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Roles of insect odorant binding proteins in communication and xenobiotic adaptation

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Odorant binding proteins (OBPs) are small water-soluble proteins mainly associated with olfaction, facilitating the transport of odorant molecules to their relevant receptors in the sensillum lymph. While traditionally considered essential for olfaction, recent research has revealed that OBPs are engaged in a diverse range of physiological functions in modulating chemical communication and defense. Over the past 10 years, emerging evidence suggests that OBPs play vital roles in purifying the perireceptor space from unwanted xenobiotics including plant volatiles and pesticides, potentially facilitating xenobiotic adaptation, such as host location, adaptation, and pesticide resistance. This multifunctionality can be attributed, in part, to their structural variability and effectiveness in transporting, sequestering, and concealing numerous hydrophobic molecules. Here, we firstly overviewed the classification and structural properties of OBPs in diverse insect orders. Subsequently, we discussed the myriad of functional roles of insect OBPs in communication and their adaptation to xenobiotics. By synthesizing the current knowledge in this field, our review paper contributes to a comprehensive understanding of the significance of insect OBPs in chemical ecology, xenobiotic adaptation, paving the way for future research in this fascinating area of study.

KEYWORDS

xenobiotics, semiochemicals, adaptation, co-option, host location, pesticide resistance

1 Introduction

The ability to perceive and differentiate various chemical stimuli present in a set environment is paramount to an organism's success (1–4). Insects, the most successful group of animals on Earth, have developed a sophisticated olfactory system that has widely contributed to this success. Insect olfactory systems are known for their remarkable sensitivity and the ability to integrate odorant blends through distributed specificity of receptor tuning profiles (5–7). The classification and integration of these profiles in different portions of "odor

space" rely on structures like the mushroom body and lateral horn of the protocerebrum, enabling precise discrimination of pheromone blends or subtle differences in plant odor blends (5, 8). Insect olfaction is composed of several transmembrane receptors and soluble and insoluble proteins, which collaborate harmoniously to receive, process, interpret, and ultimately react to external stimuli (3). The key olfactory proteins involved in this process include odorant binding proteins (OBPs), odorant receptors (ORs), ionotropic receptors (IRs), odorant degrading enzymes (ODEs). and sensory neuron membrane proteins (SNMPs) (3). ORs form a heteromeric complex with a ubiquitous coreceptor coined odorant receptor co-receptor (Orco) that is omni-present in every functional OR complex and is highly conserved among all insects (3). In general, exogenous odorants or volatiles enter the sensillum lymph through cuticular pores and are subsequently bound and solubilized by OBPs, wherein this OBP-odorant complex is transported across the sensillum to a candidate OR for transduction (3, 9) (Figure 1). Once the OBP-odorant complex (or the odorant alone) is bound to a receptive OR, a transduction cascade is triggered, which leads to action potentials transmitting from olfactory receptor neurons to the higher integration centers within the protocerebrum. Odorants must be deactivated rapidly by ODEs or scavengers once this occurs, otherwise efficiency of olfactory processes will be impaired via prolonged exposure of the respective odorant inducing overstimulation. Numerous lines of evidence suggest that many ODEs such as cytochrome P450s, glutathione S-transferases (GSTs), carboxyl/cholinesterases (CCEs) are involved in degrading volatile molecules during the deactivation process (3, 10–13). Some studies indicate that prior to degradation by ODEs, pheromones undergo deactivation through their binding to OBPs (e.g., pheromone binding proteins, PBPs). Additionally, these OBPs serve as scavengers, contributing to the decline of the receptor potential after stimulus offset. This implies the existence of a broader molecular mechanism beyond enzymatic degradation (3, 14–17).

Within the realm of olfaction processing, OBPs play a vital role as the primary mediators connecting the external environment with ORs (7, 9). OBPs are frequently necessary for safeguarding exogenous hydrophobic volatiles against degradation prior to their interaction with the corresponding ORs. This protection occurs following the initial uptake, binding, and transportation of these volatiles within the aqueous sensillum lymph. The delivery of the exogenous volatiles to the OR triggers an elicited response, allowing for the recognition of volatiles from hosts or natural enemies and identification of pheromones of potential mates. Following the stimulation of ORs by exogenous molecules, OBPs may also participate as molecular traps, preventing neuron oversaturation (1–3, 17–20). In addition, evidence shows that OBPs may play essential roles in cleaning the perireceptor space from undesirable xenobiotics, including plant volatiles and pesticides. This function potentially contributes to host plant adaptation and pesticide resistance (20–27). Despite their primary role as olfactory proteins, recent research has identified OBPs to be involved in a variety of physiological roles in insects outside of olfactory tissues, owing in part to their structural variability and efficacy in the transporting, sequestering, and concealing of various hydrophobic molecules (2, 3, 9, 28–30).

Roughly half of insect species are phytophagous, forming a close relationship with the host plants they feed and interact with (31). During the coevolution of insects and plants over hundreds of millions of years, insects have evolved diverse mechanisms to adapt to numerous xenobiotics (12, 13, 32–34). Olfaction in insects may serve as an "Achilles heel" - a target for plant defense because of its remarkable sensitivity, critical importance, and vulnerability (22). OBPs serve as the primary point of contact for the insect olfactory system with xenobiotics, playing a principal role in modulating chemical communication and defense. Here, we initially summarize the classification and structural properties of OBPs in various insect orders. Then we focus on the variety of functional roles of OBPs in insect communication and adaptation to xenobiotics. Our review

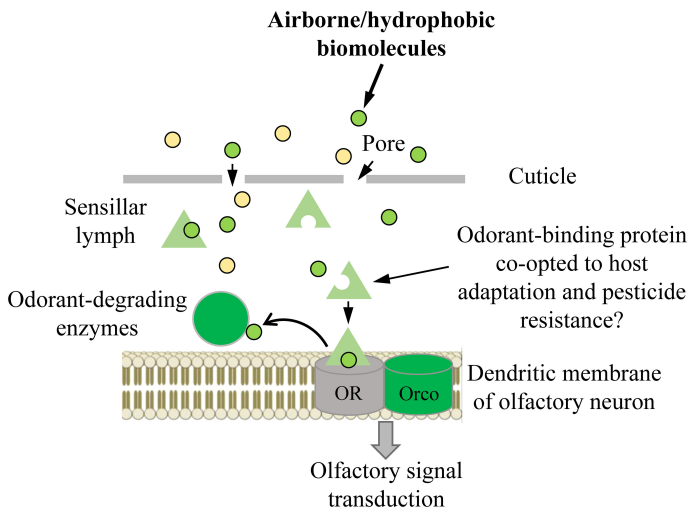

FIGURE 1
Schematic summary of the odor path. OR, odorant receptor (in some cases, it can involve other olfactory receptors, such as ionotropic receptors); Orco, co-receptor for OR.

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concludes with prospective thoughts on future studies that could expand our knowledge of OBPs and their diverse functions in chemical ecology and xenobiotic adaptation.

2 Classification and structural characteristics of insect OBPs

Insect OBPs are small water-soluble extracellular proteins, ranging from between roughly 100 to ~200 amino acid residues, with very little sequence similarity within OBPs of the same species (1). Initially described in Lepidoptera (16), these proteins were categorized into three separate subfamilies based on the amino acid sequences and differential expression patterns: pheromone binding proteins (PBPs), general odorant binding proteins (GOBPs), and antennal binding proteins (ABPs) (1, 16). However, a primary challenge with this classification methods arises from the significant variation observed in the amino acid sequences, ligand binding affinity, differential expression, and functional roles beyond Lepidoptera, extending even to functions beyond chemosensation (35, 36). Therefore, there was a pressing need for a more comprehensive and flexible classification method to accurately characterize their diverse functional roles and implications. Currently, insect OBPs are generally divided into three primary groups based on the number of conserved cysteine residues and interlocked disulfide bridges: 1) Classic OBPs (e.g. *Chrysopa pallens* CpalOBP4, PDB ID:6JPM), which have six conserved cysteine residues that participate in three disulfide bridges; 2) Minus-C OBPs (e.g. *Apis mellifera* AmelOBP14, PDB ID:3S0A), featuring four or five conserved cysteine residues and two disulfide bridges; 3) Plus-C OBPs (e.g. *Anopheles gambiae* AgamOBP7, PDB ID:3R1P), which possess eight or more conserved cysteine residues, four or more disulfide bridges, and a conserved proline residue (Figure 2) (36). Among these groups, Classic OBPs are the most frequently identified type of OBPs in every insect genome (Table 1; Figures 2, 3). Phylogenic analysis of insect OBPs have shown that Classic OBPs seem to be the basal group, and other Minus-C and Plus-C groups of OBPs are subgroups of the Classic OBPs (39). This may suggest that Minus-C and Plus-C OBPs likely diverged from the Classic OBPs (39–41) (Figure 2). However, the relative composition of OBPs in an insect genome can vary greatly, as some OBP groups may feature a larger expansion in one group of insects as compared to others, as has been observed in certain beetle species (35, 42–47) (Figure 3A; Table 1). There is a group of OBPs that has been termed "atypical OBPs" characterized by 10 or more conserved cysteines, a long C-terminus, a conserved proline residue, and four or more disulfide bridges, which is recorded in several mosquito and locust species, suggesting this group of genes may be recently evolved in these species (36, 48–50). Additionally, groups of insect OBPs that exist outside of the three primary structural groups can be found in certain insects, such as double domain OBPs that are found exclusively in certain wasp species (51) and Dimer OBPs that are found in some species of dipterans and lepidopterans (Figures 3A–C; Table 1) (39, 51). In certain insect groups, there is a complete absence of an entire primary group of OBPs; for instance, honey bees lack of plus-C OBPs all together (Figure 3B; Table 1) (40). The amount of OBP genes in an insect genome can vary greatly among species, ranging from as low as 7 in *Ceratosolen solmsi* to as high as 111 in *Aedes aegypti* (Table 1). The reason why certain insect species possess a higher number of OBPs while others have relatively few remains unclear. However, this disparity can likely be attributed to the insects' unique lifestyles, evolutionary processes, and wide variety of environments (39).

Despite the high diversity and variation among insect OBPs, this group of proteins has some hallmark features. In addition to the extremely conserved cysteine residues, insect OBPs typically have two to four interconnected disulfide bridges (e.g., a pattern of C1-C3, C2-C5, and C4-C6) that play a vital role in stabilizing the protein (52–58) (Figure 2). Furthermore, six α-helices, which may vary in number in certain cases, synergistically work with the interlocked disulfide bridges to further enhance the protein's stability. Specific α-helices may be involved in forming a

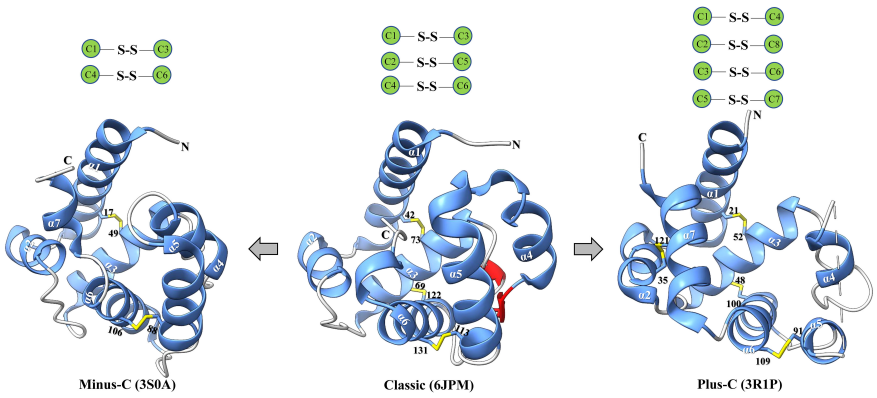

FIGURE 2
Major classes of insect OBPs. Beginning from the left, minus-C (e.g. *Apis mellifera* AmelOBP14, PDB ID:3S0A); Classic (e.g. *Chrysopa pallens* CpalOBP4, PDB ID:6JPM); Plus-C (e.g. *Anopheles gambiae* AgamOBP7, PDB ID:3R1P). Blue indicates α-helices; yellow indicates disulfide bridge; red indicates strands; and lastly grey indicates coils. Black text indicates a conserved cysteine residue, white text indicates an α-helix. Below each protein is the corresponding class of the odorant binding protein and the protein database reference used to generate the specific protein. Three-dimensional protein structures were constructed using the program ChimeraX.

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TABLE 1 Number of Odorant Binding Protein genes and classification in genomes or transcriptomes of 37 insect species.

Order	Species	Total	Classic	Minus-C	Plus-C	Other*	Reference [$]
Blattodea	*Blatella germanica*	109	38		71	0	(1)
	Periplaneta americana[†]	60	37	3	20	0	(2)
	Zootermopsis nevadensis	29	19	3	7	0	(2)
Coleoptera	*Anoplophora glabripennis*	52	20	31	1	0	(3)
	Dendroctonus ponderosae	31	18	12	1	0	(4)
	Holotrichia oblita[†#]	29	19	7	3	0	(5)
	Holotrichia parallela[†#]	25	15	6	4	0	(6)
	Leptinotarsa decemlineata[#]	59	14	43	1	1	(7)
	Tenebrio molitor[†]	19	10	8	0	1	(8)
	Tribolium castaneum[#]	49	20	21	1	7	(9, 10)
Diptera	*Aedes aegypti*	111	39	0	27	45	(11)
	Anopheles gambiae	69	29	0	20	20	(11)
	Anopheles stephensi	44	27	0	7	10	(12)
	Culex quinquefasciatus	109	69	0	12	28	(11)
	Drosophila melanogaster	52	28	7	15	2	(13-15)
Hemiptera	*Acyrthosiphon pisum*	15	13	0	2	0	(16)
	Adelphocoris lineolatus[†]	14	12	0	2	0	(17)
	Bemisia tabaci	8	5	1	2	0	(18)
	Riptortus pedestris	49	41	0	8	0	(19)
	Tropidothorax elegans[†]	19	14	0	5	0	(20)
Hymenoptera	*Aphidius gifuensis*[†]	14	12	2	0	0	(21)
	Apis florea[#]	22	13	9	0	0	(22)
	Apis mellifera[#]	21	13	8	0	0	(22, 23)
	Bombus terrestris[#]	16	16	0	0	0	(24)
	Ceratosolen solmsi	7	7	0	0	0	(25, 26)
	Cotesia vestalis	20	18	2	0	0	(27, 28)
	Nasiona vitripennis[#]	90	72	8	0	10**	(29)
Lepidoptera	*Bombyx mori*[#]	44	29	9	6	0	(29, 30)
	Danaus plexippus[#]	32	19	6	6	1	(31)
	Heliconius Melpomene[#]	51	23	22	6	0	(31)
	Manduca sexta[#]	49	24	18	7	0	(31)
	Plutella xylostella	39	39	0	0	0	(32)
	Spodoptera frugiperda	33	25	3	3	2	(33)
Orthoptera	*Locusta migratoria*	17	11	0	5	1	(34)
	Oedaleus asiaticus[†]	15	10	1	4	0	(35)
	Schistocerca gregaria[†]	14	9	0	3	2	(35)
Thysanoptera	*Odontothrips loti*[†]	7	5	1	0	1	(36)

[†]stands for the data collected from transcriptome studies; * "Other" corresponds to unidentified OBPs or OBPs that do not fall under the classic, minus-C, and plus-C classification; ** These OBPs are minus-C OBPs, but possess a double domain in their sequence, as compared to typical minus-C OBPs in other insect species; [$] These references are listed in the Supplementary Material; [#] OBPs from these species were used in the generation of the phylogenetic trees featured in Figure 3.

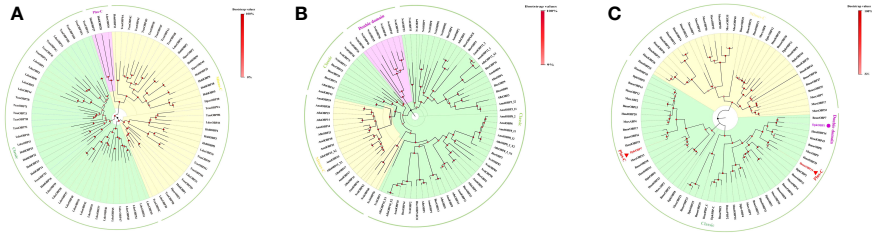

FIGURE 3
Phylogenetic analysis of insect OBPs in three major orders, and OBPs used in the analysis had been previously characterized through either proteomic or transcriptomic analyses. **(A)** Coleopteran insect OBPs from *Holotrichia oblita, Holotrichia parallela, Leptinotarsa decemlineata*, and *Tribolium castaneum*; **(B)** Hymenopteran insect OBPs from *Apis florea, Apis melifera, Bombus terrestris, and nasiona vitripennis*; **(C)** Lepidopteran insect OBPs from *Bombyx mori, Danaus plexippus, Heliconius melpomene*, and *Manduca sexta*. Phylogenetic trees were inferred by the neighbor-joining method (37) and were created using MEGA11 software (38). The trees were visualized using Figtree v1.4.4 software.

hydrophobic cavity crucial for ligand binding activity (52, 53, 58–60). The ligand binding specificity of insect OBPs exhibits significant variation, ranging from high specificity to remarkable broadness. This diversity is influenced by the overall size and shape of the binding pocket, as well as the specific amino acids lining it (54, 55). Previous studies have demonstrated that variability in amino acid identity and length of the C-terminal region can influence ligand binding affinity. For example, in a specific case, the rearrangement of amino acids within the C-terminus region of a *Drosophila melanogaster* OBP (LUSH) disrupted the formation of a salt bridge, resulting in impaired binding ability to the expected ligand 11-*cis* vaccenyl acetate, a conspecific male sex pheromone (56). The length variation in the C-terminal region also impacts the interaction of the C-terminus with the hydrophobic binding cavity. Insect OBPs with longer C-terminus regions possess a flap that can cover the entrance of the binding cavity, whereas those with shorter C-terminus regions leave their binding cavities exposed to bulk solvent (2, 61, 62). Additional research has demonstrated that pH-induced conformational changes can impact the ligand-binding capability of specific insect OBPs (52, 63–65). Notably, Lepidopteran OBPs AtraPBP1 from *Amyelois transitella* and ApolPBP from *Antheraea polyphemus* possess a C-terminal region that plays a crucial role in pheromone binding and release, triggered by changes in pH levels (66, 67). In AtraPBP1, the polar amino acid residues Glu132 and Glu141 create two salt bridges with protonated histidine residues His 80 and His95, respectively. These two salt bridges are induced by acidic conditions, promoting the formation of a seventh helix at the C-terminal region that can compete with the ligand and trigger its release (9, 66). In contrast to OBPs in Lepidoptera, the majority of Dipteran OBPs lack a sufficiently long C-terminal region to form an additional helix able to occupy the binding cavity (9, 52). Nevertheless, many Dipteran OBPs, such as AaegOBP1 (*Ae. aegypti*, PDB ID:3K1E), AgamOBP1 (*An. gambiae*, PDB ID:2ERB), CquiOBP1 (*Culex quinquefasciatus*, PDB ID:3OGN), undergo pH-depended conformation changes associated with loss of binding affinity, similar to what has been observed in Lepidopteran OBPs, indicating a distinct mechanism (9). The C-terminal region of these Dipteran insect OBP proteins instead function as a "lid" over the binding cavity, a characteristic not found in other insect groups. This lid was suggested to act as a pH-sensitive hinge, moving away from the binding cavity when pH is reduced, as the OBP-odorant complex approaches the dendritic membrane (9, 52). Moreover, the ligand binding ability of an OBP may be affected by its molecular volume. For example, in the Minus-C OBP DhelOBP21 of *Dastarcus helophoroides*, the ligand being either too small (<100 A^3) or too large (>185 A^3) can disrupt its facultative binding ability (68). Additionally, hydrophobic and hydrogen bond interactions can also influence binding efficacy of an OBP, and the absence of either can lead to substantial reductions in the binding affinity of an OBP towards a ligand (68, 69). Lastly, it is worth noting that the majority of determined crystal structures of insect OBPs reveal a tendency for dimerization upon ligand binding (59, 70–73) (Table 2). Insect OBP protein structures in both ligand-free apo forms and in complex with various ligands, have been determined using protein crystallography and nuclear magnetic resonance (NMR) spectroscopy (9, 74). A list of currently published insect OBP structures at the time of this publication has been provided in Table 2. The list includes 27 individual insect OBP structures across 17 insect species, including 10 OBP structures from species in Diptera and 7 OBP structures from species in Lepidoptera. Currently, our understanding is limited, as over half of the elucidated structures (17 out of 27) come from Dipteran and Lepidopteran insects (Table 2). Further research is crucial to comprehensively understand the relationship between the varied structures and functions of numerous OBPs from a wide range of insect species.

3 Diverse roles of insect OBPs in communication and xenobiotic adaptation

Insects encounter a diverse array of semiochemicals and xenobiotics in their environment, necessitating adaptive responses. These chemicals range from allospecific and conspecific pheromones, plant allelochemicals, volatiles, and a multitude of anthropogenic compounds, such as pesticides (34, 75–77). On one hand, insects use these chemical cues to detect their

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TABLE 2 List of 27 three-dimensional crystal structures, classification, and function of insect Odorant Binding Proteins.

Order	Species Name	Name (PDB number)	Classification	Function	Reference*
Blattodea	*Leucophaea maderae*	PBP (1ORG)	Classic	Involved in recognition of sex pheromone components: 3-hydroxy-butan-2-on and butane-2,3-diol	(37, 38)
Coleoptera	*Tenebrio molitor*	THP12 (1C3Z)	Minus-C	N/A	(39)
Diptera	*Aedes aegypti*	OBP1 (3K1E)	Classic	N/A	(40)
		OBP22 (6OG0)	Classic	Potentially involved in the recognition of fatty acids	(41)
	Anopheles gambiae	OBP1 (2ERB)	Classic	Involved in host recognition	(42-45)
		OBP7 (3R1P)	Plus-C	N/A	(46)
		OBP20 (3VB1)	Classic	N/A	(47)
		OBP47 (3PM2)	Plus-C	N/A	(48)
		OBP48 (4KYN)	Plus-C	N/A	(49)
	Culex quinquefasciatus	OBP1 (3OGN)	Classic	Modulates ovipositional preference	(50, 51)
	Drosophila melanogaster	OBP28A (6QQ4)	Classic	Involved in the detection and mediation of sensitivity to fruit-like odors	(52)
		LUSH (OBP76A) (1T14)	Classic	Involved in host and pheromone recognition through mediation of alcohol compounds	(53-55)
Hemiptera	*Megoura viciae*	OBP3 (4Z39)	Classic	Potentially involved in the recognition of alarm pheromones	(56)
	Nasovonia ribisnigri	OBP3 (4Z45)	Classic	Potentially involved in the recognition of alarm pheromones	(56)
Hymenoptera	*Apis melifera*	ASP1 (OBP1) (3BJH)	Classic	Involved in the recognition of the queen pheromone	(57-60)
		OBP5 (3R72)	Classic	N/A	To be published
		ASP2 (GOBP2) (1TUJ)	Classic	Involved in non-sexual pheromone recognition	To be published, (61, 62)
		OBP14 (3S0A)	Minus-C	Binds with the highest affinity to citralva and eugenol	(63)
Lepidoptera	*Amyelois transitella*	PBP1 (2KPH)	Classic	Involved in the recognition and transport of non-polar pheromone	(64, 65)
	Antheraea polyphemus	PBP1 (1QWV)	Classic	Involved in the recognition of sex pheromone component (E, Z)-6,11-hexadecadienyl acetate (AC1)	(66-69)
	Bombyx mori	PBP1 (1DQE)	Classic	Modulates sensitivity to the sex pheromone bombykol	(70-72)
		GOBP2 (2WC5)	Classic	Involved in the recognition and discrimination of the sex pheromones bombykol and bombykal	(73, 74)
	Epiphyas postvittana	PBP3 (6VQ5)	Classic	Involved in recognition of sex pheromone components: E11-14: OAc and E9, E11-14: OAc	(75)
	Helicoverpa armigera	PBP1 (7VW8)	Classic	Involved in recognition of sex pheromone components: to Z11-16: Ald and Z9-16: Ald	(76, 77)
	Lymantria dispar	PBP1 (6UM9)	Classic	N/A	(78)
Neuroptera	*Chrysopa pallens*	OBP4 (6JPM)	Classic	Involved in the recognition of prey host plant volatiles	(79, 80)
Orthoptera	*Locusta migratoria*	OBP1 (4PT1)	Classic	N/A	(81)

PDB, protein database; N/A, not available; OaC, acetoxy functional group; Ald, aldehyde functional group. * These references are listed in the Supplementary Material.

food, mates, and other substrates critical for their survival and reproduction. On the other hand, insects must evolve adaptation strategies to cope with "delicious poisons", which are harmful compounds disguised as attractants. These chemical cues can be exploited by host plants as a defensive measure, posing survival challenges for insects (22, 78). Recent studies have demonstrated that insect OBPs play critical roles in the uptake or release of a diverse spectrum of molecules due to their stable and compact structure, high variability in binding affinity, and efficiency transportation of hydrophobic molecules (79–81). Additionally, many proteomic and transcriptomic studies focusing solely on olfactory organs, such as antennae or maxillary palps, may not identify all OBP-encoding genes within an insect genome. This suggests that certain OBPs could be exclusively expressed in non-olfactory organs and/or appendages (2, 82–85). Recently, there are many integrative reviews of insect OBPs discussing their diverse expression and functions in chemoreception and beyond (1, 2, 9, 36, 74). Therefore, in this section, our focus will be on the roles of insect OBPs in communication, host location, and their co-opted functions in pesticide adaptation.

3.1 Pheromone detection and release

Detection of conspecific and allospecific pheromones are essential to reproductive success, survival, and overall fitness of an insect (2, 86–88). Several studies have demonstrated the role and significance of OBPs in the detection and sensitivity to pheromones across a variety of insect orders (36, 89–94) since their initial discovery in the male silk moth, by Vogt and Riddiford in 1981 (16). For example, *Bombyx mori* BmorPBP1 was suggested to be essential for the activation of the receptor *B. mori* BmorOR1 to the female released sex pheromone bombykol rather than bombykal (95–97). In the absence of BmorPBP1, only low sensitivity to bombykol was detected in transgenic *drosophila* expressing BmorOR1, however, high sensitivity and ligand specificity towards bombykol was observed in mutants expressing both BmorOR1 and BmorPBP1 (96). The affinity of BmorPBP1 to bombykol is regulated by pH-dependent conformational changes in PBP, which lead to the release of pheromones under acidic environment surrounding the OR neurons (64, 65, 89, 98). Besides BmorPBP1, conformational changes that are integral to pheromone recognition were also observed in PBPs of several other insect species (66, 99, 100). For example, in *D. melanogaster*, it was observed that LUSH PBP detects and releases the male specific sex pheromone 11-*cis*-vaccenyl acetate (cVA) to activate *D. melanogaster* OR67d neurons, linking pheromone-induced behavior with PBP-dependent activation of olfactory neurons (56, 101, 102). Additional studies demonstrated that *D. melanogaster* OBP56h influences male courtship behavior. It plays a dual role in the production of precursors to cuticular pheromones, as its expression level is linked to the expression levels of several biosynthesis enzymes (1, 103, 104). One of these cuticular pheromones, 5-tricosene, is highly expressed in males and can decrease copulation latency at high levels, potentially preventing incidences of male-male courtship (1). In *Ap. mellifera*, brood pheromone (β-ocimene) and death pheromone (oleic acid) are strong ligands for two OBPs, AmelOBP16 and AmelOBP18. Expression levels of both OBPs were found to be linked with the degree of hygienicity displayed in bee colonies, suggesting these two OBPs may play important roles in triggering honey bee hygienic behavior (105, 106). Additionally, it was found that *Ap. mellifera* AmelASP1 and *Ap. cerana* AcerOBP1 are involved in the recognition of honeybee queen pheromone (107, 108). Recently, conserved insect OBPs were identified from various aphid species and their eavesdropping predators, such as ladybird beetles, lacewings, and the marmalade hoverfly, demonstrating the potential functions of OBPs in predator-prey interactions (109–112). These OBPs play roles in detection of (E)-β-farnesene (EBF), which is the primary alarm pheromone active component in many aphid species (Hemiptera: Aphididae) and is used as chemical cue to signal danger (113–117). For example, in *Acyrthosiphon pisum*, knockdowns of *ApisOBP3* and *ApisOBP7*, that are known to bind EBF, led to the disappearance of repellent behavior caused by EBF (110, 115). The functions of related ApisOBP3 and/or ApisOBP7 proteins in EBF detection were also characterized in other aphid species by using behavioral assays, ligand-binding assays, or X-ray crystal structure examination (110, 111, 114, 118). In *Rhopalosiphum padi*, both RpadOBP3 and RpadOBP7 bound EBF and additionally, RpadOBP3 showed affinity for the ligands, EBF and several other plant volatiles, while RpadOBP7 was specific to EBF (114). Most recently, four antennae specific OBPs were functionally characterized in the aphid natural enemy, *Harmonia axyridis*. Among these OBPs, HaxyOBP15 showed a broader binding profile among various substances, including EBF and other volatiles (117). Similarly, two lacewing species OBPs, *Chrysoperla sinica* CsinOBP1 and *Chrysopa pallens* CpalOBP10, were also found to bind to EBF (112, 119).

It has been demonstrated that besides the antennae, OBPs can also be expressed in the sex glands and various other organs, participating in both the uptake and release of various pheromones. A study performed in the diving beetle *Cybister japonicus* found two OBPs specifically expressed in the foreleg and testis of male beetles, which are used for holding a female during courtship and mating, suggesting potential roles of these OBPs in chemical communication (120). The sex pheromone for this species is still unknown, therefore, further research is required to confirm the functions of these OBPs in pheromone recognition and secretion (120). Several studies have also found the presence of OBPs in the seminal fluid of a wide range of insect taxa, that are transferred to females during mating or are potentially used as oviposition deterrents on fertilized eggs (121–126). Interestingly, fruit flies possess OBPs in the seminal receptacle along with an odorant receptor, displaying the highly adaptable nature of OBPs in the insect body (121, 127). In a Lepidopteran species, *Helicoverpa armigera*, *HarmOBP10* was expressed in antennal and reproductive organs of both sexes, binding to 1-dodecene, a compound reported as an insect repellent as well as several volatile compounds, suggesting its dual roles in chemical detection and a carrier for oviposition deterrents (125).

3.2 Host location and adaptation

Recognition of odorants that are associated with an insect's host is essential for locating nutrients and ultimately reproductive success (128–130). A living host of a particular insect can vary greatly based on its life history and feeding guilds, ranging from plants to other animals or humans. Insect OBPs involved in the recognition of host semiochemicals are mainly expressed in the sensillum lymph of the antennae and assist in the adaptation of an insect to their hosts, which has been demonstrated across a diverse range of taxa (131–133). For example, it was found that *An. gambiae* AgamOBP1 is involved in the recognition and sensitivity of indole and 3-methyl indole in the antennae, the former aiding in the location of a human blood host and the latter acting as an oviposition attractant (20, 134–136). Female *A. gambiae* subjected to RNAi mediated silencing of *AgamOBP1* caused a significant reduction in the ability to perceive indole, some individuals even exhibiting a complete loss of perception (136). Another study demonstrated that *Drosophila sechellia* OBP57d and OBP57e are involved in modulating the differences in taste perception and behavioral response towards its host plant *Morinda citrifolia* (28). The characteristic odor of the ripe fruit is due to the compounds hexanoic acid and octanoic acid, that have been shown to induce a repellent effect and cause mortality in other *Drosophila* species (137). After inducing the knockdown of *OBP57d* and *OBP57e* in *D. melanogaster*, it was found that the prior repellent behavior towards ripe fruit was replaced with attraction, suggesting that both OBPs participate in the adaptation of *Drosophila* to a toxic host (28, 138). In another study, it was found that *Nilapavarta lugens* NlugOBP11 is secreted during feeding on rice and alters upregulation of the plant phytohormone salicylic acid in the brown planthopper (139). Silencing of *NlugOBP11* expression resulted in a decrease in feeding performance and eventual death, but overexpression of *NlugOBP11* in the protoplast of rice suppressed the expression of salicylic acid genes, suggesting the contribution of NlugOBP11 in host plant adaptation. In contrast to prior reports, a recent study has shown that host semiochemicals can induce an opposite effect in an insect in the absence of certain OBPs (140). After RNAi-mediated silencing of *D. helophoroides DhelOBP4*, compounds that previously elicited a strong attractant response induced a sexually dimorphic inverse effect in this ectoparasitic insect (140). Adult males no longer elicited a behavioral response and adult females exhibited a strong repellent to the herbivore induced plant volatiles, γ-terpinene and p-cymene. Although the molecular mechanism was not determined, these results may indicate the involvement of DhelOBP4 in host plant volatile recognition and/or protection of olfactory processes from potential damage by plant volatiles (140).

During the evolution of plants and phytophagous insects, plant volatiles were used as a defensive strategy to repel these insects and/or attract their respective parasitoids and predators (141). For phytophagous insects, plant volatiles are essential cues for food and oviposition (22). There is increasing evidence suggesting that plant volatiles can also function as mate-finding cues and/or stimulate sex pheromone release, which assist insects to find their mating partners (142, 143). Recently, more functional studies suggested it is a common phenomenon that insect OBPs can bind both sex pheromone components and plant volatiles, including green leaf and floral volatiles (80, 144–150). Competitive fluorescence binding assays, for instance, have shown that in the rice leaffolder, *Cnaphalocrocis medinalis*, CmedPBP4 could selectively recognize three sex pheromones and eleven rice plant volatiles (145). In the geometrid moth *Ectropis obliqua*, EoblPBP1 bound three sex pheromone components and several green leaf volatiles that had been demonstrated to attract virgin male *E. obliqua*, indicating that green leaf volatiles may act as synergists to enhance the efficacy of sex pheromones (147). It has also been found that some non-PBP OBPs play roles in sex pheromone recognition and plant volatile identification (144, 149–152). For example, the electroantennogram and competitive fluorescence binding assays revealed that a Classic OBP in *Phthorimaea operculella*, PopeOBP16 was involved in recognizing and binding several plant volatiles and sex pheromone components (150). In the Eastern Honeybee, *A. cerana*, two Classic OBPs, AcerOBP6 and AcerOBP11 as well as one Minus-C OBP, AcerOBP15, have been characterized and been linked to recognition of bee pheromones and floral volatiles, indicating these OBPs may play a dual-role in sensing various bee pheromones and host odorants (80, 146, 152).

3.3 Pesticide adaptation

Despite the remarkable sensitivity of the insect olfactory system to detect and differentiate critical odorant cues even at minute concentrations, it also can act as an attractive target for harmful plant compounds and environmental toxins (22, 24). Plant volatiles or anthropogenic toxins pose potential risks to terrestrial insects, as they can impair the processing of odorant molecules or even cause physiological damage at high doses (24). Recently, a substantial amount of evidence emerged, indicating that the gene expression of certain OBPs undergo changes in response to pesticide exposure. These OBPs may play a role in pesticide adaptation by binding, buffering, or sequestration of pesticides that have penetrated the cuticle (2, 25–27, 79, 153–159). Investigating the mechanisms underlying OBP-mediated pesticide adaptation will open new avenues to broaden our understanding of how insects adapt to their xenobiotic environment and evolution of pesticide resistance (13, 33, 160).

One of the first studies to demonstrate the potential of insect OBPs to be involved in insecticide adaptation was conducted in the diamondback moth, *Plutella xylostella* (21). The study exposed *P. xylostella* larvae to two separate selection treatment regimens: Low concentrations of permethrin (LC_5 of prior generation) only applied to the upper and center portion of the host cabbage plants and high concentrations of permethrin (LC_{50} of prior generation) uniformly applied across the entire canopy of the cabbage plant (21). It was found that upon comparing the F_1 parental generation to the selected G_{25} generation, *PxylOBP13* was upregulated in the low concentration of permethrin treatment group, implying a possible role in resistance. Lin et al. in 2018 reported that the gene expression of *SlituOBP9* in the tobacco cutworm *Spodoptera*

litura, was increased in response to chlorpyrifos and emamectin benzoate (25). After injection of dsRNA targeting *SlituOBP9*, the survival of tobacco cutworm moths exposed to chlorpyrifos for 48 hours was decreased to 7.7%, as compared to 50% in the control moths, indicating that SlituOBP9 could play a role in chlorpyrifos adaptation (25). Similarly, it was found that exposure to the herbicide butachlor caused reduced susceptibility to chlorpyrifos in the tobacco cutworm in a separate study (156). Gene silencing of one general OBP, *S. litura SlGOBP2*, decreased larval tolerance to chlorpyrifos, suggesting that olfactory recognition of butachlor by SlGOBP2 may contribute to enhanced chlorpyrifos resistance by induction of ecdysone synthesis and regulating expressions of detoxification genes (156). In the Asian citrus psyllid, *Diaphorina citri*, the expression of *DcitOBP2* was induced in response to imidacloprid exposure. When *DcitOBP2* was silenced via RNAi, susceptibility to imidacloprid was increased in *Di. Citri* adults, suggesting that DcitOBP2 is involved in imidacloprid resistance (161). Similarly, *N. lugens* NlOBP3 was associated with nitenpyram and sulfoxaflor resistance in the brown planthopper (157). Two PBPs in *Athetis lepigone*, AlepPBP2 and AlepPBP3, had high binding affinities to an organophosphate insecticide, phoxim, indicating that these two PBPs may play roles in the phoxim adaptation of this polyphagous pest (155). Similarly, a recent study demonstrated that a G protein coupled receptor, latrophilin may contribute to insecticide resistance through regulating the expression of *Tribolium castaneum TcOBPC01* and one other chemosensory gene (27). Additionally, it was also reported that an increase in larval mortality to dichlorvos and carbofuran was observed when *latrophilin* or *TcOBPC01* was silenced.

Other than acute effects on target insect pests, chemical insecticides cause serious negative effects on nontarget insects, such as parasitoid wasps and pollinators (162). Several studies reported that the OBP either showed high binding affinity to insecticides (154, 158) or the binding of OBP to floral volatile was significantly affected by insecticides (163). These studies implied that OBPs may contribute to olfaction based behavioral response to insecticides. In addition to synthetic pesticides, insect OBPs play roles in adaptation to biopesticides (e.g. essential oils) that are derived from natural materials, including plants, microorganisms, and other biological sources. For example, the *TCOBPC11* (*T. castaneum*) gene expression was induced in response to the essential oils of *Artemisa vulgaris* in the late instar larvae (26). Gene silencing of *TCOBPC11* by RNAi led to higher mortality in larvae compared with the control larvae treated with essential oils, suggesting that TCOBPC11 may play a role in resistance by sequestrating of plant essential oils and masking the toxic effects.

Host plant and pesticide adaptation might be linked due to chemical, evolutionary, and ecological evidence in detoxification and chemosensory pathways (22, 33, 34, 77, 164–166). It is possible that the capability associated with OBP-mediated pheromone or host plant adaptation in herbivorous insects has been co-opted for pesticide adaptation when they are exposed to pesticides. Most recently, research reported that insect OBPs can bind sex pheromone components, plant volatiles and pesticides (79, 153, 159). An OBP (AlepGOBP2) that was functionally characterized in the polyphagous insect *A. lepigone* showed high binding affinity to two conspecific sex pheromones ((Z)-7-dodecenyl acetate and (Z)-9-tetradecenyl acetate), two maize plant volatiles (Ocimene and (E)-β-Farnesene), and two organophosphate insecticides (chlorpyrifos and phoxim) (79). These results indicated AlepGOBP2 may facilitate recognition and adaptation to sex pheromones, plant volatiles, and insecticides all together.

In summary, current studies suggest that insect OBPs contribute to pesticide adaptation through sequestration and subsequent masking of the harmful effects of toxic compounds, or by acting as phase 0 transport proteins and shuttling toxic compounds across the cell membrane to phase I and/or phase II enzymes for further processing (27, 167–169). Whether this is accomplished solely by insect OBPs or through the assistance of other proteins, such as detoxification enzymes, remains to be elucidated.

4 Conclusion

While our understanding of insect OBPs was initially centered on olfaction, recent research conducted over the past decade has unveiled their involvement in diverse physiological processes, including communication, host location and adaptation, pesticide resistance, and reproduction. However, our comprehension of the molecular mechanisms governing OBP functions beyond olfaction remains limited due to their substantial diversity across various taxa. Recent advances in whole genomic sequences, RNA interference, gene editing, X-ray crystallography, and fluorescent competitive ligand binding assays, promise to enhance our understanding on the roles of insect OBPs towards communication and xenobiotic adaptation. This cutting-edge research will also contribute to unraveling the intricate and multifaceted mechanisms underpinning the evolutionary relationship between insects and their environment.

Author contributions

JA: Methodology, Visualization, Writing – original draft, Data curation, Investigation, Software. TM: Investigation, Software, Visualization, Resources, Writing – review & editing. HW: Resources, Software, Visualization, Writing – review & editing, Data curation, Methodology. FZ: Methodology, Resources, Visualization, Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) FZ declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/finsc.2023.1274197/full#supplementary-material

SUPPLEMENTARY TABLE 1
Summary of odorant binding proteins (OBPs) used in the creation of the phylogenetic trees (Figure 2). Sequences without a complementary accession number were adapted from prior literature, where sequences were referenced but lacked an accession number.

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