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Insect Lipid Metabolism in the Presence of Symbiotic and Pathogenic Viruses and Bacteria

Bertanne Visser and Mathilde Scheifler

Abstract

Insects, like most animals, have intimate interactions with microorganisms that can influence the insect host's lipid metabolism. In this chapter, we describe what is known so far about the role prokaryotic microorganisms play in insect lipid metabolism. We start exploring microbe-insect lipid interactions focusing on endosymbionts, and more specifically the gut microbiota that has been predominantly studied in *Drosophila melanogaster*. We then move on to an overview of the work done on the common and well-studied endosymbiont *Wolbachia pipientis*, also in interaction with other microbes. Taking a slightly different angle, we then look at the effect of human pathogens, including dengue and other viruses, on the lipids of mosquito vectors. We extend the work on human pathogens and include interactions with the endosymbiont *Wolbachia* that was identified as a natural tool to reduce the spread of mosquito-borne diseases. Research on lipid metabolism of plant disease vectors is up and coming and we end this chapter by highlighting current knowledge in that field.

Keywords

Aedes aegypti · Cholesterol · *Culex pipiens* · Diapause · Fat content · Fatty acids · Lipogenesis · Phospholipids · Phytophagous insects · *Serratia* · *Spiroplasma* · Triacylglycerols

1 Introduction

All insects harbor a diverse and extensive microbial community, referred to as the microbiota (i.e., the assemblage of microorganisms—bacteria, fungi, viruses, archaea, and protists—associated with a defined host or environment; Berg et al. 2020). The diversification and evolution of insects are closely tied to their symbiotic interactions with microorganisms that may be mutualistic, commensal, or parasitic (Cornwallis et al. 2023; Janson et al. 2008). Bacterial symbionts represent the largest part of the microbiota that can be located either on the surface of the host's body, i.e., ectosymbionts, or reside inside the host's body, i.e., endosymbionts. In insects, endosymbionts are primarily present in

B. Visser
Evolution and Ecophysiology Group, Department of Functional and Evolutionary Entomology, University of Liège – Gembloux Agro-Bio Tech, Gembloux, Belgium
e-mail: bertanne.visser@uliege.be

M. Scheifler (✉)
Institut de Biologie de l'École Normale Supérieure (IBENS), École Normale Supérieure, CNRS, INSERM, Université PSL, Paris, France

Evolution and Ecophysiology Group, Department of Functional and Evolutionary Entomology, University of Liège – Gembloux Agro-Bio Tech, Gembloux, Belgium
e-mail: mathilde.scheifler@gmail.com

the gut or in specialized cells called bacteriocytes (Baumann et al. 2006). Insects can also function as vectors for disease-causing microbes, such as dengue virus (DENV) transmitted by mosquitoes causing dengue fever in humans or plant viruses transmitted by phloem-sucking insects that can have a large effect on crops (e.g., beet, turnip, etc.). Both symbiotic and pathogenic microorganisms can have substantial effects on many different aspects of the insect host's biology.

Symbiotic bacteria are known for a plethora of effects on insect hosts. The insect microbiota, for example, can affect *i)* the host's immune system and protection against various predators, parasites, disease vectors, or pathogens; *ii)* communication and behavior among individuals of the same or of different species; *iii)* host mating preferences and reproductive systems; *iv)* host life histories and fitness-related traits (e.g., development, lifespan, fecundity); and *v)* host resilience to environmental disturbances (e.g., pesticides) (Douglas 2015; Engel and Moran 2013; Engl and Kaltenpoth 2018; Zhang et al. 2022a, b). Notwithstanding these important functions, the provisioning of essential nutrients for the insect host seems to be a primary task of gut microorganisms. Many microorganisms provide nutrients that the insect cannot synthesize, such as amino acids, B vitamins, or sterols (Douglas 2015). The bacterial endosymbiont *Buchnera aphidicola*, for example, is of primary importance for aphid development and adult life by providing essential amino acids, and in return aphids provide a stable and nutrient-rich environment (Douglas et al. 2001). Another well-known insect endosymbiont, *Wolbachia pipientis*, has been shown to supply B vitamins to its host, the bedbug *Cimex lectularius* (Hosokawa et al. 2010; Newton and Rice 2020). Nutrient provisioning by bacteria can compensate for nutrient-poor diets, aids the digestion of recalcitrant food components (e.g., degradation of cellulose in plant cell walls), and supply essential amino acids, metabolic compounds, or nutrients (Engel et al. 2012; Hu et al. 2018; Jing et al. 2020; Russell et al. 2014; Sannino et al. 2018; Tokuda et al. 2018).

Regarding nutritional interactions, symbiotic bacteria were already found to have a major impact on lipid metabolism in humans (Xu et al. 2022). For example, changes in gut bacterial communities are related to metabolic diseases, such as obesity, cardiovascular disease, and type 2 diabetes (Depommier et al. 2019; Liu et al. 2021a, b; Wang et al. 2022). Relatively little is known, however, about the role played by symbiotic microorganisms in insect lipid metabolism. Considering how microorganisms affect key metabolic interactions is important, because more than 10% of insect species rely on obligate bacterial symbionts for survival or reproduction, and many more microorganisms are facultatively associated with insects (Hilgenboecker et al. 2008; Sazama et al. 2017; Weinert et al. 2015; Wernegreen 2002). Recent work on human pathogens, mainly DENV, has, however, revealed major lipid metabolic adjustments in the insect vector incited by the virus that are of importance for viral propagation (Chotiwan et al. 2018; Perera et al. 2012; Tongluan et al. 2017).

Lipids have also been implicated in immune responses of insects, which has already been reviewed extensively (Wrońska et al. 2023; Barletta et al. 2016), and falls beyond the scope of this chapter. We set out to unite research aimed at understanding the role of prokaryotic symbiotic or pathogenic microorganisms on insect lipid metabolism. We focus on prokaryotes, i.e., bacteria and viruses, to be able to set forth and identify commonalities and differences in the ways insect host/vector lipid metabolism is affected.

2 The Impact of Symbiotic Microorganisms on Host Insect Lipid Metabolism

2.1 Influence of the Gut Microbiota

There is growing evidence that the gut microbiota plays a key role in the regulation of insect fat storage. Most studies to date have focused on the impact of gut microbiota and microbe interactions on fat metabolism of the vinegar fly *Drosophila melanogaster* (Fig. 1), which is an

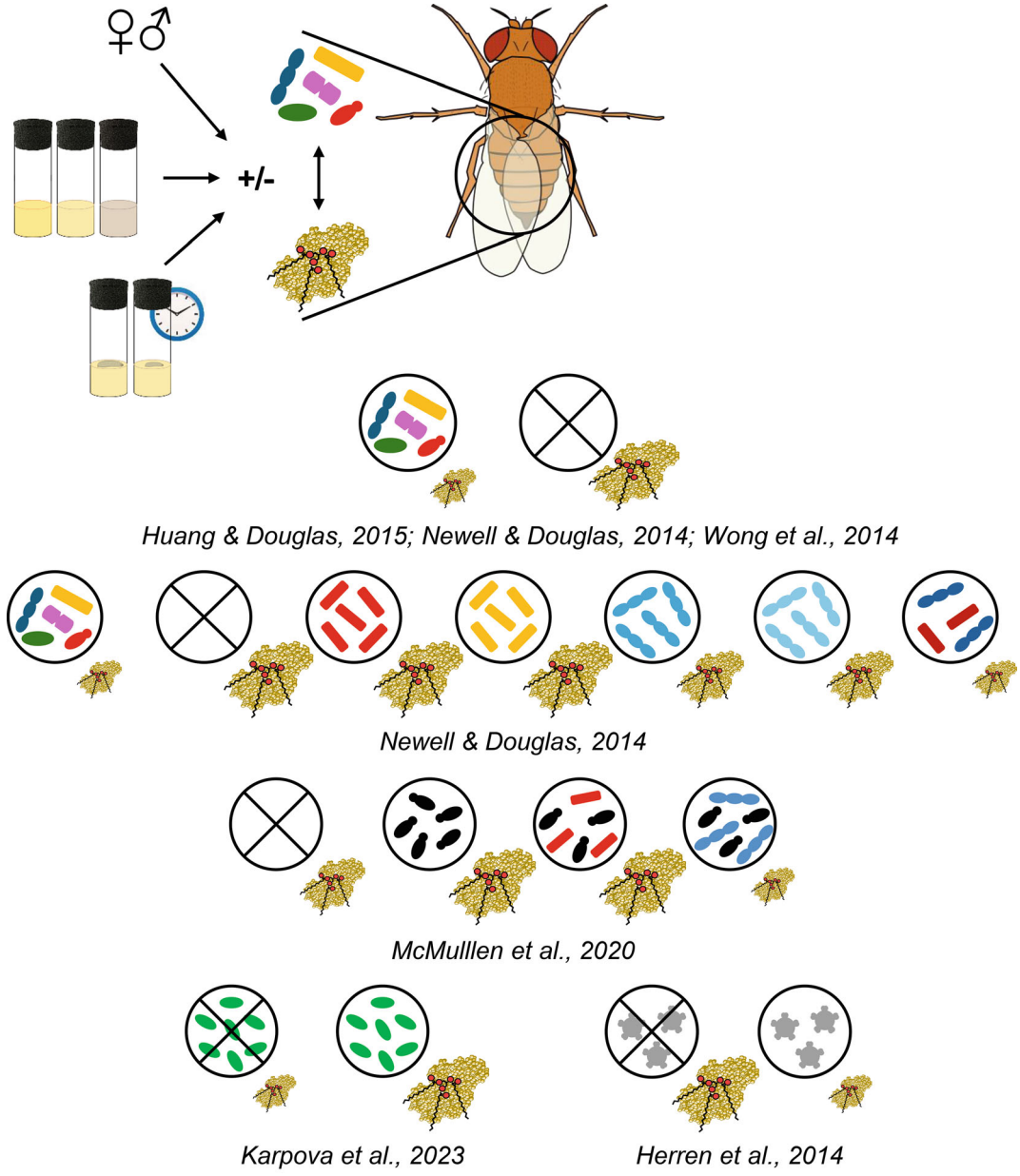

Fig. 1 Summary of microbe effects on *Drosophila melanogaster* triacylglycerol levels (i.e., storage lipids) with quantities represented by the size of the triacylglycerol graphic. A legend of microbial species is provided at the bottom of the graph. Triacylglycerol levels were compared between axenic (germ-free), mono-infected (bacteria-only or fungi-only), dual-infected (bacteria-bacteria and fungi-bacteria interactions), and conventional flies. All relevant references are provided in the figure

emerging model system in the field (Douglas 2019; Erkosar et al. 2013). Generally, *D. melanogaster* deprived of the entire microbiota (i.e., axenic/germ-free individuals) had a higher triacylglycerol content than individuals with microbiota (Huang and Douglas 2015; Newell and Douglas 2014; Wong et al. 2014; but see Ridley et al. 2012 and Henry et al. 2020 who found no difference in fat content between axenic and control *D. melanogaster flies*). The lack of bacteria that usually utilize host gut nutrients could explain the higher triacylglycerol content in axenic *D. melanogaster* flies. Overall, the multitude of studies comparing axenic and microbiota-containing *D. melanogaster* show a range of different results on triacylglycerol content, which can be explained by variation in host-related factors, such as host sex and feeding rate, as well as composition of the diet (e.g., sugar: yeast ratio, nutrient-poor or rich diet) and how each factor interacts with the microbiota and other factors (Huang and Douglas 2015; McMullen et al. 2020; Wong et al. 2014).

Interspecific bacterial interactions can lead to substantial differences in triacylglycerol content of *D. melanogaster,* where both laboratory and wild populations have relatively low-diversity gut microbiota. The *D. melanogaster* gut microbiota is commonly dominated by bacteria in the family *Acetobacteraceae* (mainly represented by the genus *Acetobacter*) and the order *Lactobacillales* (mainly represented by the genus *Lactobacillus*) (Adair et al. 2018; Chandler et al. 2011, 2012; Wong et al. 2011). Both mutualistic and antagonistic associations between *Acetobacter* and *Lactobacillus* have been found in *D. melanogaster*, depending on the bacterial species involved (Consuegra et al. 2020; McMullen et al. 2020; Sommer and Newell 2019). The impact of bacterial taxa (i.e., a total of five *Acetobacter* and *Lactobacillus* species) on *D. melanogaster* triacylglycerol content was assessed by comparing single-, dual-, or multi-species infections (compared to both axenic and conventional flies) (Newell and Douglas 2014). Combinations of bacterial taxa and effects on triacylglycerol content showed that *i)* dual-microbe infected *D. melanogaster* individuals generally had a lower triacylglycerol content than axenic and single-microbe infected individuals; *ii)* bacterial effects on *D. melanogaster* triacylglycerol levels are microbe-specific and dependent on interactions, e.g., mono-infection by *Lactobacillus brevis* and *Lactobacillus plantarum* did not lead to different triacylglycerol levels, only in interaction with *Acetobacter* were levels significantly lower; and *iii)* bacterial interactions are essential to restore the natural insect phenotype (i.e., similar to untreated flies). Newell and Douglas (2014) also highlighted that *Acetobacter tropicalis* abundance is promoted by the colonization of *L. brevis* in *D. melanogaster*. High *A. tropicalis* cell density, in turn, decreased fly triacylglycerol content in a dose-dependent manner (Newell and Douglas 2014). *Drosophila melanogaster* triacylglycerol content is thus mediated by the composition of the gut microbiota, bacterial abundance, and bacterial interactions.

The capacity of some bacteria, such as *Acetobacter* or *Lactobacillus*, to reduce *D. melanogaster* fat content (confirmed by Bozkurt et al. 2023) has been attributed to several, not mutually exclusive, processes. First, the bacteria can reduce host triacylglycerol levels via the consumption of dietary glucose, e.g., *Lactobacillus* produces lactate via the consumption of glucose, the latter being a substrate for acetyl-CoA synthesis that, in turn, is the precursor for fatty acid and subsequent fat synthesis in insects (Huang and Douglas 2015; Sommer and Newell 2019). Second, microorganisms can modulate host nutritional signaling pathways. For example, the increased production of acetic acid by *Acetobacter pomorum,* in response to the production of lactate by *Lactobacillus*, was shown to increase *D. melanogaster*'s insulin levels resulting in reduced adult fat content (Shin et al. 2011). Third, *Lactobacillus* can modulate the TOR (Target of Rapamycin) signaling pathway that also affects insulin signaling (Storelli et al. 2011). Fourth, metabolic models predicted a high release rate of succinate from *Drosophila* gut bacteria (Ankrah et al. 2021), impacting the citric acid cycle by reducing citrate levels available for fatty acid synthesis (Zhang et al. 2022a, b).

Bacteria can also interact with other microorganisms, such as fungi, affecting triacylglycerol levels differently depending on the interactions considered (Bozkurt et al. 2023; McMullen et al. 2020). For example, Bozkurt et al. 2023 showed a positive correlation between the abundances of *Acetobacter persici*, *A. pomorum* and Basidiomycota in *D. melanogaster*, as well as a negative correlation between these microbial taxa and triacylglycerol levels. In contrast, the fungus *Hanseniaspora uvarum* (order Saccharomycetales), also part of the *D. melanogaster* gut microbiota (Chandler et al. 2012), showed antagonistic interactions with *L. brevis* and *Acetobacter fabarum*. When *H. uvarum* is present, there is a negative effect on the abundance of *L. brevis*. The abundance of both *H. uvarum* and *A. fabarum* decreases when present together (McMullen et al. 2020). For the *H. uvarum*-*A. fabarum* interaction, a negative correlation was also observed between *D. melanogaster* triacylglycerol content and acetic acid that varied significantly with the presence of both *A. fabarum* and *H. uvarum*, consistent with previous studies (Newell and Douglas 2014; Sommer and Newell 2019). *Drosophila melanogaster* associated with both *A. fabarum* and *H. uvarum* had high acetic acid levels, but interestingly, triacylglycerol levels were also significantly elevated in flies only infected by the yeast *H. uvarum* (compared to axenic flies). *Hanseniaspora uvarum* was hypothesized to be a producer of acetic acid, like some other fungi (Bueno et al. 2020; Jolly et al. 2014). Interactions between *A. fabarum* and *H. uvarum* could modulate the concentration of acetic acid, reducing triacylglycerol synthesis (McMullen et al. 2020). Taken together, these results demonstrate the key role of the gut microbiota and microbial fermentation products, such as acetic acid, on the nutritional status of *D. melanogaster*, particularly with respect to fat accumulation.

In species other than *Drosophila,* only little progress has been made so far, and contrasting results have been reported regarding insect fat metabolism and fat content. In the aphid *Acyrthosiphon pisum*, axenic individuals showed increased triacylglycerol levels, in line with findings in *D. melanogaster* (Rahbé et al. 1994). In contrast, lower fat content was reported for adults of three fruit fly species, *Ceratitis capitata*, *Bactrocera tryoni*, and *Anastrepha fraterculus,* following antibiotic treatment (Ben-Yosef et al. 2008; Goane et al. 2022; Nguyen et al. 2021). Similar to findings in *D. melanogaster*, the fat content of the other fruit flies was affected by interactions between microbiota, diet, and sex (Ben-Yosef et al. 2008; Nguyen et al. 2021).

In the fruit fly *Bactrocera dorsalis*, a genomic study comparing gene expression of antibiotic-treated and control individuals revealed upregulation of *i)* fatty acid synthesis genes (e.g., fatty acid synthase (*fas*), acetyl-CoA carboxylase), *ii)* genes encoding triacylglycerol catabolism (e.g., lipases, fatty acid hydroxylase), and *iii)* downregulation of genes involved in fatty acid beta-oxidation (e.g., enoyl-CoA hydratase), suggesting a general increase of free fatty acids in the axenic insect (Xie et al. 2023). Downregulation of genes involved in lipid storage (i.e., vitellogenin) and transport (i.e., lipophorins), as well as a decrease in lipid content of the host's fat body have also been reported in *Aedes aegypti* axenic mosquitoes (Romoli et al. 2021). It has remained unclear how and why the expression of fatty acid and triacylglycerol metabolic genes changes depending on gut microbiota presence. One proposed hypothesis is that lipolysis facilitated by endosymbiotic bacteria increases the availability of different lipid types for the insect host. When no bacteria are present, the host insect is forced to start synthesizing different lipid types, while reducing fat storage (due to lower quantities of available precursors; Goane et al. 2022).

Gnotobiotic insects (i.e., insects associated with specific bacterial strains) have also been used in systems other than *Drosophila* to decipher the role of bacterial strains on host fat metabolism and fat content. In the red palm weevil *Rhynchophorus ferrugineus*, for example, a significant reduction in triacylglycerol content was reported in germ-free larvae compared to untreated larvae (Habineza et al. 2019). Introduction of the bacterium *Enterobacter cloacae* into germ-free *R. ferrugineus* larvae partially restored triacylglycerol levels, but no effect was found for

Lactococcus lactis (Habineza et al. 2019). Another study reported that gnotobiotic *Ae. aegypti* mosquitoes associated with *Flavobacterium* or *Paenibacillus* showed higher triacylglycerol levels compared to control mosquitoes, while Enterobacteriaceae and *Lysobacter* had no impact (Giraud et al. 2022). *Enterobacter cloacae* is known to synthetize various carbohydrate-modifying and glycolytic enzymes (e.g., cellulases, trehalases, glucosidases; Habineza et al. 2019), while Flavobacteria are chitinase producers (McBride et al. 2009), suggesting that bacteria other than *Acetobacter* and *Lactobacillus* can play a role in nutrient acquisition of other insect host species.

2.2 Box 1: The Influence of Microbes on Insect Fat Metabolism Associated with Diapause

Many insects have adapted to seasonal changes and low food availability by entering diapause. Diapause is a genetically and hormonally determined program that depends on various environmental signals (e.g., photoperiod, temperature) allowing insects to anticipate pending unfavorable conditions (Denlinger 2002; Denlinger et al. 2012). Diapause may occur during any stage of the insect's life cycle (e.g., embryonic, larval, pupal, or adult), depending on the insect species, and is characterized by reduced metabolic and behavioral activity (Hahn and Denlinger 2011). By delaying development from several weeks up to years, insects can synchronize their life cycle to match with periods suitable for growth, development, and reproduction. In addition to metabolic depression during diapause, insects typically increase energy stores by accumulating fat prior to diapause (Enriquez and Visser 2023). Fat reserves constitute an important source of energy to meet metabolic demands during and post-diapause (Hahn and Denlinger 2007).

Only few studies have explored the role of bacterial symbionts on fat accumulation during diapause, despite the importance of facultative and obligatory diapause for many insects (Hahn and Denlinger 2011). An exception is the work by Didion et al. (2021) that confirmed the critical importance of microbiota for diapause preparation in the mosquito *Culex pipiens*. Diapausing mosquitoes with a low bacterial load had 50% fewer fat reserves, associated with a lower dry mass and lower survival rate. In the parasitic wasp *Nasonia vitripennis*, triacylglycerol levels of diapausing larvae (ranging from 1 to 6 months of diapause) were significantly correlated with changes in microbiota composition (Dittmer and Brucker 2021). This correlation was rather weak, however, when compared to the effects of temperature and quantities of other nutrient types, such as glycerol or glucose (Dittmer and Brucker 2021).

Under laboratory conditions, Liu et al. (2016) investigated the link between gut bacterial symbionts and the metabolic shift from protein synthesis to triacylglycerol accumulation in a vegetable pest beetle, *Colaphellus bowringi,* that occurs when females enter diapause. Gut microbiota composition was slightly different between diapausing and non-diapausing individuals: positive correlations were found between diapause preparation and abundances of *Proteobacteria* (e.g., *Serratia* sp., *Sphingomonas* sp.) and *Firmicutes* (e.g., *Lactococcus* sp.), while a negative correlation was found with the abundance of *Bacteroidetes* (e.g., *Flavobacterium* sp.; but see Didion et al. (2021) that found no difference between the microbiota of diapausing and non-diapausing *C. pipiens* mosquitoes). Based on similar findings on the regulation of obesity by microbiota in mammals (Ley et al. 2005), higher abundances of *Proteobacteria* and *Firmicutes* may affect insect fat accumulation. In a more recent study, the endosymbiont *Wolbachia* appeared to reduce the lipid content (estimated by cholesterol amounts) of the parasitoid wasp *Trichogramma brassicae*, leading to a lower percentage of diapausing individuals (Rahimi-Kaldeh et al. 2019).

The above studies highlight an important functional role of the microbiota in insect diapause, although evidence of host-microbiota interactions during insect diapause remains scarce. As diapause is controlled by the insect's endocrine

system, the microbiota is expected to interact closely with the host's hormonal signaling pathways. More work is now needed to increase our understanding of how microbe-insect interactions affect diapause, and more generally how microbes affect host fat metabolism under low-temperature stress (Lv et al. 2023; Raza et al. 2020).

2.3 The Particular Case of the Endosymbiont *Wolbachia*

Wolbachia pipientis is one of the most widespread heritable bacterial endosymbionts harbored by insects, filarial nematodes, crustaceans, and mites (Serbus et al. 2008), infecting at least 65% of all known insect species (Hilgenboecker et al. 2008; Zug and Hammerstein 2012). *Wolbachia* is present in host germ line and somatic tissues, such as the fat body, salivary glands, or hemolymph (Dobson et al. 1999; Pietri et al. 2016), and can affect a wide variety of the insect host's biological functions. In mutualistic interactions, *Wolbachia* can confer fitness advantages, such as protection against viruses, resistance to heat stress or increasing learning ability, immunity, and life history traits (Arai et al. 2019; Cao et al. 2019; Farahani et al. 2017; Faria et al. 2018; Gruntenko et al. 2017; Maistrenko et al. 2016; Mazzucco et al. 2020). *Wolbachia* can also be parasitic and is perhaps best known for manipulating host reproduction in favor of its vertical transmission and spread within insect populations. *Wolbachia* can reduce population sizes, distort population sex ratios through male-killing or feminization of genetic males, induce parthenogenesis or cause cytoplasmic incompatibility (i.e., mating between individuals differing in *Wolbachia* infection status result in embryonic mortality; Charlat et al. 2001) (Dittmer and Bouchon 2018; Hurst et al. 1999; Poinsot et al. 2003; Stouthamer et al. 1999).

Host insect nutrient metabolism appears to be strongly influenced by *Wolbachia*. In *D. melanogaster*, *Wolbachia* affects fatty acid profiles, particularly the odd-chain fatty acid fraction (Molloy et al. 2016; Scheitz et al. 2013). Insects cannot synthesize odd-chain fatty acids. In *D. melanogaster* females, odd-chain fatty acids are likely supplied by *Wolbachia*, where odd-chain fatty acid levels are positively correlated to *Wolbachia* abundance ((Molloy et al. 2016; Scheitz et al. 2013). Odd-chain fatty acids have been found in the insect cuticle and body extracts in a wide variety of insect orders: Diptera (Kaczmarek et al. 2020; Sato et al. 2020), Hymenoptera (Pickett et al. 2000; Stanley-Samuelson et al. 1990), Hemiptera (Bashan et al. 2002; Cakmak et al. 2007a), Coleoptera (Howard and Stanley-Samuelson 1990; Nikolova et al. 2000), Neuroptera (Cakmak et al. 2007b), and Lepidoptera (Akinnawo and Ketiku 2000; Gołębiowski et al. 2010). The widespread occurrence among insects demonstrates that odd-chain fatty acids are fairly common components of insect lipids, although the proportion of odd-chain fatty acids is low compared to even-chain fatty acids. Odd-chain fatty acids can have a role in membrane stability and structure, as they have been found in the phospholipid fraction (Howard and Stanley-Samuelson 1990; Sato et al. 2020). Odd-chain fatty acids have also been found in the triacylglycerol fraction, and used for fat storage (Cakmak et al. 2007a, b). Odd-chain fatty acids can be acquired either by ingestion of symbiotic microorganisms that synthesize them (e.g., bacteria, yeast; Park et al. 2020; Řezanka and Sigler 2009) or synthesized de novo. In *D. melanogaster*, Sato et al. (2020) observed no significant difference in odd-chain fatty acid content between conventional and germ-free flies, suggesting that the microbiota was not involved. Instead, the incorporation of isotopic labels into the odd-chain fatty acids of *D. melanogaster* suggested de novo synthesis (Sato et al. 2020).

An increase in triacylglycerols was observed in *D. melanogaster* flies infected either with the *w*MelPlus, *w*Mel, or *w*MelCS45 *Wolbachia* strain compared to uninfected flies (Karpova et al. 2023). Contrasting results on the effect of *Wolbachia* on host fat metabolism have, however, been reported within and between mosquito species. *Wolbachia*

infection led to a decrease in triacylglycerol levels in *Ae. aegypti* (*w*Mel strain) and *Aedes fluviatilis* (*w*Aflu) (Conceição et al. 2021; Koh et al. 2020). Infection of *Ae. aegypti* with *w*Aflu further led to decreased lipid droplet size in the cytoplasm of mosquito cells (Conceição et al. 2021). In *Aedes albopictus*, *w*Mel *Wolbachia* infection decreased diacylglycerol levels by 32% compared to uninfected mosquitoes, while a 17% increase in triacylglycerols was observed in *w*MelPop-infected mosquitoes (Molloy et al. 2016). Overall, *Wolbachia* effects on various lipid types depend on host and *Wolbachia*-related factors (e.g., host species or genotype, *Wolbachia* strain; Molloy et al. 2016), as was already shown for other metabolic pathways (e.g., dopamine metabolism; Gruntenko et al. 2017).

In *Drosophila* and several mosquito species, changes in lipid types other than fatty acids and triacylglycerols were observed in the presence of *Wolbachia* (Conceição et al. 2021; Koh et al. 2020; Molloy et al. 2016). In *Ae. albopictus*, *w*Mel and *w*MelPop *Wolbachia* infection resulted in *i)* a decrease in various sphingolipids (mostly ceramides), as well as phosphatidylcholines, phosphatidylethanolamines, and diacylglycerols, and *ii)* an increase in phosphatidylglycerols and phosphatidylinositols in the host (Molloy et al. 2016). *Wolbachia* infection was also shown to differently affect *Ae. albopictus* lipids depending on the *Wolbachia* strain (i.e., either *w*Mel or *w*MelPop). Ceramide levels, for example, decreased 62% in *Ae. albopictus* infected with the *w*Mel *Wolbachia* strain compared to uninfected mosquitoes, while a decrease of only 20% was observed in mosquitoes infected with the *w*MelPop strain (Molloy et al. 2016). A mean decrease in sphingomyelins of 35% was reported in *w*Mel-infected *Ae. albopictus*, while sphingomyelins increased by 28% in *w*MelPop-infected *Ae. albopictus*. *Aedes aegypti* infected with the same *w*Mel *Wolbachia* strain also revealed a reduction of phosphatidylethanolamines and more complex forms of ceramides (e.g., glucosylceramides) (Koh et al. 2020). As sphingolipids and phospholipids play a major structural role in cell membranes (e.g., complex assembly in lipid rafts), depletion of these lipids was hypothesized to affect host membrane fluidity, curvature, and structure. Changes in the host membrane can facilitate *Wolbachia* colonization within the host (Molloy et al. 2016).

Variation in lipid levels may be related to the dependency of *Wolbachia* on the host insect for lipids. A genome sequencing study indeed revealed that a *Wolbachia* strain (*w*Mel) associated with *D. melanogaster* lost many key metabolic pathways, including pathways for fatty acid and cholesterol metabolism (Wu et al. 2004). Cholesterol is the dominant sterol in most insects, and a vital component for cell membrane stability, hormone regulation, and insect development (Behmer and Nes 2003; Jing and Behmer 2020). The *w*Mel strain thus depends completely on the host to supply fatty acids and cholesterol for its survival and proliferation (Caragata et al. 2017; Zhang et al. 2021). Like some other intracellular bacteria, *Wolbachia* resides in a host-derived vacuole (Cho et al. 2011) within tissues of insects (Dobson et al. 1999; Hughes et al. 2011; Pietri et al. 2016). *Wolbachia* is restricted to the host's Golgi-related vesicles near the endoplasmic reticulum, a site of active nutrient synthesis (Cho et al. 2011). Close positioning next to a lipid-enriched organelle allows *Wolbachia* to acquire nutrients, such as amino acids or lipids, by subverting, modifying (e.g., lipid composition), and redistributing the endoplasmic reticulum of the host to colonize the host cell at a high density (Fattouh et al. 2019).

Only few studies have so far examined the hypothesis that an essential requirement for lipids leads *Wolbachia* to manipulate host lipid metabolism. In adult *Ae. aegypti* infected by the *w*Mel and *w*MelPop *Wolbachia* strain, a decrease of 25.6% and 27.7% in total cholesterol levels was observed, respectively. A reduction in total cholesterol level suggests that *Wolbachia* may use host cellular lipids (Caragata et al. 2014). *Wolbachia* seems to compete for host cholesterol, a pattern already reported for other intracellular bacteria (e.g., *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, *Brucella abortus*; Lin and Rikihisa 2003; Watarai et al. 2002). With *Wolbachia* being located in Golgi-related vesicles, where high membrane biogenesis and cholesterol sequestration typically occur, the

bacterium has direct access to nutrients metabolized by the insect host (Cho et al. 2011; Howe and Heinzen 2006).

Recent studies highlighted that *Wolbachia* can affect gene expression of host metabolic pathways, including fat metabolism. *Wolbachia* first seems to act on the host's insulin/insulin-like-growth factor pathway (Currin-Ross et al. 2021; Ikeya et al. 2009). Whether *Wolbachia* actively regulates the insulin signaling pathway, however, remains a matter of debate, as both positive and negative regulation have been reported (Currin-Ross et al. 2021; Ikeya et al. 2009). Moreover, genes underlying host fatty acid synthesis (e.g., *fas*) were further found to be upregulated in *Wolbachia*-infected *D. melanogaster* larval stages (*w*Mel *Wolbachia* strain; Zheng et al. 2011), as well as in adult *D. melanogaster* (*w*Mel; Dou et al. 2021) and mosquitoes (*w*Mel and *w*MelPop; Rancès et al. 2012; Wimalasiri-Yapa et al. 2023), suggesting a role for *Wolbachia* in modulating the expression of host genes involved in fat metabolism.

2.4 Endosymbionts Other Than *Wolbachia* Can Also Alter Host Fat Metabolism

Some endosymbionts appear to compete with the host insect for lipids. In *Spiroplasma poulsonii*-infected *D. melanogaster* flies, for example, a significant decrease in circulating lipids, specifically diacylglycerols and sterols, was reported in host hemolymph (compared to *S. poulsonii*-free flies) (Herren et al. 2014). The bacterium *S. poulsonii* subverts and utilizes diglycerides contained in host hemolymph lipoprotein particles (i.e., an important hemolymph lipid carrier; Sieber and Thummel 2012) prior to the arrival of diacylglycerols at the fat body, resulting in lower triacylglycerol levels (as triacylglycerol synthesis and storage in the fat body largely depends on host hemolymph diacylglycerols) (Herren et al. 2014). Proliferation of *S. poulsonii* was also found to be limited by the availability of host hemolymph lipids (Herren et al. 2014). The use of host lipids by *S. poulsonii* was confirmed in a parasitic wasp, *Leptopilina boulardi,* parasitizing *D. melanogaster*. Parasitic wasps depend on a single host insect to complete development and obtain sufficient nutritional resources to fuel life (Scheifler et al. 2024). The presence of *S. poulsonii* led to direct competition with *L. boulardi* for *D. melanogaster* hemolymph lipids (Paredes et al. 2016). In the *D. melanogaster-S. poulsonii-L. boulardi* interaction, competition for lipids underlies the protective role of *S. poulsonii* for *D. melanogaster* larvae by reducing developmental success of the parasitic wasp (Paredes et al. 2016).

Other endosymbionts, such as *Serratia*, are beneficial to the insect by enhancing host fatty acid metabolism. *Serratia symbiotica*-infected aphids (*A. pisum*), for example, up-regulated the expression of genes involved in fatty acid and fat synthesis, such as *fas* and diacylglycerol-o-acyltransferase, resulting in higher triacylglycerol levels in the aphid fat body (Zhou et al. 2021). In the silkworm *Bombyx mori* fed with the symbiont *Bacillus subtilis*, changes in insect gut microbiota composition were correlated with shifts in glycerophospholipid and sphingolipid composition in the host's hemolymph (Li et al. 2022). The abundance of *Enterococcus* was, for example, negatively correlated with some lysophosphatidylcholines and lysophosphatidylethanolamines and positively correlated with some phosphocholines, suggesting a role of *Enterococcus* in the glycerophospholipid metabolism of the host *B. mori*.

3 Interference of Disease-Vector Lipid Metabolism by Human Pathogenic Microbes

3.1 Mosquito-Vector Lipid Metabolism Upon Infection with Human Pathogenic Viruses

Arthropod-borne viruses (arboviruses), such as DENV, West Nile virus, Chikungunya virus, and Zika virus (ZIKV), can cause major health problems for humans with hundreds of millions of infections leading to serious diseases and deaths (Bhatt et al. 2013; Fauci and Morens 2016; Guzman et al. 2010). Like many other

viruses, the DENV cycle is initiated with the attachment of the virus to a targeted host cell through the interaction between viral surface proteins and receptor molecules on the host cell surface (Cruz-Oliveira et al. 2015). The internalization of the virus within the infected cell involves receptor-mediated endocytosis (Mosso et al. 2008). Viral genomic RNA is then released into the cytoplasm of the host cell and translated into proteins required for RNA replication and viral particle assembly (Vial et al. 2021). Virus replication is dependent on three cellular pathways: autophagy (e.g., degradation of substrates, such as proteins or lipid droplets), actin polymerization and remodeling (e.g., vesicular trafficking), and fatty acid biosynthesis (Tongluan et al. 2017). Arboviruses are enveloped by lipids derived from the insect vector, leading the scientific community to hypothesize that viral entry, replication, assembly, and release occur in the host's cellular membranes. This led to a surge of studies on the ways in which viruses can manipulate insect vector lipid metabolism.

The fundamental role insect vector lipids play in the virus life cycle has mainly been investigated using flaviviruses, including DENV (see Ratnayake et al. 2023 and Vial et al. 2021 for recent reviews; but see Liu et al. 2021a, b for an investigation of the mechanisms by which FAS is affected following Classical Swine Fever virus infection). Analysis of the vector's fatty acid biosynthesis pathway revealed that the FAS enzyme is essential for DENV replication (Perera et al. 2012; Tongluan et al. 2017). DENV infection induces upregulation of the *fas* gene leading to de novo fatty acid synthesis, and relocalization of the enzyme FAS to sites of DENV replication (Tongluan et al. 2017). Alterations in de novo fatty acid synthesis and the role played by various *Ae. aegypti* fatty acid synthases (aaFAS) were recently investigated by Chotiwan et al. (2022). Seven distinct orthologues of human *fas* were identified, five of which produced transcripts. In females, only aaFAS1 showed high expression in both sugar-fed and blood-fed females, where diet does not seem to play a substantial role. To better understand the role played by the other *fas* orthologues, Chotiwan et al. (2022) knocked down aaFAS1 to determine if aaFAS2, aaFAS3, and aaFAS5 transcription could compensate for significantly reduced aaFAS1 transcription. While the other aaFASs showed a two-fold increase in transcription, aaFAS1 transcription remained higher following knockdown, suggesting that the other aaFASs may not be able to compensate for aaFAS1 function. Knockdown of aaFAS1 further led to a reduction of DENV replication in both mosquito Aag2 cell line and midguts, suggesting that aaFAS1 is required for DENV replication.

Interestingly, in mosquitoes, a significant increase in fat content was observed during the early stages of DENV infection, especially with higher abundances of glycerolipids, including mono-, di-, and triacylglycerols as well as other lipid types, such as glycerophospholipids, sphingolipids, or sterols (Chotiwan et al. 2018; Perera et al. 2012). Mosquito (i.e., *Aedes* sp.) fat content subsequently decreased after a few days. Increased de novo fatty acid synthesis, as well as increased transport of stored fat, suggests that these processes may be required for virus replication, dissemination, and survival during the initial stages of infection (Chotiwan et al. 2018; Perera et al. 2012).

Newly synthesized lipids are redistributed to sites of viral replication, mainly near the insect vector's endoplasmic reticulum membrane. Incorporation of different lipid types can then modify vector membrane structure, i.e., fluidity, permeability, and curvature, altering the functionality of the endoplasmic reticulum to the benefit of virus replication (Vial et al. 2021). DENV translation, replication, and assembly indeed require vector cell endoplasmic reticulum membranes that could affect the synthesis of phospholipids, critical cell membrane components. Vial et al. (2019) used high-resolution mass spectrometry to understand how phospholipid metabolism is affected in *Ae. aegypti* cells, midguts, and whole mosquitoes at various times post-infection. Phospholipidomics first revealed that aminophospholipids, including phosphatidylethanolamine (PE), phosphatidylcholine (PC), and phosphatidylserine (PS), increased at the beginning of the DENV viral cycle, but

decreased as time passed. Acylglycerol phosphate acyltransferase (AGPAT) is the rate-limiting enzyme involved in the synthesis of phospholipids (generating phosphatidic acid, a precursor for more complex phospholipids). In *Ae. aegypti,* five AGPAT isoforms were identified, with AGPAT1 being downregulated upon DENV infection (at different times depending on the level of organization, either cell, tissue, or whole organism). Vial et al. (2019) then set out to test whether AGPAT1 regulation is involved in the reconfiguration of the phospholipidome. RNA interference on mosquito cells, used to temporarily knock down *agpat1* and thus mimicking DENV infection, revealed an increase in aminophospholipids. Knockdown of *agpat1* indeed also increased DENV production. The instrumental role of *agpat1* for phospholipid remodeling was confirmed by supplementation of ethanolamine in cells with knocked down *agpat1* expression. Ethanolamine is used in the synthesis of PEs and the presence of ethanolamine in the mosquito cell medium partially restored the observed increase in aminophospholipids in DENV-infected cells. In mosquitoes, knockdown of *agpat1* led to an increase in DENV infection through the consumption or redirection of aminophospholipids.

In a follow-up study, Vial et al. (2020) set out to determine how DENV reconfigures aminophospholipids in mosquitoes, but also how aminophospholipid reconfiguration affects virus proliferation. In the first set of experiments, Vial et al. (2020) knocked down several genes involved in de novo phospholipid synthesis and monitored changes in the phospholipidome. In addition, DENV-infected mosquito Aag2 cells were supplemented with phospholipid precursors to partly restore de novo synthesis. Newly synthesized phospholipids were indeed found to be antiviral, but DENV can inhibit de novo synthesis and initiate phospholipid remodeling to modulate and create a more proviral environment. In a stable isotope tracing experiment using different labeled precursors, Vial et al. (2020) then showed that DENV induces remodeling early on during infection (0–24 h), after which de novo phospholipid synthesis takes place. To test the negative effect of de novo phospholipid synthesis in vivo, mosquitoes were fed an infected blood meal with increased levels of phospholipid precursors. When fed lower precursor levels, DENV was able to increase phospholipid reconfiguration for its own benefit, but reconfiguration was not sufficient at higher precursor concentrations. When DENV-induced remodeling is inhibited by de novo phospholipid synthesis, viral replication (rather than attachment, internalization, or translation) is reduced. Phospholipids were also found to be the main lipid type affected when *Ae. albopictus* cells were infected with ZIKV (Melo et al. 2016).

Cholesterol appears to be essential for the fusion of the lipid envelope of the viral particle with the vector membranes, allowing DENV release and replication (Blanc et al. 2011; Caragata et al. 2013, 2014; Carro and Damonte 2013). In *Ae. aegypti*, sterol carrier protein 2 (SCP-2), involved in cholesterol binding and transport, is essential for cellular cholesterol homeostasis and of importance for DENV production (Fu et al. 2015). Knockdown of SCP-2 indeed reduced DENV production in mosquito Aag2 cells. Further studies with mosquito Aag2 cells revealed that DENV reduced protein expression of low-density lipoprotein receptor-related protein 1 (LRP-1), increasing cholesterol levels and stimulating viral replication (Tree et al. 2019). In mosquitoes, however, low-density-lipoproteins contained in human blood inhibited DENV replication during an early stage of viral infection following a blood meal (also for ZIKV; Wagar et al. 2017). Vertebrate lipids thus seem to have contradictory effects on DENV. To test how DENV responds to low levels of vertebrate lipids, Marten et al. (2022) created cell lines mimicking mosquitoes "feeding" on blood (i.e., provided a normal, control, cell culture medium) or not (i.e., a lipid-depleted medium only). Lipid-depleted cells contained less cholesterol, but similar intracellular lipid levels compared to control cells, despite being smaller and showing reduced proliferation. Mosquito cells thus appear to overcome chronic lipid depletion by reducing lipolysis and increasing de novo lipid synthesis, including fatty acids synthesis. Similar amounts of DENV were found in both cell lines, meaning that mosquito cellular lipid metabolism

compensates for a lipid-depleted environment without affecting DENV infection. Cholesterol was also found to play a critical role in alphavirus (e.g., Semliki Forest virus and Sindbis virus) entry and exit in vector cells (Lu et al. 1999).

3.2 Interactions Between *Wolbachia*, Arboviruses, and Lipids

During the past decade, considerable progress has been made in developing novel methods to combat the spread of insect disease vectors, including mosquitoes, and consequently virus transmission. A promising strategy is the use of *Wolbachia* to control and limit arboviral transmission in animals, because *Wolbachia* infection can protect against viral infections (Pimentel et al. 2021). For example, *Wolbachia* can significantly reduce viral load, replication, and transmission of several natural pathogenic RNA viruses associated with the *Drosophila* genus (e.g., Nora virus or Drosophila C virus; Teixeira et al. 2008). A similar effect has also been observed for arthropod-borne viruses, such as West Nile virus or Chikungunya virus, with *Wolbachia* presence generally lowering host insect mortality rate (Glaser and Meola 2010; Hedges et al. 2008; Teixeira et al. 2008). A growing number of studies have, however, suggested that *Wolbachia* can differentially affect viral replication and transmission depending on the insect host species, host strain, and *Wolbachia* strain (Caragata et al. 2013; Hussain et al. 2013; Reyes et al. 2021). For example, replication of West Nile virus in *Ae. aegypti* mosquitoes is significantly reduced by infection with the *w*MelPop *Wolbachia* strain, but no effect was reported for the *w*Mel strain (Hussain et al. 2013).

Wolbachia blocks viral replication and transmission by priming the host's immune system (Angleró-Rodríguez et al. 2017; Bian et al. 2010; Pan et al. 2012, 2018) and/or competing with the virus for host cellular resources, such as amino acids or lipids (Caragata et al. 2013; Moreira et al. 2009). The hypothesis that modification of host metabolic pathways rather than host immune pathways forms the basis for *Wolbachia* pathogen-blocking abilities finds more empirical support. As both the virus and the bacterium are dependent on host lipids for survival and propagation, there can be extreme competition for host lipids, particularly cholesterol. Caragata et al. (2013) tested the influence of a standard, intermediate, or high-cholesterol diet on the ability of *Wolbachia*-infected *D. melanogaster* to resist Drosophila C virus. An increase in cholesterol availability via the enriched diet increased virus replication and reduced the protective effect of *Wolbachia* in a dose-dependent manner. The virus titer was indeed higher in cholesterol-enriched media, leading to earlier death of the flies. An increase in viral replication following cholesterol supplementation was also reported for *Ae. albopictus* and *Ae. aegypti*, suggesting that competition for cholesterol can also play a role in these model systems (Geoghegan et al. 2017; Schultz et al. 2017).

For *Ae. aegypti*, an increase in stored cholesterol (i.e., esterified cholesterol levels) with localized accumulation of lipid droplets in the fat body and a decrease of free cholesterol levels (i.e., potential regulators of lipid transport) were found in *Wolbachia*-infected mosquitoes, suggesting that intracellular cholesterol trafficking may be perturbed (Geoghegan et al. 2017). In *Ae. albopictus*, the abundance of other lipid types, such as sphingolipids, phosphatidylcholines, and diacylglycerols (used by bacteria to enter the cell and activate mechanisms required for bacterial dissemination; Lafont and van der Goot 2005), also decreased following *Wolbachia* infection in DENV-infected *Ae. albopictus* mosquitoes (Molloy et al. 2016). *Wolbachia* and arboviruses may thus compete for multiple lipid types, not only cholesterol. Gene expression studies support these findings, because several genes involved in fatty acid and lipid metabolism, including *fas,* acetyl-coA carboxylase, or sterol-coA desaturase, were downregulated in the presence of *Wolbachia* (Geoghegan et al. 2017; Teramoto et al. 2019). *Wolbachia*-induced metabolic changes, including increased cholesterol storage near viral replication sites, as well as disruption of vesicular trafficking,

may thus reduce energy availability needed for viral replication, thereby blocking viral proliferation and transmission (Geoghegan et al. 2017; Schultz et al. 2017, 2018).

The manner by which *Wolbachia* regulates lipid metabolism in the presence of viruses has remained largely unclear. Haqshenas et al. (2019) revealed, however, downregulation of insulin receptor abundance and phosphorylation levels in *Wolbachia*-infected lines, associated with a reduction of DENV and ZIKV proliferation. Inhibition of the insulin receptor revealed that ZIKV and DENV replication is reduced in a dose-dependent manner, suggesting a key role of insulin receptor kinase activity in virus replication. *Wolbachia* may thus reduce insulin receptor phosphorylation and kinase activity, decreasing virus replication (Haqshenas et al. 2019). Insulin was already linked to the activation of the insect host's immune system (Reyes et al. 2021), but further investigation into the underlying mechanisms is needed. Interestingly, here cholesterol could also play a role, as cholesterol is known to affect regulation of the insulin-receptor signaling pathway (Sánchez-Wandelmer et al. 2009).

Wolbachia could become a promising tool for regulating arthropod-borne virus transmission (Ant et al. 2023; Ogunlade et al. 2021). Two recent studies have, however, reported that DENV infection in mosquitoes led to a distinct lipid profile when compared to mosquitoes carrying *Wolbachia* (Koh et al. 2020; Manokaran et al. 2020). This could suggest that DENV and *Wolbachia* may use different lipid types and may not be in competition for lipids. Edenborough et al. (2021) suggested that the intra-thoracic DENV infections used in Koh et al. (2020) could inhibit the effects of *Wolbachia* and may not represent the virus-*Wolbachia* relationship in a natural infection (Fraser et al. 2017). A comprehensive view on the impact of *Wolbachia* and interactions with other microorganisms at the cellular and molecular level is now necessary to fully understand the mechanistic basis of *Wolbachia*-arbovirus interference of lipid metabolism.

4 Plant Pathogen Effects on Insect Vector Fat Metabolism

Plant pathogens represent a major threat to plant populations. In agricultural systems, plant pathogens can reduce yield and affect the quality of agricultural production. Plant pathogens indeed induce significant losses in crops worldwide, representing a major issue for global food security (Fones et al. 2020; Ristaino et al. 2021). Plant viruses can manifest in a variety of symptoms, such as yellowing, spots, necrosis, and distortions of plant structures (Jiang and Zhou 2023). Most plant viruses depend on insect vectors for their survival and transmission, typically phytophagous hemipterans (e.g., aphids, whiteflies, psyllids, leafhoppers, grasshoppers) that use their piercing, sucking mouthparts to feed on plant sap from which the virus is taken up (Hogenhout et al. 2008; Nault 1997). The insect vector then transmits the virus by subsequently feeding on sap from healthy plants.

Plant viruses are generally transmitted by insects via three modes: non-persistent, semi-persistent, and persistent (Nault 1997; Wu et al. 2022). Transmission modes differ in the time during which the insect vector can harbor the virus, ranging from minutes to hours (i.e., non-persistent), days (i.e., semi-persistent), or longer (i.e., persistent; some insects are infected during their entire life and the virus can even be transmitted to insect offspring) (Ng and Falk 2006). Non-persistent and semi-persistent viruses are mainly retained by the insect vector's stylet and foregut, respectively, while persistent viruses infect insect gut cells and are then released in the hemocoel to invade insect tissues and organs (e.g., salivary glands, reproductive system) (Hogenhout et al. 2008; Ng and Falk 2006). The persistent mode of transmission is further categorized as propagative or circulative, depending on whether the location of viral replication is in the insect body or not, respectively (Hogenhout et al. 2008).

Plant viruses have a range of effects on insect vectors by modifying, for example, insect-plant preference/choice, population growth, feeding behavior, or fitness-related traits that may in turn affect survival and transmission of the virus (Blanc and Michalakis 2016; Bosque-Pérez and Eigenbrode 2011; Colvin et al. 2006; Ingwell et al. 2012; Mauck et al. 2012; Stafford et al. 2011). Only little information is available so far on the effects of plant viruses on fat metabolism of insect vectors. Ghodoum Parizipour et al. (2021) investigated the effect of three luteoviruses (i.e., persistent circulative viruses), pea enation mosaic virus (PEMV), bean leafroll virus (BLRV), and barley yellow dwarf virus-PAV (BYDV-PAV) that cause considerable economic losses to cereal and legume fields, on the fatty acid profiles and fat content of the aphid vectors, *A. pisum*, *Aphis fabae*, and *Rhopalosiphum padi*, respectively. Fatty acid profiles differed between infected and uninfected insects in all virus-aphid interactions. In both *A. pisum*-PEMV and *A. fabae*-BRLV interactions, myristic acid (C14:0) quantities increased while an increase in palmitic acid (C16:0) was reported in *A. fabae*-BRLV and *R. padi*-BYDV-PAV associations. An increase of linoleic acid (C18:2), as well as a decrease of capric (C10:0) and oleic acid (C18:1), were also observed in the *A. pisum*-PEMV, *A. fabae*-BRLV, and *R. padi*-BYDV-PAV interactions, respectively, highlighting specific fatty acid changes depending on the virus-aphid interaction. Infection of *A. fabae* individuals by BRLV further led to a reduction of aphid fat content, while no changes in fat content were reported for the other two virus-aphid interactions (Ghodoum Parizipour et al. 2021). In another virus-aphid vector interaction involving the turnip yellows virus (TuYV) (i.e., a persistent circulative virus, one of the most important viruses infecting cultivated Brassicaceae, e.g., lettuce, broccoli, etc...) and *Myzus persicae*, virus infection also led to a reduction in fat content (Joffrey et al. 2018).

Direct and/or indirect effects of plant viruses have been proposed to explain changes in fatty acid profiles and fat content in *A. fabae* and *M. persicae* infected with BLRV and TuYV respectively. For example, direct immune responses involving lipids, including fatty acids, can protect the insect vector against virus infection (Wrońska et al. 2023). Viruses can also negatively affect plant physiology and quality, decreasing plant biomass and photosynthetic activity, in turn affecting the insect vector (Joffrey et al. 2018). Fat metabolism of the insect vector feeding from the plant sap could be negatively affected due to the lower quantity of nutrients synthetized by the plant (e.g., amino acids). Positive effects of plant virus infection on insect vector fat metabolism have also been reported. The white-backed planthopper *Sogatella furcifera*, vector of the southern rice black-streaked dwarf virus (i.e., a persistent, propagative virus) showed a significant increase in myristic (C14:0), oleic (C18:1), and palmitoleic acid (C16:1) levels in infected individuals (Zhang et al. 2018). Moreover, the small brown planthopper *Laodelphax striatellus,* infected by the maize Iranian mosaic virus (i.e., a persistent propagative virus), harbored more fat that uninfected individuals (Moeini and Tahmasebi 2019). Effects of the maize Iranian mosaic virus on *L. striatellus* fat content was further found to be stage- (i.e., nymph or adult) and sex-specific, where adults and females accumulated more fat. Lipids, including fatty acids, play a key role during viral replication (Konan and Sanchez-Felipe 2014; Lorizate and Krausslich 2011). For persistent propagative viruses, viral replication occurs in the insect tissues/organs; hence increasing and/or modifying insect fat content and fatty acid levels during infection would allow the virus to use insect lipids for replication and dissemination. Finally, an increase of fat storage generally improves insect fitness (Arrese and Soulages 2010; Scheifler et al. 2024, Box 1), allowing the insect to colonize new host plants and, thereby, improve virus transmission.

Plant pathogens other than viruses were also found to affect fat metabolism of insect vectors, including the bacterial pathogen associated with citrus greening disease, *Candidatus Liberibacter asiaticus* (CLAS), for which the Asian citrus phyllid *Diaphorina citri* is the main vector. A proteomic study on *D. citri* adults, infected by CLAS, reported an upregulation of proteins

involved in fatty acid beta-oxidation (e.g., enoyl-coA hydratase, acyl-CoA dehydrogenase; Ramsey et al. 2015), while another study found upregulation of *fas* and vitellogenin (i.e., proteins involved in lipid transport) upon infection (Kruse et al. 2018). No change in fatty acid composition was observed between uninfected and infected *D. citri* adults, yet more palmitoleic (C16:1), palmitic (C16:0), linoleic (C18:2), and stearic acid (C18:0) were found in infected nymphs compared to infected adults, suggesting that variation in fatty acid composition is stage-specific (Killiny and Jones 2018). There are thus contrasting results for fat metabolic responses of *D. citri*. Taken together, insect vector fat metabolic responses to plant pathogens are highly dependent on the insect vector-pathogen-host plant interaction considered.

Another topic that has received some attention is the impact of plant viruses and plant physiology and quality on higher trophic levels. Many parasitoids infect vectors of plant pathogens, and virus infection is expected to affect parasitoid performance. Joffrey et al. (2018) studied the effects of TuYV on a plant-aphid-parasitoid interaction, involving the aphid *M. persicae* and the parasitoid *Aphidius colemani*. Reduced photosynthetic activity and lower biomass in TuYV-infected plants led to a decrease in both body size and fat content of *M. persicae* adults. Smaller and leaner aphid adults used as hosts for the parasitoid *A. colemani* led to concomitant decreases in adult parasitoid body size, fat content, and fitness (i.e., lower egg numbers) (Joffrey et al. 2018). No differences were found in host and parasitoid body size and fat content in the aphid *A. fabae,* the parasitoid *Lysiphlebus fabarum* on beets infected with Beet yellows virus (Albittar et al. 2019). Fat storage is particularly important for parasitoids, because most species do not accumulate fat as adults (Visser et al. 2010; Visser et al. 2023; Scheifler et al. 2024). When the amount or quality of fat that can be carried over from the host is reduced due to plant pathogens, there might be negative consequences for parasitoids, a level higher up the trophic food chain. The complexity of these interactions should be studied more carefully to anticipate potential issues in agricultural systems both due to plant disease and complications in biocontrol.

5 Conclusion and Perspectives

Considering the gut microbiota, research on *D. melanogaster* has revealed that individual microbe effects on lipid metabolism appear to be strongly influenced by the metabolic activities of other co-occurring microbes. The complexity of these interactions and their impact on lipid metabolism in general must, therefore, be studied using community-based approaches (rather than mono or dual-infections; Gurung et al. 2019). Furthermore, microbiota composition differs between the sexes in several insect species, suggesting different types of interactions between male and female insect hosts and their respective microbiota (Chen et al. 2016; Fransen et al. 2017; Tang et al. 2012). Metabolic and physiological differences or requirements between the sexes could also explain why interactions between gut microbiota and host fat metabolism are sex-specific, e.g., females require more resources for egg production, mainly lipids. Future work should consider how diet composition and host-related traits, such as genotype and sex, can affect the resident microbiota (Newell and Douglas 2014; Ridley et al. 2012). Such analyses could then be extended to other insect species.

Microbes also seem to play a role in insect recognition and communication. Hertaeg et al. (2021) recently showed that endosymbiotic bacteria can alter the cuticular hydrocarbon (CHC, derived from long-chain fatty acids) composition in the aphid *A. fabae*. CHC profiles depend on the host insect's genetic background, as well as the endosymbiont strain present, which in turn impacts aphid interactions with other insects, such as ants (Hertaeg et al. 2021). We are only beginning to understand the role microbes play in lipid metabolism of insect hosts, but lipid-mediated traits, such as chemical communication, can further affect interspecific insect-insect interactions, also in species other than *A. fabae*.

Wolbachia can have widely different effects on the insect host, including lipid metabolism;

hence *Wolbachia*-insect interactions remain complex to interpret. Modifications of insect fat metabolism and other lipid types appear to depend on insect species, insect host-related traits, and *Wolbachia* strain (Koh et al. 2020; Molloy et al. 2016). Factors other than *Wolbachia* presence should be considered when studying the impact of *Wolbachia* on host fat metabolism, for example, *Wolbachia* density that can vary in response to biotic (Padde et al. 2023; Pascar et al. 2023; Serbus et al. 2008) and abiotic factors (e.g., temperature; Padde et al. 2023; Mouton 2004). We know very little about the mechanism by which *Wolbachia* can modulate insect host fat metabolism. If we want to uncover more about the intricate interplay between *Wolbachia* and insect metabolism, one could investigate lipid-related gene transcription in both the insect host and the *Wolbachia* strain under study. Such a gene-based approach allows for finding correlative data on regulatory and target genes used or exploited by both interacting partners. Once candidate gene regulators and targets have been identified, gene knockdown approaches, such as RNA interference or CRISPR-Cas9, can be used to find a functional link leading to lipid-related phenotypic effects.

Studying the nutritional interplay between symbionts and insect hosts, particularly lipids, is also highly relevant for preventing and managing major public health threats, including vector-borne viruses such as DENV and Chikungunya virus. *Wolbachia* is a promising tool for regulating insect disease vector transmission (Ant et al. 2023; Ogunlade et al. 2021) as *Wolbachia* competes with viruses for multiple host lipid types (Geoghegan et al. 2017; Molloy et al. 2016). A comprehensive overview of the role of fat in *Wolbachia* virus-blocking mechanisms is needed to promote efficient and sustainable virus control in mosquitoes.

Intricate biochemical work on the way in which pathogenic arboviruses manifest within insect mosquito vectors has led to major advancements in our understanding of lipid-virus-mosquito interactions (Vial et al. 2019, 2020, 2021). Viruses critically rely on an array of different lipid types, including fatty acids, phospholipids, and cholesterol, each fulfilling a discrete function for different viral stages. Research on plant pathogen effects on vector lipid metabolism has so far led to varying results, and if lipids are affected, only relatively simple estimates of bulk fat content have been estimated. Lipid effects on vectors could thus be due to indirect effects of infected plants or be a consequence of the viral infection itself. We propose that the research field concerned with plant pathogen-vector interactions draws parallels with the work on pathogenic arboviruses, as the mechanisms by which viruses manipulate and utilize host insect vector lipids may be similar. The use of isotope tracing, precursor supplementation, and genomic interference mechanisms may increase the resolution with which plant pathogen effects can be studied in insect vectors.

Research on the effects of microbes on insect lipid metabolism is up and coming, and we can expect microbes to play unexpected roles in host insect metabolism. The nutritional role lipids play for host insects, microbes or both often remains to be fully elucidated. The repeated evolution of endosymbioses has led to recurrent environmental compensation, where resource provisioning by the insect host has led to genome reduction and trait loss in microbes (Ellers et al. 2012). The loss of fatty acid synthesis pathways in some *Wolbachia* strains is an excellent example of an evolved evolutionary dependence on an insect host (Wu et al. 2004). We can hypothesize that intricate mechanisms to optimize the host environment have evolved in lipid-dependent endosymbionts, for example by stimulating the synthesis of fatty acids or other lipid types by the host. When considering interactions between coexisting microbes, dependence can also evolve when a microbial species provides a common resource, or public good, that is exploited by the community of microbes, also referred to as the Black Queen Hypothesis (Morris 2015). No examples have yet come to light regarding lipids as a public good of microbial origin, but nutrient metabolic interactions could be investigated using recently developed tools, such as NetMet, to predict the metabolic capacities of interacting microbes (Tal et al. 2020). Alternatively,

microbes can provide certain nutrients or precursors that are required by the host insect. A well-known example is vitamin B, where different variants are produced by a range of microbes associated with distinct insect species (Serrato-Salas and Gendrin 2023). Regarding various lipids, some microbes, including *Wolbachia*, can synthesize biotin, a co-factor required for acetyl coenzyme A, which is a central intermediary precursor for fatty acid synthesis. We have yet to explore how the synthesis of lipid precursors contributes to lipid dynamics between insect host and symbiont(s).

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