For example, Greg Lemke's group at the Salk Institute has found Mek4 on motor neurons in the spinal cord whose axons grow out to trunk muscles. They have no evidence yet, but Lemke suggests that the protein may be helping guide the axons to their target muscles.

Other researchers think the receptors do things besides guide axons. David Wilkinson at the National Institute for Medical Research in London and his colleagues have found certain Eph-related receptors in specific segments of the developing hindbrain. In a paper in press in *Development*, they show that Eph family member Sek-1 is needed in fish and frogs to keep the segment boundaries sharp. Sek-1 may do its job by preventing cells from drifting across the boundaries, says Wilkinson, but he favors another explanation in which Sek-1 instead controls the segmental identity of cells. It is too early, he cautions, to propose a single "unified role" for the Eph receptors in directing cell movements.

Biochemist Vishva Dixit of the University of Michigan supports the idea of a unified role and offers additional evidence from his lab. In the 28 April issue of *Science*, his group reported an example of an Eph receptor guiding cell movements outside the nervous system. They showed that activation of Eck on endothelial cells during inflammation causes those cells to migrate into areas where new blood vessels will form. A hint of how the receptor might affect cell movement came last year, when Dixit's group reported that the Eck receptor stimulates phosphatidylinositol 3' kinase, an enzyme that has been implicated in controlling cell movements by causing changes in the cytoskeleton.

Such findings, tantalizing as they are, amount to small bits of a jigsaw puzzle that is far from completed. But considering all the provocative clues emerging about these intriguing receptors, it will not be long before more pieces are fit into place.

–Marcia Barinaga

MALARIA RESEARCH

Inbred Parasites May Spur Resistance

Inbreeding can be dangerous, as everyone from population geneticists to historians of royal families knows, because it can fix deleterious traits such as hemophilia in a population. Now on page 1709 of this issue, Karen Day and colleagues at the University of Oxford suggest another evil role for inbreeding: It may speed the development of drug resistance in populations of malaria parasites in certain parts of the world. Although conventional wisdom blames the evolution of resistance on the widespread use of anti-malarial drugs, Day and colleagues suggest that natural geographic variation in parasite mating habits may also play a role.

These results could have major implications for efforts to protect the 2.1 billion people regularly exposed to malaria, says Donald Heyneman, a parasitologist at the University of California, San Francisco. "General strategies to control malaria in whole regions don't hold much promise," he says, because control programs may have to accommodate the geographic peculiarities of the disease.

MALARIA

Country	Bites per person per year	Parasite genotype per person (avg.)
Papua New Guinea	40–200	1.8
Tanzania	300–3000	3.2

SOURCE: K. DAY, D.WALLIKER

Day and colleagues at Oxford's Wellcome Centre for the Epidemiology of Infectious Disease in England embarked on their project in 1991 in tandem with David Walliker at the University of Edinburgh, who was analyzing the population structure of *Plasmodium falciparum*—the most lethal species of malaria parasite—in Tanzania; his study was published last year. Day and graduate student Rick Paul suspected that parasite mating habits might vary around the world, so they packed off to Papua New Guinea to do a similar experiment with researchers at the PNG Institute of Medical Research.

Their work involved 4 years of hard labor, in part because of the parasite's complicated life cycle. *P. falciparum* moves between *Anopheles* mosquitoes and humans, producing its male and female gametes inside the swollen gut of a mosquito that has just had a blood meal. When gametes of different parasitic strains mate and their genes recombine, novel, multilocus traits—such as drug resistance—can emerge. Day and colleagues dissected 16,000 New Guinean mosquitoes and analyzed the parasites inside the infected ones, studying three genetic loci. They also examined parasites from nearly 400 people—and found striking differences between their results and Walliker's. Only about 15% of the Papua New Guinea parasites were heterozygotes, compared to 65% of the Tanzanian parasites, suggesting much more inbreeding in the New Guinean population. Evolutionary biologist Francisco Ayala of the University of California, Irvine, calls this finding "one of the most important insights on the population structure of *Plasmodium* to date."

Both Walliker and Day say the key reason for the different mating patterns appears to be the local rate of transmission of the disease. In Tanzania, transmission from mosquitoes to humans is very high—people receive between 300 and 3000 infected bites per year. A single human host often carries many different strains of malaria at once, and mosquitoes are likely to take up mixed strains, allowing frequent cross-mating. But although this orgy of genetic mixing may favor the appearance of new multilocus traits, it doesn't help establish such traits in the population, explains Day. The new combinations of genes can be destroyed as often as they are created and may not hold together from one generation to another.

In contrast, in Papua New Guinea, the transmission rate of malaria is 10 times lower, which means more mating between parasites of the same strain. But there's still enough cross-mating to occasionally generate new, multilocus traits. And when these traits do arise, they are more likely to be fixed in the population, Day says. She predicts that where transmission intensity is low and parasites are inbred—as in Papua New Guinea—drug resistance may spread rapidly.

All this has the surprising result that efforts to decrease the transmission rate of malaria may inadvertently accelerate the evolution of drug resistance, says Daniel Hartl, a population geneticist at Harvard University. But, he says, "we will need to learn a lot more about the population biology of the parasite to assess the magnitude of this effect." It remains to be seen how the inbreeding effect compares with the well-known effect of drug pressure in accelerating the spread of resistance, says Walliker. Ayala agrees, saying that similar types of experiments should be conducted in other parts of the world to test Day's predictions. But not without another several thousand mosquito dissections.

–Karen F. Schmidt

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