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Biotech takes on malaria

Picture the insect that annoys you most when you are enjoying the outdoors. Did you think of a mosquito? These common pests attract a lot of attention with swats and spray, but they have also attracted the attention of scientists, particularly the mosquito *Anopheles gambiae*.

This image was provided by KidsHealth: www.KidsHealth.org

Why the interest in mosquitoes? *Anopheles gambiae* is the major mosquito vector of the malaria parasite *Plasmodium falciparum*. Each year malaria has a dramatic impact on humanity. Hundreds of millions of malaria infections and up to three million malaria-related deaths are estimated to occur each year across the globe. The countries that are hit the hardest are in sub-Saharan Africa, however, more than 40% of the global population lives in countries where the disease is endemic.

The disease

Malaria is a serious concern in many countries. The protozoan parasite *Plasmodium falciparum* is the most lethal malaria parasite. It is transmitted from one human to another by the mosquito *A. gambiae* and others in the anopheline genus. The parasite's life cycle in the mosquito begins when the mosquito bites a human infected with the disease. Blood that contains *Plasmodium* gametocytes is taken up in the mosquito's blood meal. The gametocytes form a zygote in the insect's midgut and then develop into motile ookinetes. The ookinete crosses the midgut epithelium and forms an oocyst, filled with sporozoites, on the outer surface of the epithelium. The oocyst later bursts and the worm-like sporozoites travel to the salivary glands. When the mosquito bites another human it injects the sporozoites. These journey to the liver and there develop into merozoites, which can multiply in red blood cells. A fraction of these further develop into gametocytes, ready to be taken up by other mosquitoes as the cycle continues.

The fight to beat malaria

The fight against malaria has seen several approaches. Only a few mosquito species transmit the parasite. In the past control of these carriers through massive spraying of insecticides or elimination of breeding sites has greatly limited malaria in some areas, even eradicating it in a few places. Mosquitoes, however, develop resistance to insecticides; the parasite becomes resistant to preventative and therapeutic drugs; and effective vaccines do not exist. Current controls measures have reduced the impact of malaria, but have not eliminated it.

Biotech approaches

Current research in the battle against malaria has come from the biotech front. Researchers at the Case Western Reserve University School of Medicine are developing a transgenic mosquito that one day could be added to the arsenal in the battle against malaria. The researchers created a gene, called SM1 that encodes for a protein that interferes with the development of the parasite in the mosquito. This gene was injected into the embryos of *Anopheles stephensi* mosquitoes, where it was

incorporated into the genome, and became part of the mosquito's DNA. The new protein binds to the epithelial surface of the mosquito's midgut and competes with the parasite, inhibiting its development by about 80%. The parasites that fail to cross the midgut die. Researchers are also looking for a way to inhibit the parasite's invasion of the mosquito's salivary glands. Finding ways to block the development of the parasite at various points of its development is important, as no method is 100 percent effective.

These mosquitoes have not yet been released in an attempt to replace infectious populations, as more research is required. The use of genetically modified insect vectors in the field will require considerations in terms of biosafety, ecology, and ethical, legal, and social issues.

The genomics contribution

Genomics has entered the malaria scene. In 1999, a group of experts concluded that sequencing of the *Anopheles* genome was both feasible and necessary. This initiative was launched at the *A. gambiae* Genome Summit convened in Paris in 2001. Less than two years later the sequencing of the *A. gambiae* genome is complete! The genome sequence spans 278 million base pairs and was assembled in much the same way as the fruit fly, human, and mouse genomes. This genome sequence provides an architectural scaffold for mapping, identifying, selecting, and exploiting desirable insect vector genes. It will help researchers better understand mosquito biochemistry, physiology, and behavior, as well as malaria epidemiology. This information will also aid research as described above with transgenic mosquitoes.

With the human and *Anopheles* genome sequences two corners of the infection triangle are covered. The third has in fact been taken care of as well. The DNA sequence of *Plasmodium falciparum* is almost complete. As well, a draft of the genome sequence of a related *Plasmodium* species that infects rodents has been completed. Researchers now have the genetic blueprints for the parasite, its vector, and its victim.

The *P. falciparum* sequencing proved more difficult than its vector, the mosquito. The project was started in 1996 and researchers encountered "surprisingly difficult problems." Dozens of people from four organizations laboured together to decipher the 23-million base genome. Persistence has paid off and now thanks to the genome sequence new methods to control the parasite are in development.

One Achilles' heel could be an odd subcellular component, called the apicoplast. This is found only in *Plasmodium* and its relatives. With the genome sequence a complete metabolic pathway has been put together. About 12% of all the parasite's proteins, once made, head for the apicoplast. The structure also appears to be the only place where the parasite makes the fatty acids required to survive. If this biochemical pathway can be targeted a highly effective drug-target strategy could be developed against the parasite and would not affect humans.

This is one more example of the way biotechnology is contributing to improved quality of life around the globe.

For more information:

Life cycle of the mosquito - Agriculture and Agri-Food Canada:
http://res2.agr.ca/ecorc/program2/entomology/biting_flies/english/mosquito.html

Hey! A mosquito bit me! Article at KidsHealth:
http://kidshealth.org/kid/ill_injure/aches/mosquito.html

Malaria life cycle - Malaria Foundation International:
http://www.malaria.org/LIFECYCL.HTM

What is malaria - World Health Organization fact sheet:
http://www.who.int/inf-fs/en/InformationSheet01.pdf

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