ANNUAL REVIEWS

Annual Review of Entomology

Whitefly–Plant Interactions: An Integrated Molecular Perspective

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Annu. Rev. Entomol. 2024. 69:503–25

First published as a Review in Advance on October 10, 2023

The *Annual Review of Entomology* is online at ento.annualreviews.org

https://doi.org/10.1146/annurev-ento-120120-093940

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Keywords

phloem feeding, adaptation, osmoregulation, plant immunity, effectors, genetic manipulation

Abstract

The rapid advances in available transcriptomic and genomic data and our understanding of the physiology and biochemistry of whitefly–plant interactions have allowed us to gain new and significant insights into the biology of whiteflies and their successful adaptation to host plants. In this review, we provide a comprehensive overview of the mechanisms that whiteflies have evolved to overcome the challenges of feeding on phloem sap. We also highlight the evolution and functions of gene families involved in host perception, evaluation, and manipulation; primary metabolism; and metabolite detoxification. We discuss the emerging themes in plant immunity to whiteflies, focusing on whitefly effectors and their sites of action in plant defense–signaling pathways. We conclude with a discussion of advances in the genetic manipulation of whiteflies and the potential that they hold for exploring the interactions between whiteflies and their host plants, as well as the development of novel strategies for the genetic control of whiteflies.

1. INTRODUCTION

Compared to the detailed knowledge on plant–insect interactions in chewing insects, relatively little is known about these interactions in piercing-sucking insects belonging to suborder Sternorrhyncha (144). Sternorrhynchans use their stylets to probe plant tissues intracellularly or intercellularly and feed primarily on phloem sap, an unbalanced diet with high levels of sugars and low levels of essential nutrients such as amino acids (see the sidebar titled The Phloem Tissue) (23). The suborder includes four superfamilies: aphids, scale insects, psyllids, and whiteflies (38). To date, the literature on sternorrhynchans has primarily focused on aphids, with whiteflies receiving far less attention. Whiteflies differ from aphids and other sternorrhynchans in many biological characteristics, including the production of sessile nymphs that establish a long-term and intimate relationship with their host plant (see the sidebar titled Whitefly Taxonomy) (12).

THE PHLOEM TISSUE

The phloem tissue consists of three main cell types: sieve elements, in which several major organelles are degraded, allowing an organelle-free path for transport; companion cells, which genetically and metabolically support the sieve elements; and phloem-parenchyma cells.

WHITEFLY TAXONOMY

Whiteflies are minute insects (1–3 mm in length) classified into one superfamily, the Aleyrodoidea, that includes one family, the Aleyrodidae. They use many broadleaved trees, shrubs, ornamentals, and vegetables as hosts. The Aleyrodidae consists of three extant subfamilies. The Udamoselinae contains one genus and two species, and the Aleurodicinae contains 21 extant genera. Most whiteflies belong to the Aleyrodinae, which has more than 140 genera, including the major agricultural pests *Bemisia tabaci* and *Trialeurodes vaporariorum*. *Bemisia tabaci* is a species complex with at least 40 cryptic species, of which *B. tabaci* Middle East-Asia Minor 1 (MEAM1) and Mediterranean (MED) are invasive and have spread across the globe.

In this article, we review our current understanding of fundamental aspects of whitefly interactions with their host plants. Other important topics, such as the status of whiteflies as viral vectors and whitefly management in agricultural systems, are not discussed. We refer the reader to several excellent, recent reviews on these topics (31, 49, 67, 148). We provide a comprehensive overview of the mechanisms that whiteflies have evolved to overcome the nutritional limitations and osmotic challenges of feeding on plant phloem sap. We also highlight the principal functions of the gene families involved in the perception, evaluation, and manipulation of the plant hosts, as well as in primary metabolism and metabolite detoxification. Within this context, we outline new discoveries on horizontal gene transfer and plant immune signaling. The last two sections provide new insights on the future of whitefly control and identify gaps in our current knowledge that provide research opportunities for the future.

2. WHITEFLIES FEED ON A NUTRITIONALLY POOR AND UNBALANCED DIET

2.1. Plant Phloem Content Imposes Feeding Challenges

Like other groups of the Sternorrhyncha, whiteflies feed on phloem sap, a diet consisting mainly of sugars, amino acids, and inorganic ions. Phloem sap is a less threatening diet relative to other

APOPLASTIC PHLOEM-LOADING

Sucrose moves intercellularly via plasmodesmata, microscopic channels enabling transportation between plant cells, to arrive in phloem-parenchyma cells. Sucrose is exported into the phloem extracellular space (apoplast) by specialized transporters. Subsequently, sucrose is imported into the companion cells by specialized transporters and moves through plasmodesmata into the sieve-tube.

plant tissues, as it contains lower levels of toxins and feeding deterrents (23, 86). Still, this unique feeding niche imposes two main challenges: the sugar barrier and the nitrogen barrier (23).

The sugar barrier is encountered during phloem feeding due to the high concentrations of sugars in phloem sap. In apoplastic phloem-loading plants, the main sugar (sucrose) can reach concentrations of approximately 1.4 M (see the sidebar titled Apoplastic Phloem-Loading) (86). In polymer-trap loading, the combined concentrations of raffinose, stachyose, and sucrose in the phloem sap can reach approximately 750 mM (44, 66). In addition, plants with abundant sugar alcohols also have high levels of sucrose (350–650 mM) in their phloem sap (99). Feeding on these high-sugar diets can cause osmotic instability, resulting in the transfer of water from the hemolymph to the gut and subsequent osmotic collapse of cells and desiccation (23).

In contrast, the nitrogen barrier is due not to an excess or paucity of total amino acids in the phloem sap, but rather to the underrepresentation of essential amino acids (86). Comparison of the amino acid composition of phloem sap in 36 plants indicated that 10 essential amino acids (arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine) constituted approximately 21% of the total amino acids, whereas three amino acids (histidine, methionine, and tryptophan) were present at <1% (127). This is in sharp contrast to the ratio of essential to nonessential amino acids (1:1.1) in whitefly proteins, as deduced from the *Bemisia tabaci* and *Trialeurodes vaporariorum* genomes.

Below, we discuss the biochemical and physiological mechanisms that whiteflies have evolved to overcome the high osmolarity in their gut and cope with the extreme limitation of essential amino acids, cofactors, and vitamins in their diet.

2.2. The First Layer of Efficient Osmoregulation in Whiteflies: Sugar Transformations

Unlike aphids, whiteflies primarily modulate their ingested sugars by isomerization of sucrose (20) (**Figure 1**). One example of the isomerization of sucrose is the synthesis of trehalulose, which is the major disaccharide detected in *B. tabaci* honeydew (>30% of total carbohydrate) (13, 14). Trehalulose is synthesized by rearranging the glycosidic bond of sucrose from the two to the one position of fructose (**Figure 1**). This rearrangement does not directly reduce osmotic pressure, as one disaccharide is replaced by another. However, the rate of trehalulose hydrolysis is approximately 10% of the rate of sucrose hydrolysis, ameliorating osmotic stress. Therefore, trehalulose contributes to the ability of whiteflies to maintain metabolic homeostasis (53, 119, 120). The synthesis of trehalulose might be a specific characteristic of the *B. tabaci* species complex, as *Bemisia afer*, *Bemisia berbericola*, and seven other whitefly species produce very low or negligible levels of trehalulose (13). Moreover, *T. vaporariorum* and *Trialeurodes abutilonea* have evolved a different osmoregulatory solution. These whiteflies produce significant amounts of the disaccharide turanose (47) (**Figure 1**), which, like trehalulose, is slowly digested (138).

Polymer-trap loading: sucrose movement to the companion cells is mediated by plasmodesmata, but trisaccharides and tetrasaccharides are synthesized from sucrose before entering the sieve-tube for long-distance transport

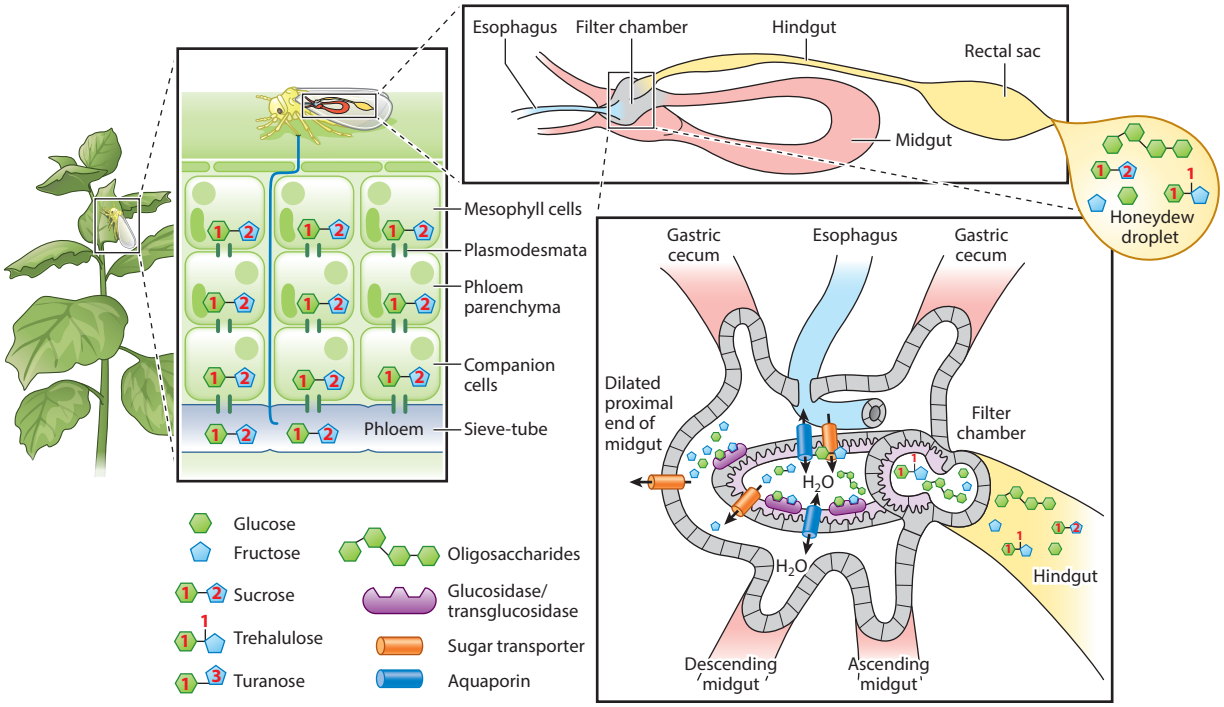

Figure 1

Osmoregulation in whiteflies. (*Left*) In plants, photosynthetically active mesophyll cells of source leaves synthesize and export sucrose long distances through the phloem to nonphotosynthetic sink tissues. Whiteflies feed (*blue line*) from the sieve-tube, a conducting element of the phloem formed by end-to-end longitudinally connected sieve elements. Panel adapted from images created with BioRender.com. (*Right*) Whiteflies tolerate the high osmotic pressure generated by sugars in the phloem sap by complementing osmoregulation mechanisms. According to Ghanim et al. (35) and Walker et al. (143), the ingested phloem sap flows over the filter chamber as it leaves the esophagus. We hypothesize that the two cell layers of the filter chamber (e.g., the outer midgut epithelium cell layer and the inner Malpighian cell layer) harbor sucrose isomerization and gut α-glucosidase or -transglucosidase activities, as well as transporters that selectively transport sugar and water molecules. These activities facilitate osmoregulation by allowing the partitioning of ingested carbohydrate between rapid excretion and assimilation (118). Once in the lumen of the filter chamber, the sugars proceed through the remainder of the hindgut to the anus for excretion as honeydew droplets. Following Shakesby et al. (128), we propose that water might also move in the reverse direction (e.g., from the filter chamber to the dilated proximal end of the midgut lumen) through water-specific protein channels (aquaporins), resulting in dilution of the fluids entering the descending midgut. Panel adapted with permission from (*top*) Ghanim et al. (35) and (*bottom*) Walker et al. (143).

Whiteflies also produce longer oligosaccharides (>2 hexose units), which helps to reduce the osmotic pressure per unit sugar mass (46, 47, 152). These oligosaccharides are likely to be the product of gut α-glucosidases that also have transglucosidase activity [e.g., glycoside hydrolase family 13 (GH13)] (57, 90). During GH13-mediated transglucosylation, sucrose is hydrolyzed to fructose and glucose. Glucose is subsequently transferred to an acceptor hydroxyl group on another glucose monomer or a glucose oligomer to prevent the accumulation of free glucose monomers (20, 109) (**Figure 1**). Depleting free glucose levels is important for homeostasis because, unlike free fructose, only some of the free glucose in the gut is taken up for respiration and other metabolic needs of phloem-feeding insects (4). Interestingly, it was recently shown that the transglucosylation reactions in *B. tabaci* are not limited to carbohydrate substrates. Sucrose can also serve as a glucose donor during the production of glucosylated derivatives of plant-defense compounds, such as glucosinolates and cyanogenic glycosides (27, 90) (**Figure 1**).

2.3. The Second Layer of Efficient Osmoregulation in Whiteflies: Movement of Water Between Adjoining Gut Tissues

Phloem-feeding insects also use water cycling across the alimentary tract epithelium for osmoregulation (128, 140). Whiteflies and many other hemipteran xylem and phloem feeders use aquaporins (water-specific protein channels) for water transport. Aquaporins are expressed in the filter chamber (69, 96), a structure connecting the esophagus and foregut directly to the hindgut (35) (**Figure 1**). The whitefly filter chamber shunts excess water and some solutes from the anterior digestive system directly into the hindgut, while the remaining ingested nutrients continue into the midgut, where they can be absorbed (96, 143). However, this strategy could exacerbate the sugar barrier dilemma, as it has the potential to increase the osmotic pressure of the fluids entering into the midgut.

In the pea aphid (*Acyrthosiphon pisum*), it was proposed that water movement occurs in the reverse direction (e.g., from the hindgut to the anterior midgut), resulting in dilution of the fluids entering the midgut (4, 116, 128). Although this model is attractive, there are unresolved issues that caution against applying the aphid theory to the osmoregulation processes in whiteflies (**Figure 1**). First, the reverse flow of water from the hindgut into the foregut has not been described in any hemipteran phloem feeder other than the pea aphid (96). Second, ingested phloem sap should passage through the filter chamber on the way to either the hindgut or midgut. As such, the filter chamber should harbor sucrose isomerization and gut α-glucosidase or -transglucosidase activities to facilitate the correct partitioning of ingested carbohydrate between excretion and assimilation (118) (**Figure 1**). The location of these important functions in whiteflies is currently unknown.

2.4. Amino Acid, Vitamin, and Cofactor Synthesis in Whiteflies: A Cooperative Effort Involving Microbial Endosymbionts

To overcome the limitations of feeding on a diet poor in nitrogenous compounds, whiteflies have established long-term relationships with bacterial symbionts (123, 170). All whiteflies harbor the obligatory or primary symbiont *Candidatus* Portiera aleyrodidarum (*Portiera* below) inside specialized cells called bacteriocytes (37). *Portiera* and whiteflies cooperate to synthesize all essential amino acids, as well as carotenoids and lipoate (87, 122, 125). In addition, individual whiteflies may harbor one or more facultative or secondary bacterial symbionts from the genera *Hamiltonella*, *Arsenophonus*, *Rickettsia*, *Wolbachia*, *Cardinium*, *Hemipteriphilus*, and *Fritschea* (170). *Hamiltonella* and *Arsenophonus* display some characteristics of primary symbionts and produce essential nutrients such as cofactors, vitamins, and lipids (114, 123, 149). The other facultative or secondary symbiotic bacterial genera also collaborate biochemically by producing macromolecules that convey fitness advantages to the insect host when it is adapting to the distinctive metabolite profiles of different plant hosts (103, 127). To date, there is only one report that demonstrates that endosymbionts can have a non-nutritive effect enhancing the performance of whiteflies on a plant host (131). In this case, the *B. tabaci* that harbor *Hamiltonella* have decreased expression of jasmonic acid (JA)-responsive antiherbivore genes, as well as reduced defense-related enzyme activity. This is mediated by increases in the defense hormone salicylic acid (SA) in whitefly-infested tomato plants. The response is triggered by a <3-kDa nonproteinaceous molecule in the saliva of the *Hamiltonella*-carrying whiteflies.

2.5. Gut Microbiome of Whiteflies Involved in Plant Adaptation

Until recently, the role of the microbial community that inhabits the gut lumen of whiteflies in host plant adaptation had not been explored. These bacteria are located in the right place to enable whitefly adaptations to plant metabolism, as food processing initiates in the gut. Previously,

it was presumed that phloem-feeding insects, such as whiteflies, would harbor a limited set of gut-associated ectosymbionts. This was largely based on the simple gut morphology of whiteflies, which does not support colonization, and their relatively bacteria-free phloem diet (28, 58). However, recent studies have indicated that the gut-associated microbial community of *B. tabaci* is more complex than was anticipated, including species from the *Acinetobacter*, *Bacillus*, *Micrococcus*, *Moraxella*, *Mycobacterium*, *Pseudomonas*, *Staphylococcus*, and *Sphingomonas* genera (5, 51, 124). Santos-Garcia et al. (124) showed that whitefly acquisition of gut-associated bacteria is strongly affected by the identity of the plant host. In addition, a significant enrichment of the microbiome with *Mycobacterium* was correlated with an increase in *B. tabaci* (MEAM1) performance on pepper plants considered to be toxic (124). Considering the transient and unpredictable nature of gut microbiota acquisition events, it is clear that further studies are required to evaluate the generality of these discoveries.

3. GENOMICS OF WHITEFLY–PLANT INTERACTIONS

3.1. Current Status of Whitefly Genomic Resources

Currently, 12 whitefly genome assemblies are available in public domains: two from *T. vaporariorum* and 10 from *B. tabaci* (seven species). The estimated genome size of *T. vaporariorum* is approximately 787.5 Mb (approximately 16,000 high-confidence genes) (158), and that of *B. tabaci* is approximately 610–657 Mb (approximately 14,300–15,300 genes) (16, 17, 157). In transcriptomic analyses, the most studied whitefly species are *T. vaporariorum* and *B. tabaci*, with 12 and 89 BioProject data sets in public domains, respectively. To date, fewer than 10 of these analyses focused on the transcriptome responses of whiteflies to feeding on host plants.

3.2. Host Plant Sensing and Perception

Chemosensation plays a significant role in the ability of insects to locate plants and evaluate their potential as suitable hosts (129). Several terpenoids were found to repel *B. tabaci* from tomato plants and to elicit a receptor response in the insect's antennae (8, 9). Moreover, olfactometer tests have evaluated whitefly behavioral responses to plant-produced volatile blends and/or individual volatiles to identify compounds that attract or repel whiteflies (25, 78, 97, 139). These studies identified the green leaf volatiles (GLVs) (*E*)-2-hexenal and 3-hexen-1-ol as attractants that influence host plant selection and oviposition in whiteflies (78). Furthermore, terpenoids such as D-limonene, β-myrcene, and (*E*)-β-ocimene are volatiles that repel whiteflies (139).

The major multigene families involved in chemosensation include odorant-binding proteins (OBPs), chemosensory proteins (CSPs), olfactory receptors (ORs), and gustatory receptors (GRs) (121). Eight OBPs and 19 CSPs were annotated in the genomes of *B. tabaci* MEAM1 and MED. The combined numbers of OBPs and CSPs in *B. tabaci* are similar to those found in other phloem-feeding hemipterans and are substantially lower than the numbers detected in other insect orders (147, 171). The *B. tabaci* OBPs belong to three clades (Minus-C, Plus-C, and Classic). Four OBP genes (*OBP2*, *OBP3*, *OBP4*, *OBP8*) are expressed at high levels in the head relative to other tissues in both the MEAM1 and MED species. In contrast, the 19 *B. tabaci* CSPs are expressed in multiple tissues. The CSPs are distributed across all hemipteran major phylogenetic clades, with one lineage-specific expansion (*BCSP1*, *BCSP3*, *CSP13*, *CSP17*, *CSP18*, *CSP19*) (147, 171). Whitefly genomes contain fewer ORs (9–20 predicted genes) than other closely related groups within the Sternorrhyncha (47–102 predicted genes) (136). Although whitefly *GR* genes have yet to be fully annotated and characterized, two recent publications report the identification of four putative sugar-sensing *GR* genes in *B. tabaci*. One of the genes, *BtabGR1* (LOC109040290), displays significant sucrose specificity when expressed in *Xenopus* oocytes. Silencing of *BtabGR1* significantly

interferes with the ability of *B. tabaci* adults to discriminate between non-phloem and phloem concentrations of sucrose (2, 72). To date, no other functional studies have been successful in elucidating the specific role(s) of OBP, CSP, and OR proteins in perception and evaluation of plant-derived metabolites by whiteflies. Several plant-derived compounds that are perceived by whiteflies have been identified. These compounds provide opportunities for the future study of whitefly chemoperception (73, 80, 146).

Adaptation to a well-defended host plant: a process in which, after multiple generations, generalist insects display improved performance on the less-suitable host plant

3.3. Diet Digestion

Comparative transcriptome analyses in *B. tabaci* identified midgut-specific genes encoding proteins that hydrolyze or form (by transglycosylation) α-glucosidic linkages (GH13), transport sugars, and degrade phloem proteins (by cathepsin B proteases) (167). These gene families are expanded (1.7- to 2.5-fold) in the *B. tabaci* genome relative to those of other closely related phloem-feeding insects (17, 90, 165). In addition, these genes display marked changes in their expression when whiteflies shift between host plants (91, 111, 135, 159). The differential expression of GH13 enzyme and sugar transporter genes during host shifts may allow whiteflies to maintain sugar homeostasis (91). The specific role of cathepsin B proteases in host adaptation is less clear. Their over- or underexpression could be related to changes in the whitefly's ability to degrade phloem proteins for nitrogen salvaging and/or to counteract plant defenses (40, 117). Lastly, during long-term (multiple generations) adaptation to a well-defended host plant, both *B. tabaci* and *T. vaporariorum* overexpress large numbers of genes encoding structural constituents of the insect cuticle (Gene Ontology 0042302) (111, 135). The possible role this function plays in whitefly host adaptation remains unclear but may relate to physical changes (e.g., exoskeleton hardening, increased body volume and/or muscle content) that enhance survivorship and reproduction on well-defended plants. Modifications of the insect cuticle may allow stylets to more efficiently navigate to the phloem, increase desiccation tolerance, and/or avoid entrapment by leaf trichomes (111, 135, 156).

3.4. Detoxification Mechanisms of Plant Secondary Metabolites

Whiteflies possess the enzymatic machinery to detoxify plant secondary metabolites. Detoxification occurs in three phases and mainly involves five major protein families: cytochrome P450 monooxygenases (P450s), UDP-glycosyltransferases (UGTs), glutathione S-transferases (GSTs), carboxylesterases (CCEs), and ATP-binding cassette transporters (ABCs) (92, 111) (**Table 1**). Comparison of the numbers of detoxification genes in whiteflies (*B. tabaci* and *T. vaporariorum*), several hemipterans, and nonhemipteran species suggests that, at the family level, there is no significant expansion or contraction of any of the detoxification families in whiteflies when compared to other insects. While the *B. tabaci* and *T. vaporariorum* genomes contain comparable numbers of *GST*, *UGT*, and *ABC* genes, the numbers of predicted *P450* and *CCE* genes in *T. vaporariorum* are markedly reduced compared to *B. tabaci* (92, 111). In addition, at the subfamily level, there were significant expansions and contractions of gene numbers in four of the five detoxification families between the genomes of *B. tabaci* and *T. vaporariorum* (111). These data suggest independent evolution of the detoxification toolbox in the two whiteflies.

Multiple studies have detected differential expression of genes from the five major detoxification families in response to host plant shifts. This was observed in a whitefly species feeding on different hosts, as well as when different whitefly species feed on the same host (for examples, see 92, 111, 136, 150, 160). In a small number of these studies, gene-silencing assays that targeted specific detoxification genes were performed, and the results of these assays provided support for the roles of specific proteins in the detoxification of plant metabolites (26, 41, 94, 154). To date, only five studies have directly linked the activity of a specific detoxification protein

Table 1 Detoxification gene families

Species and order	Cytochrome P450 monooxygenases	UDP-glucosyltransferases	Glutathione S-transferases	Carboxylesterases	ATP-binding cassette transporters	References
Bemisia tabaci (Hemiptera)	130	51	25	51	50	3, 17, 111, 137, 155
Trialeurodes vaporariorum (Hemiptera)	80	42	26	31	46	111, 158
Acyrthosiphon pisum (Hemiptera)	84	58	20	29	54	1, 81, 112
Diaphorina citri (Hemiptera)	60	17	19	20	44	42, 84
Nilaparvata lugens (Hemiptera)	68	46	13	29	32	68, 79, 95, 179
Anopheles gambiae (Diptera)	111	26	31	51	55	1, 108, 113
Drosophila melanogaster (Diptera)	90	34	39	35	56	1, 22, 113
Bombyx mori (Lepidoptera)	83	45	23	87	51	1, 61, 83
Tribolium castaneum (Coleoptera)	134	43	35	63	73	1, 10, 178

and the production of modified (and detoxified) plant metabolites by *B. tabaci*. These include the detoxification of hydrolyzed aliphatic and indolic glucosinolates via conjugation to glutathione by the GST BtGSTs5 (26), cyanogenic glycosides and glucosinolates via conversion to nonactive glucosylated derivatives by the GH13 enzymes BtSUC2 and BtSUC5 (27, 90), glucosinolates via desulfation by a glucosinolate sulfatase (94), and phenolic glucosides via the addition of malonate by the malonyltransferase enzyme BtPMaT1 (154). Two additional detoxification protein families, the superoxide dismutases and arylsulfatases, may also contribute to *B. tabaci*'s ability to detoxify the plant-defense compounds reactive oxygen species and glucosinolates, respectively (33, 93).

3.5. The Presence and Function of Horizontal Gene Transfers in the Genome of Whiteflies

An interesting new development in whitefly biology and genomics is the discovery that the *B. tabaci* (MEAM1) genome harbors multiple horizontal gene transfers (HGTs). Li et al. (77) examined 218 high-quality genomes of diverse insect groups. They found that the *B. tabaci* genome has acquired more HGTs (170 genes) than the other insect species examined. In addition, Gilbert & Maumus (36) identified 24 HGT events in *B. tabaci*. When overlaps in these data sets are removed, the *B. tabaci* genome harbors 184 HGTs. The HGTs were acquired from diverse sources, including bacteria (41.3%), fungi (36.4%), plants (19.6%), a virus (0.54%), and other lineages (1.08%). With one exception, the contribution of these gene acquisitions to the fitness of the new whitefly host has yet to be elucidated and presents an exciting new avenue of research. Xia et al. (154) demonstrated that *B. tabaci*'s acquisition of a plant-derived phenolic glucoside malonyltransferase gene promotes survival on tomato plants, as this HGT gene allows *B. tabaci* to neutralize phenolic glucosides. This elegant study provides a clear demonstration of how HGT events can provide an evolutionary shortcut for gaining novel and advantageous functions that contribute to adaptation to host plants (64).

EFFECTORS

Effectors are pathogen- or pest-derived macromolecules (proteins, small RNAs, or chemicals) delivered into the plant to alter the function or structure of plant cells. In the context of plant immunity, effectors can trigger plant defenses (elicitors), suppress PTI (virulence factors), activate ETI (avirulence factors), alter plant development, or provoke gall formation. Effectors are delivered via insect saliva, oviposition fluids, insect honeydew, or frass and can be insect or endosymbiont derived. Putative effectors are identified via bioinformatic pipelines using transcriptome or proteome data or creative genetic screens.

4. PLANT RESISTANCE TO WHITEFLIES

After whiteflies choose a suitable host for colonization, whitefly mouthparts (stylets) pierce the plant cuticle and weave between mesophyll cells to find the phloem (143, 144). Whiteflies cause minimal cellular damage, as they initiate a small number of probes into mesophyll cells only when in close proximity to the phloem. The breach of plant cell walls and plasma membranes, the disturbance of extracellular macromolecular structures while traveling toward the phloem, and the delivery of gelling and watery saliva along the stylets' path introduce chemical signals called molecular patterns that trigger the basal plant defense response known as pattern-triggered immunity (PTI).

Using these molecular patterns, plants can rapidly perceive phloem-feeding insects and activate core immune-signaling networks, which are also used for microbe perception and defense (29, 100, 130). Plants deploy defenses locally and systemically to limit damage, impair whitefly performance, and attract natural enemies (144). To suppress PTI, whiteflies and other insects secrete proteinaceous or chemical effectors that interfere with the deployment of defenses (see the sidebar titled Effectors) (98, 130). In recent years, we have gained a substantial knowledge of the phytohormone-regulated signaling pathways that are induced and suppressed by whitefly feeding. Knowledge is also emerging about the effectors that interfere with or activate these defense-signaling pathways.

Molecular patterns: chemicals secreted into plant cells by microbes (MAMPs), pathogens (PAMPs), or herbivores (HAMPs) or released after damage (DAMPs) to trigger plant immunity

Pattern-triggered immunity (PTI): a set of conserved molecular responses, including ROS production, activated by perception of molecular patterns by membrane-associated pattern recognition receptors

***Pathogenesis-related protein* (*PR*) genes:** induced by pathogens or pests and abiotic stress; some *Arabidopsis PR* genes regulated by SA, JA, or ET are used as sentinels for specific defense-signaling pathways

4.1. Basal Immunity and Its Role in Whitefly Performance

At the core of herbivore defense are the traits controlled by the defense phytohormones JA, SA, ethylene (ET), and abscisic acid (ABA) (29) (**Figure 2**). *Bemisia tabaci* induces JA- and SA-regulated defenses to enhance its success on its hosts by promoting phloem consumption, fecundity, and adult survival and accelerating nymph development time (62, 169, 174, 175). Based on *B. tabaci* performance on JA- and SA-defense mutants and after JA and SA treatments, we know that SA suppresses the JA-regulated defenses that antagonize nymph development and production of volatiles to attract natural enemies (134, 169, 172, 175). In addition, the SA-regulated volatile blends emitted from whitefly-infested plants prime the defenses of neighboring noninfested plants, making them more suitable hosts for whitefly nymph development (173). When assessing plant defense responses to whiteflies, it is critical to recognize that SA- and JA-signaling networks may have differences ranging from subtle to profound in different plant species, ecotypes, or varieties relative to the model plant *Arabidopsis* (34). Examples include the differences in defense signaling and regulation of *Pathogenesis-related protein* (*PR*) genes in *Arabidopsis*, tomato (110) and cassava (34, 52).

While the roles of SA and JA in basal immunity to *B. tabaci* are established, the molecular mechanisms that orchestrate cross-talk between the SA- and JA-signaling pathways after whitefly infestation are only now becoming clear (**Figure 2**). For the most part, the specific defense traits

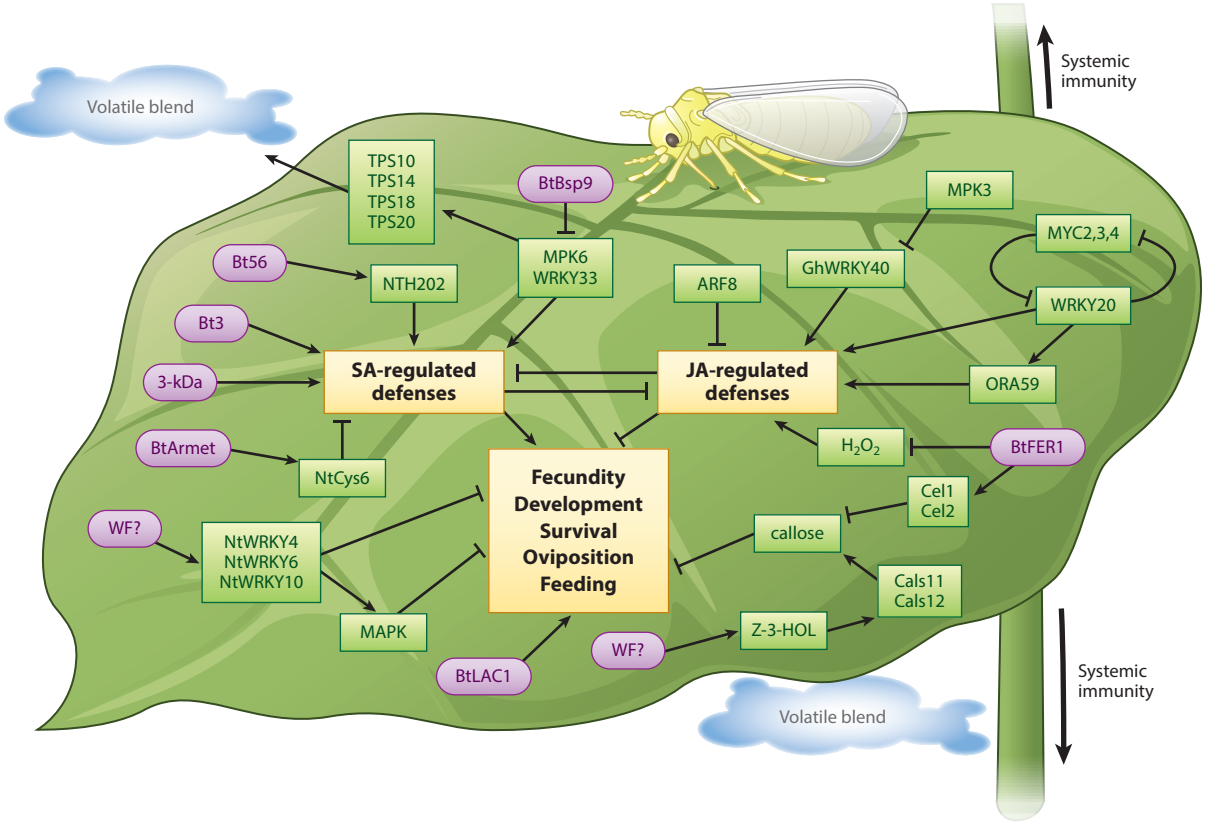

Figure 2

Plant immune signaling and influence of whitefly effectors. This figure leverages knowledge about whitefly interactions with several host plants and, while speculative, provides a framework for understanding the defense networks important for whitefly control. After perception of whiteflies, plants activate salicylic acid (SA) and jasmonic acid (JA) immune-signaling networks locally and systemically. Transcription factors, proteases, and MAP kinases with demonstrated roles in regulating immunity to whiteflies are shown (*green*). Whiteflies secrete proteinaceous and chemical effectors (*violet*) to activate or interfere with the deployment of defenses; a subset of known whitefly effectors are shown. The majority of whitefly effectors (Bsp9, Bt9, Bt56, Bt3, 3-kDa) characterized to date activate SA signaling to promote whitefly success, and some of their targets are known. The whitefly effector Bsp9 perturbs the emission of volatile blends to make plants more attractive to conspecifics. *Bemisia tabaci* Arg-rich mutated in early stage of tumors (BtArmet) may be a rheostat to fine-tune SA-regulated immunity. The SA- and whitefly-induced WRKY4, 6, and 10 are induced by an unknown effector (WF?) and interfere with whitefly fecundity and survival. Effectors that activate defenses are less well characterized. An unknown effector (WF?) promotes C6 volatile production to enhance callose deposition and to prime defenses for subsequent whitefly attack. BtFER1 counters by blocking JA-mediated immunity and callose deposition. Another effector (BtLAC1) interferes with whitefly success via undetermined mechanisms that are SA and JA independent. Figure adapted from images created with BioRender.com.

(i.e., phytochemicals, proteins, and macromolecules) that directly contribute to the basal immunity against whiteflies have yet to be elucidated. Furthermore, the molecular and chemical mechanisms that distinguish whitefly-resistant and -susceptible plants are only now beginning to be understood (11, 34, 75, 107).

4.2. Immune Regulators: WRKY and KNOX-Like Transcription Factors

Transcription factors are key regulators of plant immunity to phloem-feeding insects (32), and WRKY and KNOX-like transcription factors are important in basal immunity to whiteflies (**Figure 2**). WRKY transcription factors regulate biotic and abiotic stress responses and, in some

cases, have been associated with regulating SA- and/or JA-defense pathways (151). To date, six WRKYs are known to regulate basal immunity to whiteflies.

The *Gossypium hirsutum* (cotton) *WRKY20* controls whitefly performance and is an activator of JA and suppressor of SA signaling (177). *GhWRKY20* was discovered as encoding a protein critical for cotton leaf curl Multan virus (CLCuMuV) infectivity, but it also influences the success of its vector *B. tabaci* and other herbivores. *WRKY20* suppresses whitefly fecundity on both cotton and *Arabidopsis*; retards whitefly nymph development in *Arabidopsis*; limits the growth of cotton bollworm larvae; and, surprisingly, enhances aphid fecundity. AtWRKY20 participates in a negative feedback loop with the JA-responsive transcription factors AtMYC2, AtMYC3, and AtMYC4 to modulate JA-regulated immunity against herbivores. AtWRKY20 upregulates indolic glucosinolate–related genes and downregulates aliphatic glucosinolate–related genes. Furthermore, AtWRKY20 regulates the ERF branch of JA signaling by directly activating *ORA59*, which directly activates the JA-responsive *PDF1.2*. Both *AtORA59* and *AtPDF1.2* are important in whitefly success, as reduced levels of these proteins promote whitefly oviposition (177). Finally, by regulating the SA–JA cross-talk regulator AtORF59, AtWRKY20 is a negative regulator of SA-responsive genes (**Figure 2**).

WRKY: a set of plant-specific transcription factors with roles in abiotic and biotic stress, plant growth, metabolism and senescence; these proteins have a shared WRKY and zinc-finger motif enabling DNA binding

Nicotiana tabacum's *WRKY4*, *WRKY6*, and *WRKY10* and *Solanum lycopersicum*'s *WRKY33* have a role in regulating defenses against whiteflies. *NtWRKY4*, *NtWRKY6*, and *NtWRKY10* were identified as upregulated by whitefly feeding in a tobacco digital gene-expression library (166). These *WRKY*s are SA regulated, are nonresponsive to JA, and control traits that antagonize whitefly fecundity; however, these genes do not impact *B. tabaci* survival. Each of these WRKYs interacts with multiple mitogen-activated protein (MAP) kinases (WIPK, SIPK, NTF4-1, NTF4-2, NRK1) in vitro and in vivo. While whitefly fecundity was not influenced by silencing of the MAP kinases, the cosilencing of *NTF4-1* and *NTF4-2* marginally enhanced whitefly survival. These data suggest that these MAP kinases may act in a functionally redundant fashion or that additional interactors are critical for modulating *WRKY4*, *WRKY6*, and *WRKY10* action.

The role of *SlWRKY33* in tomato's defense against whiteflies was revealed by its interactions with the *B. tabaci* MEAM1 effector Bsp9. Bsp9 was identified in a screen for effectors that activate or antagonize expression of the JA-signaling pathway (145). After activation by MPK6, WRKY33 enhances expression of four terpene synthases (TPS10, TPS14, TPS18, TPS20) that synthesize whitefly-repellent volatiles. By interacting with WRKY33, Bsp9 prevents *TPS* gene expression and promotes the emission of a whitefly-induced volatile blend that makes tomatoes more attractive to conspecifics. In addition, BtBsp9 promotes phloem feeding, fecundity, SA accumulation, and SA-marker gene expression and suppresses JA-regulated defenses. An ortholog of Bsp9 from *B. tabaci* MED (Bt56) was identified in tobacco (161). Bt56 has the same functions as BtBsp9, but it also increases whitefly survival on tobacco. Bt56 interacts with the tobacco NTH202 (a KNOX-like transcription factor) to enhance SA-regulated responses (161) (**Figure 2**). Bt56 function appears to be highly conserved in other *B. tabaci* species (161).

Comparisons of whitefly-resistant and -susceptible cotton transcriptomes and network modeling have implicated *GhWRKY40* as a potential defense-signaling hub (76). In *Arabidopsis*, WRKY40 has a role in PTI and regulates SA-, ET-, and JA-responsive genes (7). *WRKY40*, *ERF1*, *JAZ1*, and *AOC4* transcripts are more abundant in noninfested resistant than susceptible cotton, suggesting a role of *GhWRKY40* in whitefly resistance. Consistent with this theory, virus-induced gene silencing (VIGS) of cotton's *MPK3* causes a rise in the number of *WRKY40*, *ERF1*, *JAZ1*, and *AOC4* transcripts in whitefly-resistant cotton. Inactivation of the MPK3–WRKY40 pathway by *MPK3* silencing compromises cotton's basal resistance to whiteflies, as evidenced by increases in egg deposition and numbers of nymphs and adults on both resistant and susceptible genotypes (76). The impacts of silencing *GhWRKY40* on resistance have yet to be tested.

As increasing numbers of transcriptomes for whitefly-resistant and -susceptible crops become available, it will be interesting to determine if the orthologs of the six WRKYs highlighted above are important in basal resistance or strictly correlated with the enhanced resistance traits that are displayed in whitefly-resistant crops. It is also noteworthy that mechanisms of plant resistance to whiteflies may not always be associated with the activation of SA- or JA-dependent defenses. Resistance to the Latin American whitefly *Aleurotrachelus socialis* in *Manihot esculenta* (cassava) and the cabbage whitefly *Aleyrodes proletella* in *Brassica oleraceae* (cabbage) appears to imparted, at least in part, by ABA (11, 34).

4.3. The Importance of Post-Transcriptional Processes in Whitefly Immune Responses

Small RNAs (sRNAs) regulate a plethora of developmental and biotic- or abiotic-stress responses in eukaryotes, and our understanding of the role of cross-kingdom RNA communication in plant–herbivore interactions is just emerging (15, 18). Whitefly saliva delivers sRNAs into tomato phloem (141), and some of these sRNAs may target genes to suppress plant defense. Furthermore, whitefly-induced changes in plant microRNA (miRNA) profiles and putative miRNA targets have been identified in tobacco, tomato, and cotton (43, 75, 168). The roles of these miRNA targets in tomato and tobacco defense against whiteflies are yet to be established at the molecular level (43, 168). Some of the miRNAs and downstream target genes in whitefly-resistant and -susceptible cotton have possible roles in JA and auxin signaling and as immune receptors (75). Some of the miRNA target loci produce phased small interfering RNAs (phasiRNAs) enabling target locus regulation. VIGS of one of the phasiRNA targets, *ARF8*, resulted in increased auxin, JA, and JA-Ile accumulation and upregulation of JA-response genes after whitefly infestation; the silencing of *ARF8* may protect plants from whitefly foraging (75). Our understanding of post-transcriptional processes that regulate basal immunity and/or resistance to whiteflies is beginning to emerge, as is our knowledge of the roles of translation and post-translational control in defense against the Hemiptera (82, 89, 153, 176).

4.4. Whitefly Effectors with Different Modes of Action

Armet (Arg-rich mutated in early stage of tumors) was originally discovered as an aphid effector that increases levels of SA and SA-responsive gene expression (21). Mechanistically, *B. tabaci* Armet (BtArmet) is distinct, as it decreases levels of SA and expression of SA-sentinel genes and does not impact levels of JA, JA-Ile, or JA-response gene RNAs (24). BtArmet may be a rheostat that fine-tunes the magnitude of the SA response, balancing immunity and growth or development. BtArmet enhances whitefly performance by promoting phloem feeding, adult survival, and fecundity on tobacco plants (24). While interactors of other insect Armets are not known, BtArmet interacts with the tobacco Cys endoprotease inhibitor (NtCys6) (24). VIGS of NtCys6 only partially recapitulates BtArmet-overexpressing tobacco, as only whitefly fecundity is enhanced. BtArmet's ability to enhance survival on tobacco may be conferred by another of BtArmet's putative interactors (24).

The recently identified whitefly effector BtE3 increases SA levels, induces SA-sentinel gene expression, and suppresses JA-marker genes without altering JA levels (106). BtE3 was identified based on its ability to suppress the *Blumeria glumae*–induced hypersensitive response in tomato and tobacco. BtE3 is a whitefly-specific Cys-rich salivary protein that is secreted into the phloem to promote phloem feeding, adult survival, and fecundity. Its molecular partners and the mechanism by which it enhances whitefly performance remain unknown.

Two *B. tabaci* MED effectors—Ferritin1 and Laccase1—enhance whitefly survival on tomato but do not influence fecundity (132, 162). Neither BtLAC1 nor BtFer1 regulates phytohormone

levels after whitefly infestation. BtFer1 is a ferroxidase that attenuates H_2O_2 levels and callose deposition (132, 164). Consistent with H_2O_2 as an activator of JA-regulated defense genes in tomato (104), BtFer1 downregulates the JA-signaling pathway. JA promotes the emission of the C6 volatile Z-3-hexenol, which stimulates SA accumulation, expression of callose synthase genes (*Cals12* and *Cals11*), and callose deposition (164); Z-3-hexenol interferes with whitefly oviposition and feeding and promotes emission of a volatile blend that attracts parasitoids (163). BtFer1 also interferes with whitefly-induced callose deposition by inducing the callose-hydrolyzing enzyme genes (*Cel1* and *Cel2*) to promote whitefly phloem consumption and survival (132, 142). While the role of the BtLAC1 effector is currently unknown, it may detoxify tomato metabolites that are encountered by whiteflies (162). Alternatively, BtLAC1 may promote the rapid oxidative gelling of sheath saliva (45).

Finally, three whitefly effectors (S2G4, 6A10, and 2G5) were identified based on their ability to stimulate systemic acquired resistance to above-ground and below-ground pathogens (70). While the *2G5* and *S2G4* genes encode novel, whitefly-specific proteins with unknown functions, *6A10* encodes the large subunit ribosomal RNA, making it a nonproteinaceous effector. The mechanisms of action of these effectors in whitefly–plant interactions have yet to be deciphered. It is clear from comparisons of salivary-gland transcriptomes with transcriptomes from other organs or treatments, and in the papers cited above, that a large number of candidate whitefly effectors remain to be explored (50, 161). Understanding the molecular complexities of effectors and their role in triggering or suppressing host plant defense–signaling pathways should allow for the development of new and cogent strategies for the control of this devastating global pest.

5. GENE SILENCING, GENOMIC MANIPULATION, AND GENETIC CONTROL OF WHITEFLY PESTS

5.1. Gene Silencing Technologies Can Be Used to Interfere in Whitefly–Host Plant Interactions

Targeted silencing of genes in whiteflies is an efficient somatic-based assay that enables tests for the role of gene products that modulate the interactions between whiteflies and host plants. RNA interference (RNAi) uses double-stranded RNAs (dsRNAs) to silence genes. RNAi is dependent on the processing of the dsRNA into 21-nt siRNAs by the Dicer protein of the siRNA pathway (6). The reader is directed to recent excellent reviews on RNAi technology in whiteflies (19, 39, 55, 56, 60, 133). Delivery of RNAi can be achieved by feeding whiteflies an artificial diet containing dsRNA, direct injection of dsRNAs into the whitefly, or feeding whiteflies transgenic plants expressing the dsRNA. RNAi delivery of intact dsRNAs into the cells of the whitefly can be compromised by the presence of dsRNases in the lumen of the whitefly gut (48, 88).

RNAi technology could potentially be applied to the control of whiteflies in the field, provided that reproducible and reliable levels of gene silencing can be obtained. RNAi-based control of whiteflies could be achieved through the generation of transgenic plants resistant to whitefly infestation or through the efficient and reliable delivery, by spraying, of an RNAi-based pesticide on the crop plants. A recent advance has been the use of RNAi bound to a MgFe-layered double hydroxide, termed BioClay (54), which, when sprayed on the adaxial side of leaves, effectively delivers dsRNAs for gene silencing.

5.2. Gene Knockout in Whiteflies by CRISPR-Based Approaches

CRISPR/Cas-based genetic technologies now provide the opportunity to make mutants cost-effectively and precisely by editing of and insertion of genes into hemipteran genomes (105). There is only one reported example of CRISPR/Cas9-based technology being deployed in *B. tabaci*

MEAM1. A modified Cas9 endonuclease and single guide RNAs (sgRNAs) to the eye-color gene *white* were injected into the abdomens of gravid females using the ReMOT (Receptor-Mediated Ovary Transduction of cargo) technique of delivery (48). Frequencies of nymphs or adults with white or bright red or orange-colored eyes varied between 0.2% and 2.5% (48). Analysis of five mutant G0 offspring confirmed CRISPR-mediated mutagenesis at two of the five sgRNA targets of the *white* gene. Crossing mutant males with wild-type females generated 90 wild-type G1 offspring. Eye pigmentation mutants were observed in the G2 generation in a ratio significantly less than expected from Mendelian inheritance, possibly due to a female bias in the colony or to reduced viability of the *white* mutants, as has been shown in some other insect species (63, 65, 115). However, DNA sequence confirmation of these G2 mutants was not reported (48). The low frequencies of G0 mutagenesis, combined with the inability of the ReMOT technology to generate knockin mutations, may limit the versatility of this technique in whiteflies (105).

Homing-gene drive: a mechanism of quickly spreading a genetic payload through a population; the gene drive contains genes that enable copying and insertion of the payload into a specific site of a chromosome each generation

Further innovations in CRISPR/Cas9-mediated gene editing in whiteflies are needed. We have performed microinjections of *B. tabaci* MEAM1 preblastoderm embryos with Cas9 protein and sgRNAs and successfully generated heritable mutations in genes of the ommochrome biosynthesis pathway (P. Atkinson and L. Walling, unpublished observations). The generation of whitefly strains with mutations in key genes associated with phytochemical detoxification, suppression of plant immunity, or interference of viral transmission is feasible and would provide key tools for interrogating whitefly–plant interactions.

5.3. Genetic Control of Haplodiploids: The Contemporary Genetic Control Approaches that Are Applicable to Whiteflies

Once high-efficiency methods for gene editing and gene insertion in whiteflies are in place, genetic control strategies for whiteflies can be pursued. Two challenges will be encountered in developing these strategies for whiteflies. First, unlike mosquitoes or other dipterans, in which only females need to be controlled, in whiteflies, both males and females will need to be controlled, as both sexes cause significant economic damage through direct feeding and virus transmission. This effectively removes the possibility of releasing large numbers of gene-edited males in any genetic control strategy, which has been pursued in other systems (101, 102, 126). The second challenge is that whiteflies are haplodiploid. Therefore, any genetic control strategy that is dependent on the presence of a sex chromosome unique to one sex or the manipulation of the sex ratio cannot be used in whiteflies or other haplodiploid species (74, 85). Furthermore, since whitefly males are haploid, homing-gene drives that convert one chromosome by its homologous partner in a heterozygote cannot occur in males; this limits the drive mechanism to females (85). Gene drives in haplodiploid insects are therefore predicted to progress more slowly and develop resistance to gene drive more rapidly than in diploid species (74, 85).

Recent gene-modeling experiments performed in haplodiploid pest species (the wasp *Vespula vulgaris* and the mite *Varroa destructor*) provide some possible guidance (30, 71). In the wasp, these models predict that gene drives using complete male sterility will fail due to the loss of the male mutants. Models based on partial male sterility predict that release of large numbers of partially sterile males can achieve population suppression; however, large mass releases of whiteflies are not realistic due to direct and indirect damage to crops. Gene-drive strategies to manage or eradicate the *Varroa* mite that are based on male or female fertility have been modeled. These strategies are likely to be unsuccessful unless large quantities of the gene-edited mites were deployed.

In both species, models predicted that neutral gene drives may be feasible, and similar strategies could be implemented for whiteflies. Strategies based on removing insecticide resistance alleles, spreading a toxin precursor (that could be later activated by an environmental inducer), and preventing transmission of begomoviruses are possible options. Moreover, models predict that a

homing-gene drive that targets essential haplosufficient female fertility (or potentially female viability) genes in haplodiploids maybe an effective control strategy. These models indicate that genetic control could be developed for these pest insects even when the genetic load on the target population is high (85). This drive would take longer to reach fixation and achieve population suppression than the same drive in diploids; however, it could be achieved within 30 generations with a 1% release level (85). For whiteflies, this may represent a possibility of eliminating an invasive whitefly species within several seasons. Furthermore, there is some optimism that these new approaches may be acceptable to stakeholders in agriculture and to the general public (59).

Haplosufficient female fertility: condition in which one copy of a gene is sufficient for the wild-type function

6. CONCLUSIONS AND PRIORITIES FOR FUTURE RESEARCH

Within three decades, the scientific community has identified many of the strategies that whiteflies have evolved to counterbalance the challenges and limitations of feeding on phloem sap. The accumulating genome sequences, transcriptomes, proteomes, and metabolomes have provided a glimpse of the underlying molecular mechanisms deployed by whiteflies to successfully feed and reproduce on their plant hosts. The roles of some specific effectors and of digestive and detoxification genes in regulating plant immunity and host adaptation have been established (**Figures 1** and **2**). However, many significant gaps in our knowledge remain, providing opportunities for future investigation.

We currently do not understand the chemical or mechanical cues that whiteflies use to find their feeding site deep within the leaf. It has been proposed that whiteflies find sieve elements by sensing sucrose, pH, or other chemical gradients from the leaf surface to the vascular bundle. However, there is no unequivocal proof for this theory, nor have the putative molecular mechanism(s) been identified. Furthermore, our current understanding of chemosensation in whiteflies is limited. With the exception of the GRs, the main multigene families have been elucidated, but neither their expression site(s) nor putative ligands have been identified. In addition, the mechanisms used by whiteflies to sense changes in diet content and regulate their digestive processes and energy homeostasis are unknown. There is a need for further explorations of the genomic diversity across the different clades of the whitefly superfamily. Target genera could include *Dialeurodes* (including the *citri* complex of species) and *Aleurotrachelus* (Aleurodicinae), as well as potentially *Paraleyrodes* and *Aleurodicus* (Aleyrodinae). These groups diverged long ago from both *Bemisia* and *Trialeurodes*. Therefore, identifying orthologous genes and convergence and/or parallel evolutionary events will deepen our understanding of their biology and may shed light on the success of some whitefly species as pests.

While the strategies that whiteflies use to manipulate host plant immunity are becoming more clear, we also need a deeper understanding of the complement of effectors and their targets that enable whiteflies to adapt to different hosts. With the advent of single-cell technologies for proteomics, metabolomics, and transcriptomics, we should be able to gain insights into the responses of plant cells along the whitefly's stylet paths to the phloem in resistant and susceptible plants. In addition, the defense traits that underly whitefly resistance, as well as basal immunity, need to be identified.

Lastly, we urgently need efficient gene-editing systems for whiteflies. This technology is critical both for creating null mutations to interrogate all aspects of whitefly biology and for designing CRISPR/Cas9-based gene-drive technologies for controlling species that are important agricultural pests.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This work was supported by the Bill and Melinda Gates Foundation through the University of Greenwich grant OPP1058938 to S.M. and L.W., Israel Science Foundation grant 1643/22 to S.M., United States–Israel Binational Agricultural Research and Development grant IS-5085-18 coordinated by all three authors, US Department of the Interior Defense Advanced Research Projects Agency grant 956006142 to L.W. and P.A., and a UC Riverside Research and Economic Development Proof-of-Concept grant to L.W. and P.A. We thank Osnat Malka for her critical reading of this review. We apologize to colleagues whose articles were not cited due to space limitations.

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