BT-R3 mediates killing of the malaria vector Anopheles gambiae by Bacillus thuringiensis

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Researchers at The University of Texas at Dallas (UTD), led by Dr. Lee Bulla, have demonstrated for the first time the selective cytotoxicity of *Bacillus thuringiensis* subsp. *israelensis* Cry4B toxin is mediated by BT-R3. The Cry toxins produced by *Bacillus thuringiensis* exert their insecticidal activity by binding with high-affinity to their cognate cadherin receptors located on the surface of epithelial cells that line the midgut of susceptible insects. In the case of *Anopheles gambiae*, binding of the Cry4B toxin by BT-R3, in turn, triggers an internal signaling event that turns on a cell death pathway. The novelty of the research done by the UTD scientists is that they were able to establish the direct involvement of the BT-R3 receptor, cloned from *Anopheles gambiae*, in mediating toxicity of the Cry4B toxin in living cells. The research reported in this article in the July 2013 issue of *Experimental Biology and Medicine* is a culmination of proteomics, genomics and bioinformatics strategies developed in the Bulla laboratory.

Validation of BT-R3 as a functional receptor for Cry4B exemplifies the power of proteomics, genomics and bioinformatics to identify target proteins such as the BT-R3 receptor. The process of target selection starts with data mining of archived protein sequences available in various genome and proteome databases, and results in the selection and annotation of candidate proteins based on their potential to mediate insecticidal action. It brings together genome- and proteome-based target identification and target-directed screening for validating the action of insecticidal proteins such as the Cry4B toxin—engineered or otherwise. Targets selected for consideration can then be analyzed in silico by

docking calculations, molecular dynamics simulations and other techniques to characterize appropriate target interactions with chemically or genetically altered Cry toxins.

Dr. Mohamed Ibrahim, senior author of the paper, said "this kind of strategy will facilitate protein design for creation of new customized Cry proteins and peptide mimics that might be more effective than the natural toxins themselves against *Anopheles gambiae* and other mosquitoes, and, hopefully, less able to bring about insect host resistance."

New approaches are needed in the area of malaria control because no effective vaccine currently exists and no available anti-malarial medications have been designed or discovered that impede parasite resistance with long-term use. A few drugs have been able to provide relief to patients but a preventive anti-malarial vaccine is yet to be developed. Certainly, genetic modification of wild mosquito vector populations to reduce vectorial capacity is fraught with unknown and hidden trials and tribulations.

Dr. Steve Goodman, Editor-in-Chief of *Experimental Biology and Medicine* said "Lee Bulla and his colleagues have combined genomics, proteomics and in silico analysis to establish the role of the cadherin receptor BT-R3 in the killing action of Cry4B mosquito toxin. Understanding of this Cry4B-BT-R3 complex will allow the design of custom proteins and peptides to help control the spread of malaria by mosquitoes".

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