No antibodies, no problem: Researchers identify how mosquito immune system attacks specific infections

October 18 2012

Mosquito. Image: UCLA.

Researchers at the Johns Hopkins Bloomberg School of Public Health have determined a new mechanism by which the mosquitoes' immune system can respond with specificity to infections with various pathogens, including the parasite that causes malaria in humans, using one single gene. Unlike humans and other animals, insects do not make antibodies to target specific infections. According to the Johns Hopkins researchers, mosquitoes use a mechanism known as alternative splicing to arrange different combinations of binding domains, encoded by the same AgDscam gene, into protein repertoires that are specific for different invading pathogens. The researchers' findings were published October 18 in the journal *Cell Host & Microbe* and could lead to new

ways to prevent the spread of a variety of mosquito born illnesses.

Mosquitoes and other insects use their primitive innate immune systems to successfully fight infections with a broad spectrum of viruses, bacteria, fungi and parasites, despite the lack of antibodies that are part of the more sophisticated human immune system. The effectiveness of the human immune system is to a large degree based on the ability to produce an enormous variety of antibodies containing different immunoglobulin domains that can specifically tag and label a pathogen for destruction. This great variety of pathogen-binding antibodies is achieved by combining different immunoglobulin gene segments and further mutate them through mechanisms called somatic recombination and hypermutation. While mosquitoes also have genes encoding immunoglobulin domains, they lack these specific mechanisms to achieve pathogen recognition diversity.

The Johns Hopkins researchers discovered a different way by which mosquitoes can combine immunoglobulin domains of a single gene called AgDscam (Anopheles gambiae Down Syndrome Cell Adhesion Molecule) to produce a variety of pathogen-binding proteins. The AgDscam gene is subjected to a mechanism called alternative splicing that combines different immunoglobulin domains into mature AgDscam proteins, depending on which pathogen has infected the mosquito. The researchers showed that this alternative splicing is guided by the immune signal transducing pathways (analogous to electrical circuits) that they previously demonstrated to activate defenses against different malaria parasites and other pathogens. While alternative splicing of the AgDscam gene does not nearly achieve the degree of pathogen recognition diversity of human antibodies, it does nevertheless vastly increase the variety of pathogen binding molecules.

"Using antibodies to fight infection is like fishing with a harpoon—it's very targeted. The mosquito's innate immune system is more like fishing

with a net—it catches a bit of everything," explained George Dimopoulos, PhD, senior investigator of the study and professor with the Johns Hopkins Malaria Research Institute. "However, we discovered that immune pathway-guided alternative splicing of the AgDscam gene renders the mosquito's immune net, so to speak, more specific than previously suspected. The mosquito's immune system can come up with approximately 32,000 AgDscam protein combinations to target infections with greater specificity."

Dimopoulos and his group are developing a malaria control strategy based on mosquitoes that have been genetically modified to possess an enhanced immune defense against the malaria parasite Plasmodium. One obstacle to this approach is the great variety of Plasmodium strains that may interact somewhat differently with the mosquito's immune system.

"Some of these strains may not be detected by the engineered immune system proteins that mediate their killing. Our new discovery may provide the means to create genetically modified mosquitoes that can target a broader variety of parasite strains, like casting a net rather than shooting with a harpoon," said Dimopoulos.

Malaria kills more than 800,000 people worldwide each year. Many are children.

More information: "Anopheles NF-kB –Regulated Splicing Factors Direct Pathogen-Specific Repertoires of the Hypervariable Pattern Recognition Receptor AgDscam" was written by Yuemei Dong, Chris M. Cirimotich, Andrew Pike, Ramesh Chandra and George Dimopoulos.

Provided by Johns Hopkins University Bloomberg School of Public Health