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Genetic analysis of mosquito detection of humans

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Mosquitoes detect the presence of humans by integrating chemosensory, thermal, and visual cues. Among these, odors are crucial for mosquito host detection. Insects have evolved a diverse repertoire of receptors to detect their plant and animal hosts. Genetic analysis of these receptors in *Drosophila* has set the stage for similar studies in mosquitoes. The diversity of the cues involved in mosquito host-seeking has made designing behavioral control strategies a challenge. The sensory receptors that are most important for mosquito detection of humans can now be determined using genome editing. Here, we will review our current understanding of the salient cues that attract mosquitoes, their receptors, and suggest ways forward for novel olfaction-based vector control strategies.

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Introduction

Female mosquitoes use a combination of cues to find their vertebrate hosts and blood-feed. Their feeding behavior not only annoys us, but creates a potent pathway for disease transmission. For example, *Aedes aegypti* are vectors of viral diseases such as yellow fever, dengue, chikungunya and Zika [1,2]. Certain mosquito species like *Ae. aegypti* and the malaria vector, *Anopheles gambiae*, have evolved a preference for humans, which makes them efficient vectors for disease transmission [3,4]. *Ae. aegypti* mosquitoes have evolved a preference for human hosts (anthropophily) from an ancestral subspecies that does not prefer humans (zoophily) [5,6•]. Host discrimination requires olfactory receptor function and has been linked to specific receptors that have increased expression and odor sensitivity in anthropophilic *Ae. aegypti* [6•,7]. From these studies, it is clear that *Ae. aegypti* uses olfaction to find their human hosts. Along with olfaction, other sensory pathways are also likely to participate in the detection of humans by mosquitoes. A comprehensive understanding of the cues that attract mosquitoes to humans, the receptors that detect them, and the neural circuits they activate will provide the necessary insight to develop new strategies to disrupt host-seeking behavior. To achieve this goal, genetic tools are now available.

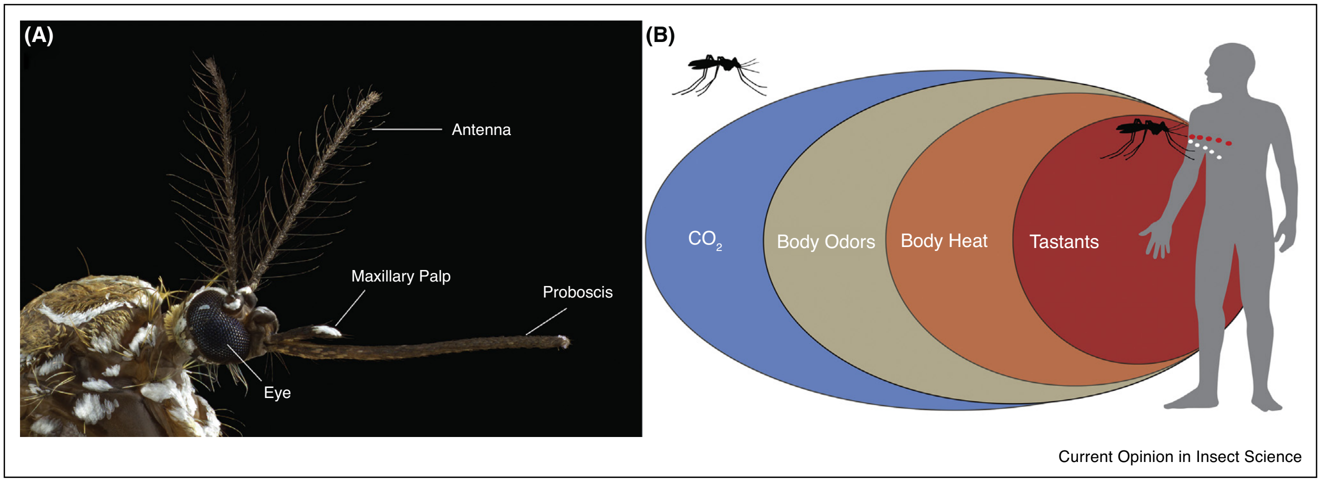
Our ability to understand the molecular basis of mosquito behavior has been enhanced by the recent development of genome editing tools such as CRISPR-Cas9 RNA-guided nucleases, TALE-effector Nucleases (TALENS) and Zinc Finger Nucleases (ZFNs) in *Anopheles* and *Aedes* [8]. These approaches can be employed to facilitate targeted mutagenesis at any gene of interest to determine their contribution to host detection and blood feeding. These techniques could also be used to integrate genetic tools into the mosquito genome to map the neural circuits that enable these behaviors. Targeted mutagenesis of olfactory receptors have already been successfully performed in *Ae. aegypti* [7,9•]. These techniques have already identified multiple genetic pathways that mosquitoes employ to detect their hosts, but many questions remain. This review seeks to survey the progress made in understanding the molecular mechanism of mosquito host detection.

Human cues

Odor is a critical cue that signals the presence of a host to mosquitoes [10]. Human odor is a complex blend of chemicals [11]. Skin microbiota plays a large role in generating volatile compounds that attract mosquitoes [12]. In *Ae. aegypti* and *An. gambiae*, odors that elicit both electrophysiological and behavioral responses have been found. Among these compounds are lactic acid, ammonia, ketones, sulfides [13–15], 1-octen-3-ol [16], and carboxylic acids [17]. The odors emanating from a host are sensed via olfactory receptors, which can be found on the mosquito antennae, maxillary palps, and proboscis (Figure 1a, [18]). Exposing female mosquitoes to carbon dioxide (CO_2) induces flight takeoff and sustained flight [19]. CO_2 is detected by gustatory receptors that are expressed in the capitate peg sensilla of the maxillary palps [20]. Identifying which components of the diverse set of human odor-ligands are the most salient is a key step in understanding how mosquitoes detect humans.

Heat attracts mosquitoes to their hosts at close range [21]. Mosquitoes will land on inanimate objects set at human body temperature in the presence of CO_2 [9•,22]. Electrophysiological studies revealed that there is an antagonistic pair of thermosensitive neurons within the

Figure 1



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Olfaction enables mosquitoes to detect human hosts.
(a) Image of an *Ae. aegypti* mosquito showing the sensory organs involved in host detection and blood feeding. The antenna and maxillary palp detect odors emanating from the host. The proboscis detects taste cues and may also perceive odors. The eyes sense visual features in the environment and allow for flight navigation towards the host. (Photograph courtesy of artist Alex Wild) **(b)** Mosquitoes detect human hosts using combination of cues. At a distance, they sense CO_2 exhaled from human's breath. As they move closer, they sense odor and heat that emanate from the host, they land on the skin where they taste with the taste receptors on their legs and mouth parts. When they bite, they can either infect the host with pathogens carried by their saliva (white dots) or become infected with the host's blood (red dots).

coeloconic sensilla of the *Ae. aegypti* antennal tip where one sensillum is tuned to temperature rise and the other is sensitive to cold [23]. The integration of the responses from these two sensilla has been proposed to allow mosquitoes to respond to temperature changes and host thermal cues. The response to thermal cues may depend on the background ambient temperature, which would necessitate that mosquitoes possess a mechanism for sensing thermal contrast. The *TRPA1* receptor allows mosquitoes to avoid warm objects that exceed host body temperature, aiding the detection of thermal cues [24•]. The sensor(s) that allow mosquitoes to detect attractive heat cues are still unknown. Ionotropic Receptors (IRs) that are temperature responsive have been found in *Drosophila* [25,26]. Further studies are needed to identify whether these receptors or others are important for mosquitoes to detect the temperature of their hosts.

Mosquitoes are also guided by visual cues to fly towards their hosts [27]. Adult mosquitoes possess compound eyes that are sensitive to varying light intensity [27]. It has been documented that photoreceptors in night-biting mosquitoes, such as *An. gambiae*, adjust to varying light intensity by regulating rhodopsin levels. This could enhance visual sensitivity to a potential host in low light conditions [28]. Unlike *Anopheles*, visual cues are proposed to be more crucial for day-biting mosquitoes including *Aedes* and *Culex*, but little is known about this. Visual cues likely play an intermediate role in host detection by integrating long-range odor plume tracking with shorter-range cues [29•]. For instance, CO_2 or human odor can increase the ability of mosquitoes to pay attention to visual cues by enhancing visual flight navigation to the host [30,31]. Understanding the connection between olfactory sensitivity, flight navigation, and visual target selection will help to identify the behavioral neural circuits that enable mosquito host-seeking.

While female mosquitoes are guided by other cues to fly towards their hosts (Figure 1b), the tastants on the skin likely promote blood feeding once they land. After landing, they soon pierce the skin and draw blood from small blood vessels [31]. The mouthparts of the female mosquito are highly specialized for blood feeding and contain sensory hair cells which help locate blood under the skin [32•]. The *An. stephensi* proboscis does not only respond to taste but also detects thermal cues [22]. The transcriptome of the *Ae. aegypti* proboscis has been recently identified providing a complete list of genes expressed in this tissue [33]. Genetically manipulating the chemoreceptors expressed in the proboscis could provide insight into mosquito biting behavior and possibly provide evidence for a role in host detection during flight. The contact cues on human skin and the receptors that sense them remain for the most part elusive.

Multimodal integration of human cues

Genetic analysis has demonstrated that mosquitoes integrate multiple stimuli to find their hosts. One of the most striking examples is the gating of multiple cues by CO_2 [9•]. *Ae. aegypti* mosquito attraction requires at least two cues. For example, neither thermal cues, nor lactic acid