Researchers discover how mosquitoes avoid succumbing to viruses they transmit

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Mosquitoes are like Typhoid Mary. They can spread viruses which cause West Nile fever, dengue fever, or yellow fever without themselves getting sick. Scientists long thought that the mosquito didn't care whether it had a virus hitchhiker, but have now discovered, "There is a war going on," said Zach Adelman, assistant professor of entomology at Virginia Tech.

The war is at the cellular level, between the host and invading RNA – the strands of code that produce different kinds of viral proteins.

The mediators that balance the interactions between mosquito and virus are virus-derived short-interfering RNAs (viRNAs), which are generated by the mosquito's immune response to infection. "If the mosquito is not able to cut up the virus genome into viRNAs, an otherwise invisible infection becomes fatal-- for both the mosquito and the virus. In other words, to complete the circle and be transmitted back to a vertebrate host, the virus must submit, to some extent, to the mosquito's antiviral response," said Kevin M. Myles, assistant professor of entomology at Virginia Tech.

Myles, Adelman, and their Ph.D. students, who are with the Vector-borne Disease Research Group at Virginia Tech, report their findings about the war between the mosquito immune system and viruses in the *Proceedings of the National Academy of Sciences (PNAS)*, scheduled to appear in the Online Early Edition the week of December 1-5, 2008. The article is, "Alphavirus derived small RNAs modulate pathogenesis in

disease vector mosquitoes," by Myles; Michael R. Wiley of Ambler, Pa.; Elaine M. Morazzani of Vienna, Va.; and Adelman.

"We asked, "How is it that the mosquito can control the pathogenicity of these viruses so well, while humans with our more complex immune systems, often develop disease when infected?" said Myles.

The researchers used the arthropod-borne virus Sindbis -- a model virus for a wide variety of mosquito-transmitted viruses, such as chikungunya and eastern equine encephalitis, both of which cause serious diseases in humans. They infected a mosquito called Aedes aegypti, an important vector of yellow fever and dengue. In response, the mosquito immune system generated viRNAs, which make up 10 percent or more of total cellular small RNAs. "The proportion of the small RNAs that are viRNAs was surprising," the article states.

The researchers then altered the Sindbis genome so that it would carry a protein known to suppress the ability of a cell to cut up virus genomes into viRNAs. "We can't yet knock-out the mosquito's immune response, so we had to alter the virus," Adelman said.

The research also represents the first application of next generation high-throughput sequencing to characterize small RNAs from mosquitoes infected with an arbovirus – a virus that is transmitted by an arthropod vector , said Myles. The researchers used an Illumina machine capable of generating more than four million sequences from one sample. "It is powerful technology," said Myles.

The discovery provides a potential target for fighting mosquito-borne diseases – by upsetting the balance so the virus kills the mosquito. "We didn't know it was possible to unleash this kind of pathogenic potential in the mosquito," Myles said.

"We would still have mosquitoes biting us, but they would not be transmitting viruses," said Adelman.

Additional research will be required to determine how to manipulate the mosquitoes' immune response towards this end," said Myles.

The paper also discusses the potential of therapeutic approaches using knowledge gained from studying viRNAs from infected mosquitoes to control the pathogenesis of these viruses in mammalian hosts.

Source: Virginia Tech