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Genetic Analysis of Mosquito Detection of Humans

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Abstract

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.

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.

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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 to map the neural circuits that enable these behaviors. Targeted mutagenesis of the olfactory receptors has been successfully performed in *Ae. aegypti* and has been linked to a reduction in host attraction [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 CO₂ induces flight takeoff and sustained flight [19]. CO₂ is detected by gustatory receptors that are expressed in the capitate peg sensilla of the maxillary palp [20]. Identifying which components of the diverse set of human odor-ligands are the most salient is 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 CO₂ [9*, 22]. Electrophysiological studies showed that there is an antagonistic pair of thermosensitive neurons within the 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, *An. gambiae* adjust to varying light intensity by regulating the 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 hematophagous *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, CO₂ 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 the field 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 [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 CO₂ [9*]. *Ae. aegypti* mosquito attraction requires at least two cues. For example, neither thermal cues, nor lactic acid are attractive on their own. If CO₂ is combined with either of these cues, mosquito attraction is greatly enhanced. If sensitivity to CO₂ is lost, as in *Gr3* mutants, this synergistic effect of CO₂ does not occur. Host odor may also gate mosquito responses to hosts [7]. Mutant mosquitoes lacking the olfactory receptor co-receptor (*orco*) gene have reduced attraction to human odor, but in the presence of CO₂, there was no difference between the wild-type and *orco* mutant mosquitoes [7]. In addition, both *Gr3* and *orco* mutants respond normally to human arm in olfactometer assays [7, 9*]. Taken together, these results demonstrate that mosquitoes have robust and redundant mechanisms to detect human hosts. The disruption of one pathway is unlikely to eliminate mosquito host-seeking. Employing multiple sensory pathways may increase the chance of a mosquito successfully targeting a host.

Mosquitoes may also integrate odor with taste cues in response to hosts. Riabinina et al., [34] recently documented that olfactory receptor neurons (ORN) expressing the *orco* gene project from the labella on the proboscis to the suboesophageal zone (SEZ) of the brain, and suggests that the SEZ may integrate odor and taste cues during blood feeding. This region of the insect brain has been shown to be critical for taste integration in *Drosophila* [35]. In *Ae. aegypti*, *in vivo* calcium imaging revealed the activation of some ORs by some volatile compounds in the blood, and removing the function of the ORs in the stylet impairs blood feeding [31]. Clearly, the ability to integrate host sensory cues represents an essential mechanism employed by mosquitoes to guide host detection and blood-feeding behavior.

Molecular sensors of human cues

Insects have evolved complex repertoires of chemosensory receptors to respond to their environment including: odorant receptors (ORs), ionotropic receptors (IRs) and gustatory receptors (GRs) [36]. In *Drosophila*, the ORs are expressed in the dendrites of ORNs. The sensillar lymph surrounding the ORNs is densely packed with odorant-binding proteins (OBPs) that are hypothesized to be involved in odorant uptake and odor delivery to the ORs, but their role remains unclear [37]. The neural processing of olfactory information has been extensively studied in *Drosophila* [38, 39]. The axons of the ORNs project to the antennal lobe where they synapse with projection neurons (PN). In turn, PNs convey olfactory information to the mushroom body (MB) and lateral horn (LH) of the brain which subsequently leads to a behavioral response. How mosquitoes process host cue information has not been well established, but the lessons from *Drosophila* are likely to apply.

In *Drosophila*, ORs form a heteromeric complex with *orco* for their targeting to the cell membrane [40, 41]. The OR pathway plays a critical role in mosquito preference for human hosts and DEET repellency [7, 42]. ORs from *An. gambiae* have been comprehensively deorphanized using the *Drosophila* empty neuron system [43]. These ORs tested seemed to be narrowly tuned to several odor components that emanate from humans such as 1-octen-3-ol (present in human breath), 2,3-butanedione (by-product of metabolized sweat) and indole (human sweat volatile) [43]. The narrow tuning of these ORs may serve to improve cue salience [44].

The IRs are expressed in the dendrites of the ORNs innervating the coeloconic sensilla [45]. There are at least two IR co-receptors, *Ir8a* and *Ir25a*, and possibly a third, *Ir76b* [45, 46]. These co-receptors form an odor-responsive ion channel complex with odor-selective IRs. *Drosophila* IRs respond primarily to amines and acids while ORs respond to esters and alcohols [47]. Beyond olfaction, *Drosophila* IRs play a role in taste [48, 49], moisture and temperature sensing [25, 26], and possibly in the auditory system [50]. Although GRs are usually involved in taste [35], specialized GRs have been implicated in other sensory modalities in insects including light sensing [51], warmth sensing [52], and CO₂ detection [53]. Excluding the Grs that detect CO₂, it remains unknown whether the orthologues of these receptor genes respond to similar stimuli in mosquitoes [9*].

Behavioral vector control strategies

Given that olfaction is key for mosquitoes to detect their human hosts, identifying new odors that modulate mosquito olfactory receptor function is a promising approach to combatting mosquito-borne disease [54, 55] (Fig. 2). This can be accomplished using high-throughput screening assays to identify synthetic and natural compounds that activate receptors associated with repellency or inhibit receptors associated with attraction [56]. This strategy can help develop novel spatial mosquito repellents or create odor baits for traps that reduce mosquito populations. Our current understanding of mosquito host detection makes it likely that effective odor-baited traps would need to include multiple cues such as CO₂ and heat to recreate the multimodal sensory experience that drives mosquitoes to their hosts. Next generation mosquito repellents could block multiple chemosensory pathways to render the

human host “invisible”. As an alternative, new repellents that overstimulate a specific chemosensory pathway could cause mosquitoes to avoid humans. To accomplish this important goal, we will need to know the specific receptors that enable mosquito attraction and repellency.

Summary

We have reviewed what is known about the multiple cues that attract mosquitoes to humans and their molecular sensors. Host-seeking is not completely abolished even when either the CO₂-sensing or OR pathways were disrupted in *Ae. aegypti* [7, 9*]. This clearly shows that multiple cues must be considered to understand how mosquitoes find their human hosts. Our current knowledge is not sufficient to develop new behavioral control strategies, but sets the stage for further studies. To efficiently develop these new strategies, we need to have a comprehensive understanding of how mosquitoes detect their human hosts from the perception of cues at the periphery, to the integration of the information in the central nervous system, and finally, to the motor circuits that drive the behavior. Genome editing tools such as CRISPR-Cas9 and other genetic manipulations such as using the GAL4-UAS system to mark or manipulate neural circuits could play a significant role in addressing how the mosquito’s brain responds to human cues [57]. We have learned so much from the genetic analysis of *Drosophila* behavior. Using similar approaches to understand mosquito behavior may provide the mechanistic insight to break the cycle of mosquito-borne disease transmission.

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References and recommended reading

Papers of interest, published before the period of the review, have been highlighted as:

*of interest

1. Severson DW, Behura SK. Genome investigations of vector competence in *Aedes aegypti* to inform novel arbovirus disease control approaches. *Insects*. 2016; 7(4):58.
2. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. *N Engl J Med*. 2016; 374(16): 1552–63. [PubMed: 27028561]
3. McBride CS. Genes and odors underlying the recent evolution of mosquito preference for humans. *Curr Biol Elsevier*. 2016; 26(1):R41–6.
4. Takken W, Verhulst NO. Host preferences of blood-feeding mosquitoes. *Annu Rev Entomol*. 2012; 58(1):433–453. [PubMed: 23020619]
5. Brown JE, Evans BR, Zheng W, Obas V, Barrera-Martinez L, Egizi A, Zhao H, Caccone A, Powell JR. Human impacts have shaped historical and recent evolution in *Aedes aegypti*, the dengue and yellow fever mosquito. *Evolution*. 2014; 68:514–525. [PubMed: 24111703]

- 6*. McBride CS, Baier F, Omondi AB, Spitzer SA, Lutomiah L, Sang R, Ignell R, Vosshall LB. Evolution of mosquito preference for humans linked to an odorant receptor. *Nature*. 2014; 515(7526):222–7. The study provides molecular insight into how *Aedes aegypti* became anthropophilic. [PubMed: 25391959]
7. DeGennaro M, McBride CS, Seeholzer L, Nakagawa T, Dennis EJ, Goldman C, Vosshall LB. *Orco* mutant mosquitoes lose strong preference for humans and are not repelled by volatile DEET. *Nature*. 2013; 498:7455.
8. Reegan AD, Ceasar SA, Paulraj MG, Ignacimuthu S, Al-Dhabi NA. Current status of genome editing in vector mosquitoes: A review. *Biosci Trends*. 2016
- 9*. McMeniman CJ, Corfas RA, Matthews BJ, Ritchie SA, Vosshall LB. Multimodal integration of carbon dioxide and other sensory cues drives mosquito attraction to humans. *Cell*. 2014; 156(5): 1060–1071. This study describes the contribution of *Aedes aegypti Gr3* and carbon dioxide to the integration of cues that mosquitoes use to find their human hosts. [PubMed: 24581501]
10. Takken W, Knols BG. Odor-mediated behavior of afrotropical malaria mosquitoes. *Annu Rev Entomol*. 1999; 44:131–157. [PubMed: 9990718]
11. Bernier UR, Kline DL, Barnard DR, Schreck CE, Yost RA. Analysis of human skin emanations by gas chromatography/mass spectrometry. 2. Identification of volatile compounds that are candidate attractants for the yellow fever mosquito (*Aedes aegypti*). *Anal Chem*. 2000; 72(4):747–56. [PubMed: 10701259]
12. Verhulst NO, Takken W, Dicke M, Schraa G, Smallegange RC. Chemical ecology of interactions between human skin microbiota and mosquitoes. *FEMS Microbiol Ecol*. 2010; 74(1):1–9. [PubMed: 20840217]
13. Davis EE, Sokolove PGJ. Lactic acid-sensitive receptors on the antennae of the mosquito, *Aedes aegypti*. *Comp Physiol*. 1976; 105:43.
14. Braks MA, Meijerink J, Takken W. The response of the malaria mosquito, *Anopheles gambiae* to two components of human sweat, ammonia and L-lactic acid. *Physiol Entomol*. 2001; 26:142–148.
15. Bernier UR, Kline DL, Posey KH, Booth MM, Yost RA, Barnard DR. Synergistic attraction of *Aedes aegypti* (L.) to binary blends of L-lactic acid and acetone, dichloromethane, or dimethyl disulfide. *J Med Entomol*. 2003; 40(5):653–6. [PubMed: 14596278]
16. Majeed S, Hill SR, Birgersson G, Ignell R. Detection and perception of generic host volatiles by mosquitoes modulate host preference: context dependence of (R)-1-octen-3-ol. *R Soc Open Sci*. 2016; 3:160467. [PubMed: 28018630]
17. Smallegange RC, Qiu YT, Bukovinszkiné-Kiss G, van Loon JJA, Takken W. The effect of aliphatic carboxylic acids on olfaction-based host-seeking of the malaria mosquito *Anopheles gambiae sensu stricto*. *J Chem Ecol*. 2009; 35(8):933–43. [PubMed: 19626371]
18. Montell, C., Zwiebel, LJ. Mosquito sensory systems. In: Raikhel, AS., editor. *Progress in Mosquito Research. Adv Insect Physiol*. Vol. 51. 2016. p. 293-328.
19. Dekker T, Carde RT. Moment-to-moment flight manoeuvres of the female yellow fever mosquito (*Aedes aegypti* L.) in response to plumes of carbon dioxide and human skin odour. *J Exp Biol*. 2011; 214:3480–3494. [PubMed: 21957112]
20. Lu T, Qiu YT, Wang G, Kwon J, Rutzler M, Kwon H, Pitts R, van Loon J, Takken W, Carlson J, Zwiebel L. Odor coding in the maxillary palp of the malaria vector mosquito *Anopheles gambiae*. *Curr Biol*. 2007; 17:1533–1544. [PubMed: 17764944]
21. Khan AA, Maibach HI, Strauss GW, Fenley WR. Quantification of effect of the several stimuli on the approach of *Aedes aegypti*. *J Econ Entomol*. 1966; 59(3):690–694. [PubMed: 5932265]
22. Maekawa E, Aonuma H, Nelson B, Yoshimura A, Tokunaga F, Fukumoto S, Kanuka H. The role of proboscis of the malaria vector mosquito *Anopheles stephensi* in host-seeking behavior. *Parasit Vectors*. 2011; 4:10. [PubMed: 21272298]
23. Gingl E, Hinterwirth A, Tichy H. Sensory representation of temperature in mosquito warm and cold cells. *J Neurophysiol*. 2005; 94:176–185. [PubMed: 15673550]
- 24*. Corfas AR, Vosshall LB. The cation channel *TRPA1* tunes mosquito thermotaxis to host temperatures. *eLife*. 2015; 4:e11750. The behavioral mechanism underlying heat-seeking behavior in *Aedes aegypti* was examined. [PubMed: 26670734]

25. Enjin A, Zaharieva EE, Frank DD, Mansourian S, Suh GSB, Gallio M, Stensmyr MC. Humidity sensing in *Drosophila*. *Curr Biol*. 2016; 0(0):1352–8.
26. Knecht ZA, Silbering AF, Ni L, Klein M, Budelli G, Bell R, Abuin L, Ferrer AJ, Samuel AD, Benton R, et al. Distinct combinations of variant ionotropic glutamate receptors mediate thermosensation and hygro-sensation in *Drosophila*. *eLife*. 2016; 5:e17879. [PubMed: 27656904]
27. Muir LE, Kay BH, Thorne MJ. *Aedes aegypti* (Diptera: Culicidae) Vision: response to stimuli from the optical environment. *J Med Entomol*. 1992; 29(3):445–50. [PubMed: 1625292]
28. Moon YM, Metoxen AJ, Leming MT, Whaley MA, O'Tousa JE. Rhodopsin management during the light–dark cycle of *Anopheles gambiae* mosquitoes. *J Insect Physiol*. 2014; 70:88–93.
- 29*. van Breugel F, Riffell J, Fairhall A, Dickinson MH. Mosquitoes use vision to associate odor plumes with thermal targets. *Curr Biol*. 2015; 25(16):2123–2129. This study showed carbon dioxide can enhance mosquito recognition of visual cues during host-seeking. [PubMed: 26190071]
30. Hawkes F, Gibson G. Seeing is believing: the nocturnal malarial mosquito *Anopheles coluzzii* responds to visual host-cues when odour indicates a host is nearby. *Parasit Vectors*. 2016; 9(1):320. [PubMed: 27260254]
31. Krenn HW, Aspöck H. Form, function and evolution of the mouthparts of blood-feeding arthropoda. *Arthropod Struct Dev*. 2012; 41:101e118. [PubMed: 22317988]
- 32*. Jung WJ, Baeck SJ, Perumalsamy H, Hansson BS, Ahn YJ, Kwon HW. A novel olfactory pathway is essential for fast and efficient blood-feeding in mosquitoes. *Sci Reports*. 2015; 5:13444. This study showed that chemosensation in the stylet is important for mosquitoes to blood-feed.
33. Matthews BJ, McBride CS, DeGennaro M, Despo O, Vosshall LB. The neurotranscriptome of the *Aedes aegypti* mosquito. *BMC Genomics*. 2016; 17:32. [PubMed: 26738925]
34. Riabinina O, Task D, Marr E, Lin C-C, Alford R, O'Brochta DA, Potter CJ. Organization of olfactory centres in the malaria mosquito *Anopheles gambiae*. *Nature Communications*. 2016; 7:13010.
35. Liman ER, Zhang YV, Montell C. Peripheral coding of taste. *Neuron*. 2014; 81(5):984–1000. [PubMed: 24607224]
36. Suh E, Bohbot JD, Zwiebel LJ. Peripheral olfactory signaling in insects. *Curr Opin Insect Sci*. 2014; 6:86–92. [PubMed: 25584200]
37. Pelosi P, Zhou J-J, Ban LP, Calvello M. Soluble proteins in insect chemical communication. *Cell Mol Life Sci*. 2006; 63:1658–1676. [PubMed: 16786224]
38. Joseph RM, Carlson JR. *Drosophila* Chemoreceptors: A Molecular Interface Between the Chemical World and the Brain. *Trends in Genetics*. 2015; 31:683–695. [PubMed: 26477743]
39. Sachse S, Beshel J. The good, the bad, and the hungry: how the central brain codes odor valence to facilitate food approach in *Drosophila*. *Curr Opin Neurobiol*. 2016; 40:53–58. [PubMed: 27393869]
40. Larsson MC, Domingos AI, Jones WD, Chiappe ME, Amrein H, Vosshall LB. *Or83b* encodes a broadly expressed odorant receptor essential for *Drosophila* olfaction. *Neuron*. 2004; 43:703–714. [PubMed: 15339651]
41. Benton R, Sachse S, Michnick SW, Vosshall LB. Atypical membrane topology and heteromeric function of *Drosophila* odorant receptors *in vivo*. *PLoS Biol*. 2006; 4:e20. [PubMed: 16402857]
42. Xu P, Choo Y-M, De La Rosa A, Leal WS. Mosquito odorant receptor for DEET and methyl jasmonate. *Proc Natl Acad Sci U S A*. 2014; 111:16592–16597. [PubMed: 25349401]
43. Carey AF, Wang G, Su CY, Zwiebel LJ, Carlson JR. Odorant reception in the malaria mosquito *Anopheles gambiae*. *Nature*. 2010; 464:66–71. [PubMed: 20130575]
44. Bohbot JD, Pitts RJ. The narrowing olfactory landscape of insect odorant receptors. *Front Ecol Evol*. 2015; 3:39.
45. Benton R, Vannice KS, Gomez-Diaz C, Vosshall LB. Variant ionotropic glutamate receptors as chemosensory receptors in *Drosophila*. *Cell*. 2009; 136:149–162. [PubMed: 19135896]
46. Abuin L, Bargeton B, Ulbrich MH, Isacoff EY, Kellenberger S, Benton R. Functional architecture of olfactory ionotropic glutamate receptors. *Neuron*. 2011; 69:44–60. [PubMed: 21220098]

47. Silbering AF, Rytz R, Grosjean Y, Abuin L, Ramdya P, Jefferis GS, Benton R. Complementary function and integrated wiring of the evolutionarily distinct *Drosophila* olfactory subsystems. *J Neurosci*. 2011; 31:13357–13375. [PubMed: 21940430]
48. Hussain A, Zhang M, Uçpunar HK, Svensson T, Quillery E, Gompel N, Ignell R, Grunwald Kadow IC. Ionotropic chemosensory receptors mediate the taste and smell of polyamines. *PLoS Biol*. 2016; 14(6):e1002505. [PubMed: 27327409]
49. Zhang YV, Ni J, Montell C. The molecular basis for attractive salt-taste coding in *Drosophila*. *Science*. 2013; 340(6138):1334–8. [PubMed: 23766326]
50. Senthilan PR, Piepenbrock D, Ovezmyradov G, Nadrowski B, Bechstedt S, Pauls S, Winkler M, Möbius W, Howard J, Göpfert MC. *Drosophila* auditory organ genes and genetic hearing defects. *Cell*. 2012; 150:1042–1054. [PubMed: 22939627]
51. Xiang Y, Yuan Q, Vogt N, Looger LL, Jan LY, Jan YN. Light-avoidance-mediating photoreceptors tile the *Drosophila* larval body wall. *Nature*. 2010; 468(7326):921–926. [PubMed: 21068723]
52. Ni L, Bronk P, Chang EC, Lowell AM, Flam JO, Panzano VC, Theobald DL, Griffith LC, Garrity PA. A gustatory receptor paralog controls rapid warmth avoidance in *Drosophila*. *Nature*. 2013; 500(7464):580–584. [PubMed: 23925112]
53. Jones WD, Cayirlioglu P, Kadow IG, Vosshall LB. Two chemosensory receptors together mediate carbon dioxide detection in *Drosophila*. *Nature*. 2007; 445(7123):86–90. [PubMed: 17167414]
54. Chen S, Luetje CW. Identification of new agonists and antagonists of the insect odorant receptor co-receptor subunit. *PLoS One*. 2012; 7(5):e36784. [PubMed: 22590607]
55. Jones PL, Pask GM, Romaine IM, Taylor RW, Reid PR, Waterson AG, Sulikowski GA, Zwiebel LJ. Allosteric antagonism of insect odorant receptor ion channels. *PLoS One*. 2012; 7(1):e30304. [PubMed: 22272331]
56. Rinker DC, Jones PL, Pitts RJ, Rutzler M, Camp G, Sun L, Xu P, Dorset DC, Weaver D, Zwiebel LJ. Novel high-throughput screens of *Anopheles gambiae* odorant receptors reveal candidate behaviour-modifying chemicals for mosquitoes. *Physiol Entomol*. 2012; 37:33–41.
57. Jones WD. The expanding reach of the GAL4/UAS system into the behavioral neurobiology of *Drosophila*. *BMB Rep*. 2009; 42:705–712. [PubMed: 19944010]

Highlights

Olfaction is key for mosquitoes to detect their human hosts.

Redundant mechanisms exist in the mosquito host-detection system.

Optimizing odor-baited traps may require multiple cues including CO₂ and heat.

Novel mosquito repellents could modulate the chemoreceptors that detect humans.

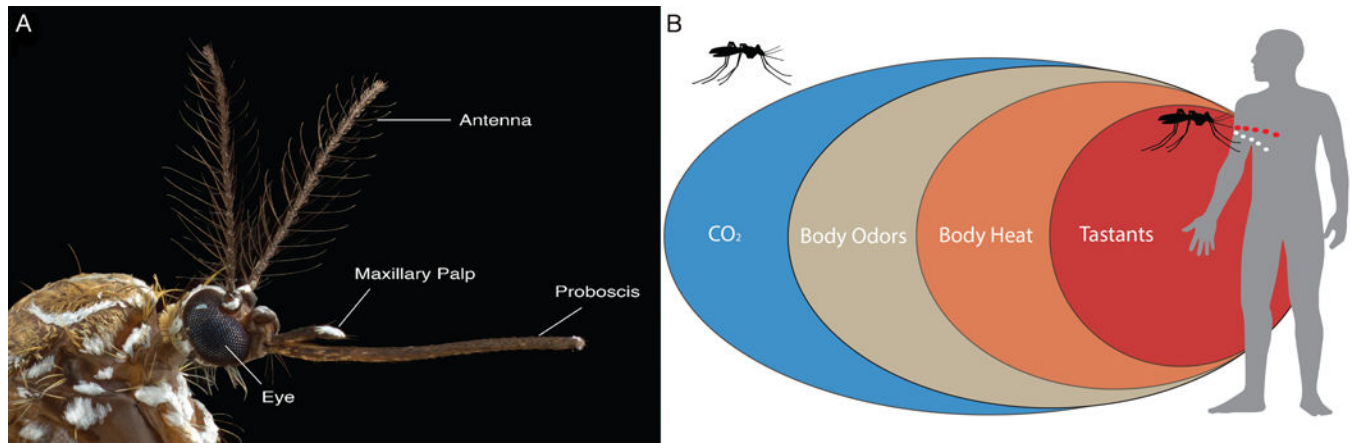


Figure 1. Olfaction enables mosquitoes to detect human hosts

(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 CO₂ 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).

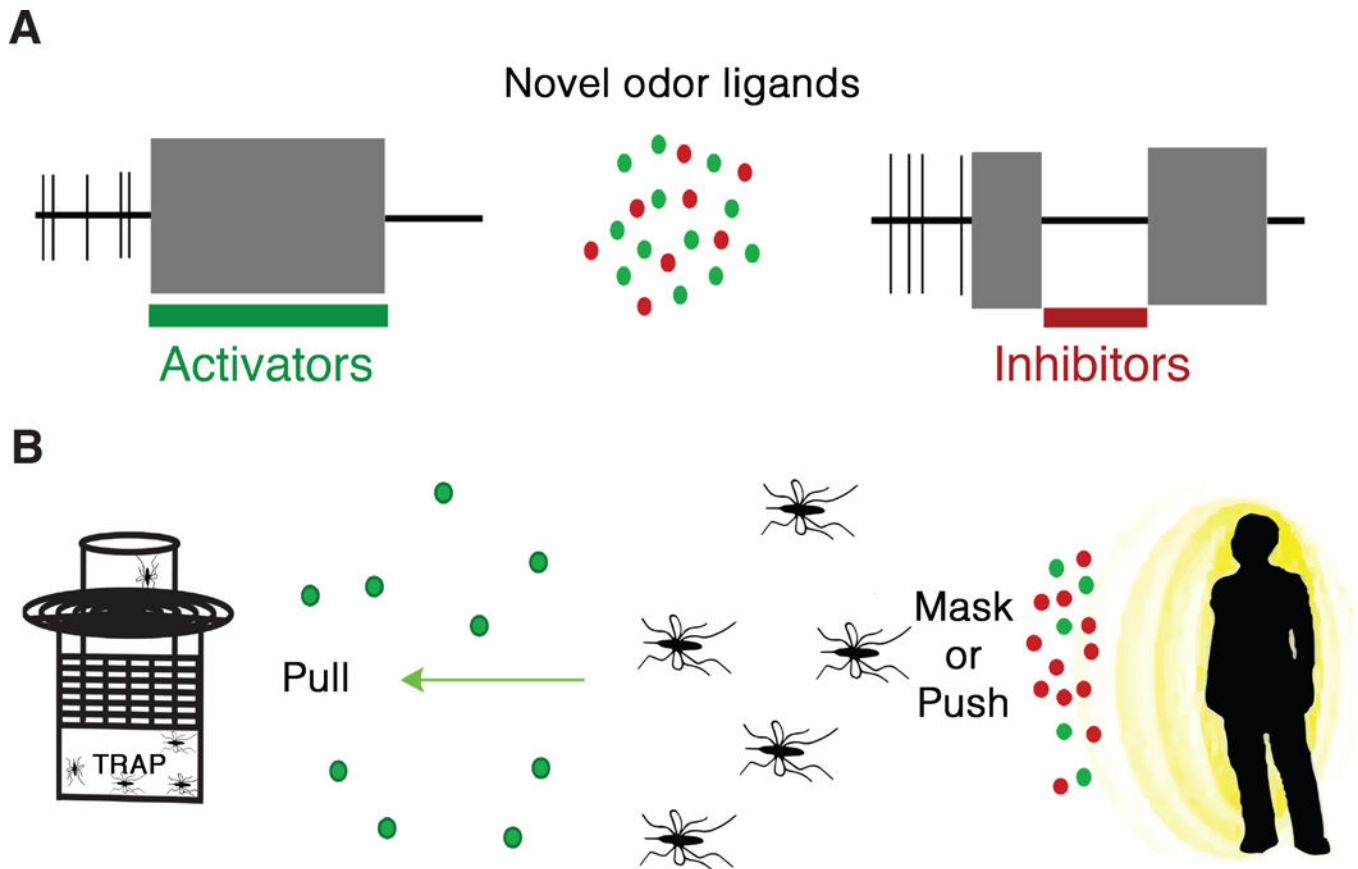


Figure 2. Designing novel mosquito attractants and repellents

Novel vector control measures can be designed after identifying the salient cues that mosquitoes use to find their hosts and the receptors that perceive them. (A) Cartoons of single sensillum recordings of olfactory receptor neuron (ORN) responses to novel odor ligands. New volatile compounds that activate (green) or inhibit (red) the activity of the ORNs could be used to control mosquito behavior or reduce mosquito populations. (B) Push-pull strategies for mosquito behavioral control. Mosquitoes can be led to a trap containing odors that attract them (pull). Odors that either mask or constitutively activate olfactory receptor function could cause mosquitoes to avoid humans (mask/push).