Bacillus thuringiensis Cry4B toxin kills Anopheles gambiae, a principal vector of malaria

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Researchers at The University of Texas at Dallas (UTD), led by Dr. Lee Bulla, have characterized a protein produced by the soil bacterium *Bacillus thuringiensis* subsp. *israelensis* (Bti), which is highly toxic against *Anopheles gambiae*, the principal mosquito vector of malaria. The protein toxin, which has been known for a number of years, is produced in a complex of other protein toxins, called Cry toxins, which also have mosquitocidal activity against other species of mosquito. The novelty of the research done by the UTD scientists is that they differentially fractionated all the native Cry proteins contained in the Bti complex, collectively cloned and expressed the genes responsible for their production and determined that one of the toxins (Cry4B) has very high toxicity to a Permethrin-resistant strain of *An. gambiae*, compared to the other Cry toxins of the complex.

The publication of this article in the April issue of *Experimental Biology and Medicine* coincides with World Malaria Day (April 26th). According to the World Malaria Report 2011, malaria is prevalent in 106 countries of the tropical and semi-tropical world. The main strategies for controlling malaria involve anti-malarial drugs, vaccines and insecticides. A few drugs have been able to provide relief to patients but a preventive anti-malarial vaccine is yet to be developed. Drug resistance is a major problem in the treatment and prophylaxis of malaria because malaria parasites have developed resistance against many different drugs.

Insecticide-treated bed nets are considered key in fighting malaria. Only pyrethroid insecticides are approved for use on insecticide-treated bed nets. One such pyrethroid used widely on bed nets is Permethrin, a neurotoxicant whose mechanism of action is similar to that of organochlorines such as DDT. Permethrin is classified by the United States Environmental Protection Agency as "Likely to be Carcinogenic to Humans".

Recent studies indicate an increase in Permethrin resistance by *An. gambiae*, which is placing into question the effectiveness of nets. Indeed, the number of malaria cases has begun to increase due, in part, to the growing resistance by mosquitoes to Permethrin being used on bed nets.

The upturn in resistance, particularly to Permethrin, by *Anopheles* species has prompted concern that malaria, a disease once thought to have been eradicated in many countries, is resurgent. Therefore, it is not surprising that there is renewed interest in environmentally safe and sustainable methods for vector control aimed at reducing reliance on chemical insecticides.

"What makes the work so exciting," said Dr. Mohamed Ibrahim, senior author of the paper, "is that the mosquitocidal activity against Permethrin-resistant mosquito by the Bti strain used in this study is significantly greater than that of similar strains used in commercial vector control products distributed in various parts of the world."

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said "Bulla and colleagues have tackled an important problem in global health, the resistance developed by *Anopheles gambiae*, a major vector of malaria, to varied insecticides. In this study they demonstrate that Cry4B, a protein produced by *Bacillus thuringiensis*, effectively kills even insecticide (Permethrin) resistant forms of the mosquito larvae. Therefore, this group is suggesting an alternative, chemical free, approach to the control of malaria".