**A receptor for human sweat**

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When we sweat, our pores excrete a compound called lactic acid. Since the 1960s, scientists have known that lactic acid can elicit attraction in mosquitoes but how they sense this compound has been elusive until now. Mosquitoes are hard-wired for seeking a vertebrate host to obtain a blood meal. This innate behavior along with their ability to transmit diseases has made mosquitoes the deadliest animal in the world.

Mosquitoes have detectors of chemicals emitted from our body that allow them to find us through their sense of smell (olfaction). Our lab’s focus is to use genetics to identify the mosquito receptors that are responsible for detecting their human and plant hosts. In our recent paper, we have found a receptor pathway in the mosquito that senses human odors including lactic acid. Mosquitoes have three main classes of chemosensory receptors that they use to interpret information from their environment. To locate a host for a blood meal, female mosquitoes detect carbon dioxide (CO2) from our breath using the gustatory receptor (GRs) family of chemosensory receptors. They are then attracted to volatile compounds emitted from the host which they sense using olfactory receptors (ORs) and ionotropic receptors (IRs). Upon landing on a host, they likely use GRs and IRs to taste the skin and decide whether to feed.

In a previous study, the olfactory receptor co-receptor (*orco*) was genetically removed. This told us that without the OR chemosensory pathway, female mosquitoes were still attracted to humans in the presence of CO2, meaning that there were other genes responsible for host detection in mosquitoes. Our hypothesis was that human odor specific receptors would have to be part of a pathway that is distinct from both GRs and ORs. Additionally, we focused our efforts on finding chemosensory receptors that are localized to the antennae, the mosquito’s nose, because these genes should be involved in olfaction, not taste or other senses. IR8a fit the profile and we began our studies.

In order to assess whether the *Ir8a* gene was indeed a receptor for human sweat, we first used a genome editing tool to insert a red fluorescent protein into *Ir8a* to eliminate the gene’s function and mark the mutants with a red glow. To determine the odors detected by *Ir8a* mutants, we initially recorded the electrical responses of the mutant antennae and compared them to normal mosquitoes. These recordings showed that *Ir8a* mutants were unable to respond to carboxylic acids and more importantly lactic acid, a major component of human sweat.

We then wanted to understand if the loss of IR8a made it harder for mosquitoes to find humans. Olfactometer experiments give us the ability to score mosquito attraction by placing a human subject’s arm in a controlled environment where mosquitoes can fly upwind to get close to the arm, but not bite them.Normal mosquitoes and *orco* mutants show no difference in host attraction when CO2 was added to this assay. While *Ir8a* mutant attraction is reduced approximately by half when compared to normal mosquitoes. The reduction in *Ir8a* mutant attraction did not change if CO2 was present or not. This finding suggests that the *Ir8a* pathway functions in guiding the mosquito to humans using a specific subset of odors that other receptors do not detect.

To identify how the different olfactory pathways tune mosquito host-seeking behavior, we tested attraction of double mutants *Ir8a*/*orco* and *Ir8a*/*Gr3*. The *Ir8a*/*orco* double mutant significantly reduced attraction when compared to the *Ir8a* mutant but only in the absence of CO2. Whereas, the *Ir8a*/*Gr3* mutant showed no difference in host-seeking compared to the *Gr3* mutant. Therefore, *Gr3* senses CO2 and activates the detection of human odors by the OR and IR pathways.

Our findings describe a key new player in mosquito host detection, IR8a, advancing our understanding of the mosquito olfactory code. Mosquitoes are first attracted by CO2 which is exhaled from the breath of vertebrates and indicates a living animal. Activated mosquitoes then use ORs and IRs to discern the host’s odor signature. We now want to find the odor-tuned receptors that detect lactic acid and other human acidic volatiles. To do this, we will express the odor-tuned IRs along with the co-receptor *Ir8a* and assess their responses to a panel of odors. This will increase our understanding of how the mosquito’s deadly behavior works and provide molecular targets for mosquito repellent design.