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Immune system 'circuitry' that kills malaria in mosquitoes identified

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Researchers at the Johns Hopkins Malaria Research Institute have, for the first time, determined the function of a series proteins within the mosquito that transduce a signal that enables the mosquito to fight off infection from the parasite that causes malaria in humans. Together, these proteins are known as immune deficiency (Imd) pathway signal transducing factors, are analogous to an electrical circuit. As each factor is switched on or off it triggers or inhibits the next, finally leading to the launch of an immune response against the malaria parasite. The study was published June 7 in the journal *PLoS Pathogens*.

The latest study builds upon earlier work of the research team, in which they found that silencing one gene of this circuit, Caspar, activated Rel2, an Imd pathway transcription factor of the Anopheles gambiae mosquito. The activation of Rel2 turns on the effectors TEP1, APL1 and FBN9 that kill malaria-causing parasites in the mosquito's gut. More significantly, this study discovered the Imd pathway signal transducing factors and effectors that will mediate a successful reduction of parasite infection at their early ookinete stage, as well as in the later oocyst stage when the levels of infection were similar to those found in nature.

"Identifying and understanding how all of the players work is crucial for manipulating the Imd pathway as an invention to control malaria. We now know which genes can be manipulated through genetic engineering to create a malaria resistant mosquito" said George Dimopoulos PhD, professor in the Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health.

To conduct the study, Dimopoulos's team used a RNA interference method to "knock down" the genes of the Imd pathway. As the components were inactivated, the researchers could observe how the mosquito's resistance to parasite infection would change.

"Imagine a string of Christmas lights or other circuit that will not work when parts aren't aligned in the right sequence. That is how we are working with the mosquito's immune system," explained Dimopolous. "We manipulate the molecular components of the mosquito's immune system to identify the parts necessary to kill the malaria parasites."

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

More information: "Anopheles Imd pathway factors and effectors in infection intensity-dependent anti-Plasmodium action", *PLoS Pathogens*.

Provided by Johns Hopkins University Bloomberg School of Public Health