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Lipid Metabolism in Parasitoids and Parasitized Hosts

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Abstract

Parasitoids have an exceptional lifestyle where juvenile development is spent on or in a single host insect, but the adults are free-living. Unlike parasites, parasitoids kill the host. How parasitoids use such a limiting resource, particularly lipids, can affect chances to survive and reproduce. In part 1, we describe the parasitoid lifestyle, including typical developmental strategies. Lipid metabolism in parasitoids has been of interest to researchers since the 1960s and continues to fascinate ecologists, evolutionists, physiologists, and entomologists alike. One reason of this interest is that the majority of parasitoids do not accumulate triacylglycerols as adults. Early research revealed that some parasitoid larvae mimic the fatty acid composition of the host, which may result from a lack of de novo triacylglycerol synthesis. More recent work has focused on the evolution of lack of adult triacylglycerol accumulation and consequences for life history traits. In part 2 of this chapter, we discuss research efforts on lipid metabolism in parasitoids from the 1960s onwards. Parasitoids are also master manipulators of host physiology, including lipid metabolism, having evolved a range of mechanisms to affect the release, synthesis, transport, and take-up of lipids from the host. We lay out the effects of parasitism on host physiology in part 3 of this chapter.

Keywords

Bracovirus · Fat · Fitness · Host-parasitoid interaction · Parasitic wasp · Polydnavirus · Symbiosis · Teratocyte · Venom

1 Introduction

There are many intricacies when it comes to the fat metabolism of parasitoids. Parasitoids have a unique lifestyle, where development takes place inside or on a single host (usually another insect or an arthropod), but the adults are free-living (Godfray 1994) (Fig. 1). During development, the parasitoid consumes the host and its nutritional resources, sometimes only partly or in its entirety in successive steps (Cuny and Poelman 2022), ultimately leading to death of the host. Parasitoidism thus constitutes a parasitic relationship between a parasitoid and its host that differs from parasites in the extent to which the host is harmed, because parasitoids kill their host (Lafferty and Kuris 2002). The parasitoid lifestyle evolved repeatedly in insects, including independent occurrences in beetles, flies,

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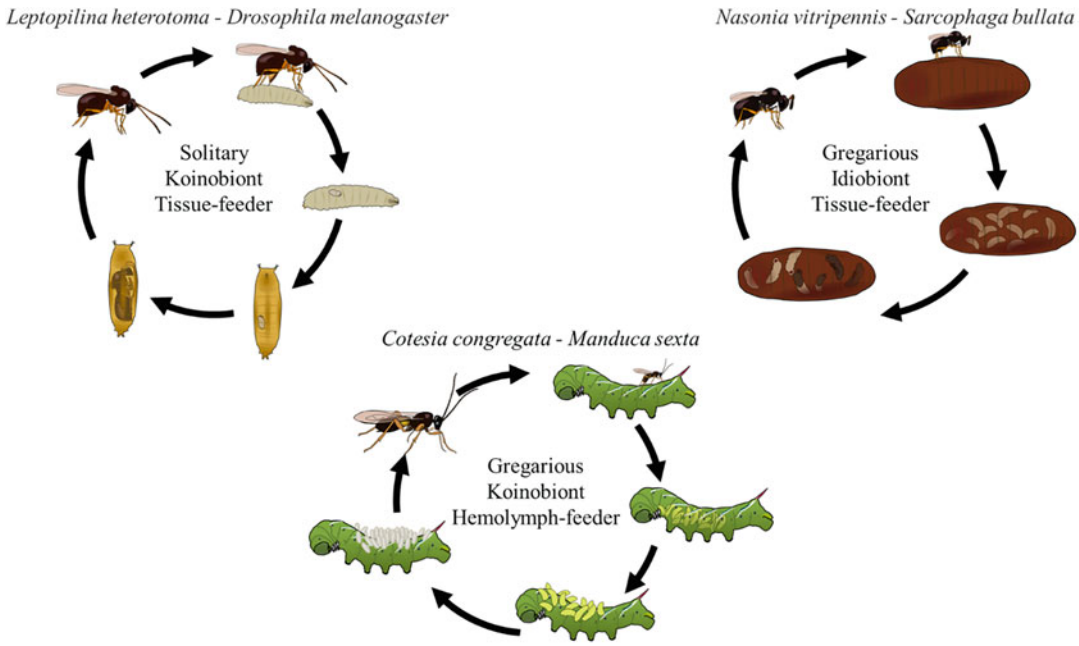

Fig. 1 The parasitoid life cycle showing the different effects on host development (idiobiont versus koinobiont), as well as parasitoid oviposition (solitary versus gregarious), and feeding strategies (hemolymph versus tissue-feeder). Represented species include the amber wasp *Leptopilina heterotoma* on the host *Drosophila melanogaster*, the parasitoid *Cotesia congregata* on the host *Manduca sexta,* and the parasitoid *Nasonia vitripennis* on the host *Sarcophaga bullata*

butterflies, and lacewings (Eggleton and Belshaw 1992, 1993), but Hymenoptera (bees, ants, wasps, and sawflies) is the most speciose order when it comes to parasitoids (and potentially species in general, see Forbes et al. 2018). The large breadth of parasitoid species worldwide, the unique lifestyle, and the plethora of strategies used by parasitoids to parasitize their hosts make them valuable and interesting biological model systems (Hoddle et al. 1998; Liu et al. 2015; Matthews et al. 2009; Quicray et al. 2023; Werren and Loehlin 2009; Whitfield et al. 2017). This is true not only from a basic, fundamental scientific perspective, but also for the applied sciences, because parasitoids play a key role in regulating both natural and agricultural insect communities (i.e., as biocontrol agents against insect pests; Jervis 2005).

This chapter starts with an overview of research done on lipid metabolism of insect parasitoids, from earlier works in the 1960s to the most recent developments in part 2. Host fatty acid composition and fat content, as well as the ability of parasitoids to manipulate host lipids and availability, is of critical importance for both immature and adult parasitoids. Part 3 focuses on the different mechanisms by which parasitoids can manipulate the fat metabolism of their hosts.

2 Fatty Acid Synthesis and Fat Accumulation in Parasitoids

Parasitoids have been of particular interest to biologists regarding lipid metabolism. There has, however, been some recent debate between researchers studying parasitoid lipid metabolism, mainly in terms of semantics (Visser et al. 2023). To avoid confusion about definitions and terminology related to lipid metabolism, the use of stricter definitions that emphasize the difference between the processes of fatty acid synthesis and

triacylglycerol/fat accumulation has recently been proposed (Visser et al. 2023). This distinction is important, because these two processes are not synonymous with one another: fatty acids can be synthesized even if triacylglycerols are not accumulated. The main interest of evolutionary ecologists studying lipid metabolism in parasitoids has been focused on the accumulation of triacylglycerols in adults, because energy stored in the form of fat reserves can have a major impact on life histories and fitness (see Box 1 for a brief overview of the link between fat content and life histories in parasitoids). Parasitoids represent a curious case where triacylglycerols are generally not accumulated in response to superfluous feeding, unlike other animals that will readily accumulate triacylglycerols under the same nutritional conditions (Visser et al. 2010; Visser and Ellers 2008). While previously referred to as the "lack of lipogenesis" or "lack of lipid synthesis", this phenomenon is now referred to as the "lack of adult triacylglycerol/fat accumulation" in parasitoids (Visser et al. 2023), with fat being used synonymously with triacylglycerol. We continue part 2 of this chapter with a chronological account of the work done on lipid metabolism, with the main focus on fatty acid synthesis and fat accumulation in insect parasitoids.

Box 1: Survival of the Fattest: Stored Triacylglycerol Levels Impact Longevity, Reproduction, and Other Fitness-Related Traits in Parasitoids

Triacylglycerols are the most comprehensive form in which energy can be stored, both in terms of the storage space needed within a cell and the higher caloric content per unit of weight (Arrese and Soulages 2010). Oxidation of triacylglycerols further releases twice as much water compared to glycogen (i.e., another major metabolite for energy storage). Taking all this into consideration, it is not surprising that fat plays a critical role for insect life histories, including parasitoids (Jervis et al. 2008). We use earlier work on the *Drosophila*-parasitizing braconid wasp *Asobara tabida* as a case study to reveal the close link between fat reserves and life history traits (see Colinet et al. 2006; Giron and Casas 2003a; Le Lann et al. 2014; Luo et al. 2010; Muller et al. 2017; Sheng et al. 2019 for similar findings in other parasitoid species).

Under laboratory conditions, *A. tabida* females can emerge with 0.04 mg or ~ 20% total body fat (Visser et al. 2010), but triacylglycerol levels never exceed those at emergence for the remainder of adulthood (Ellers 1996; Le Lann et al. 2014; Visser et al. 2010), as depicted in Box Fig. 1a. Unlike most other insects (and animals) that rapidly build up triacylglycerol stores when fed a surplus of sugars (see Box Fig. 1b for *Drosophila melanogaster* as an example; Visser et al. 2010), triacylglycerol content in *A. tabida* (without access to hosts) decreases quickly during the first week of life, and then more steadily at a rate of ~0.004 mg per week thereafter (for comparison: when starved, *A. tabida* triacylglycerol-use is ~0.004 mg per day). Moreover, *A. tabida* strains with higher fat content also live longer (Ellers 1996). Fat reserves are thus correlated with adult survival and used to fuel adult life.

Among other metabolic roles, a critical job of the fat body is to store lipids. Fat bodies can become so hypertrophied with lipids that they may fill much of an insect's abdomen. Triacylglycerol levels are correlated with body size in arthropods in general (Lease and Wolf 2011), as well as in *A. tabida* (Ellers 1996; Ellers et al. 1998). Larger, fatter females also have more eggs in their ovarioles (Ellers et al. 1998), and *A. tabida* females can emerge with ~160 yolk-poor (i.e., hydropic) eggs (Carton et al. 1986; Le Lann et al. 2014). Many more eggs can be produced during life (i.e., synovigeny; Box Fig. 2; Jervis et al. 2001), with realized fecundity ranging between 580 and 630 eggs when hosts are available

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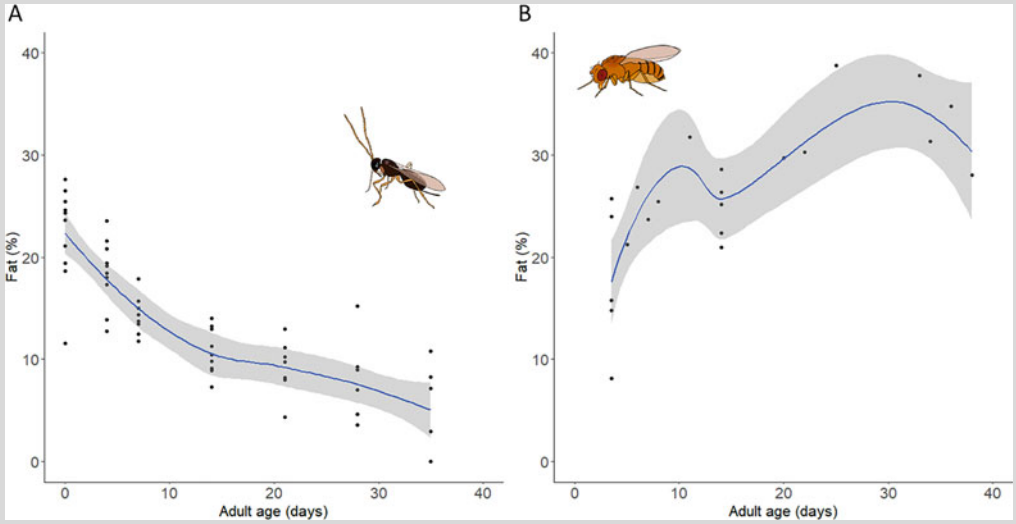
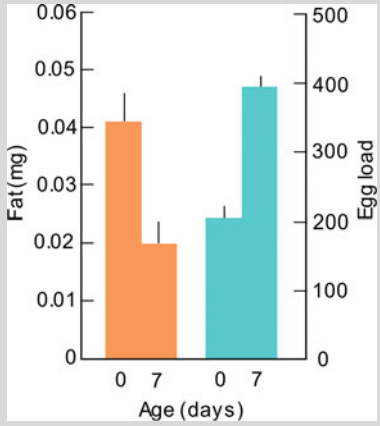


Box Fig. 1 The proportion of fat (in %) in adult *Asobara tabida* (**a**), and *Drosophila melanogaster* (**b**) throughout life. Based on data from Ellers (1996) and redrawn from Service (1987)



Box Fig. 2 Amount of fat (mean + 1 s.e.) and egg load (mean + 1 s.e.) of *A. tabida* females originating from a population in Kos, Greece, at emergence and 7 days after emergence (with access to food). Redrawn from Ellers and van Alphen (1997)

in excess (Ellers and van Alphen 1997). Similar to lipid-use in non-ovipositing females (Box Fig. 1a), allocation of fat reserves toward reproduction is highest during the first week of life. If the energetic cost of maintenance is similar between ovipositing and non-ovipositing females, then ~25 ng fat is allocated into each egg during the first week of life (based on data of Ellers 1996, and Ellers and van Alphen 1997 for the same population). In *A. tabida,* once fat has been used for reproduction, these reserves cannot be used anymore for other functions (in contrast to some other parasitoid species that can resorb eggs; Jervis et al. 2001). Limiting fat reserves can, therefore, lead to so-called trade-offs in life history traits, because energy can be invested either into reproduction or maintenance/survival (Ellers 1996) or early versus late reproduction (Seyahooei et al. 2020).

Field experiments using a release-recapture approach revealed that dispersal of laboratory-reared *A. tabida* females is size-dependent (Ellers et al. 1998). Larger, fatter females can disperse over larger distances (>15 m) compared to smaller females. Wild-caught *A. tabida* were generally smaller than laboratory-reared females, and size decreased as the season progressed (from July to September). Larger wild-caught females burned more fat than smaller females and carried more eggs at the time of capture. Another study

(continued)

examined the size of field-caught *A. tabida* females over several months (June to October) (Ellers et al. 2001). Female size varied, but larger, fatter females were generally captured at the start and the end of the field season. This pattern may be explained by the differences in temperature throughout the field season, with higher temperatures being reached during summer leading to an increase in metabolic activity and lipid oxidation. Alternatively, fat females have a selective advantage when entering and emerging from diapause early and late in the season, as large fat stores are required to survive months at low environmental temperatures (Ellers and van Alphen 2002).

2.1 Early Studies on Parasitoid Larval Fatty Acid and Triacylglycerol Synthesis

Parasitoid fatty acid metabolism started to receive some attention in the late 1960s. Several researchers took an interest in hymenopteran parasitoids, because unlike other insects (e.g., dipterans and lepidopterans; Barlow 1964, 1965, 1966), some wasps did not seem to have their own characteristic fatty acid composition. Rather than a species-specific qualitative and quantitative fatty acid composition, several wasp species seemed to duplicate the fatty acid composition characteristic of their host. Bracken and Barlow (1967) were the first to investigate this intriguing phenomenon in the ichneumonid parasitoid *Exeristes comstockii*. Using unparasitized larvae of various hosts (the dipteran host *Lucilia sericata,* the lepidopteran host *Galleria mellonella*, and the sawfly host *Neodiprion sertifer* (basal Hymenoptera)) that show substantial interspecific quantitative differences in fatty acids, *E. comstockii* larvae readily duplicated the distinctive fatty acid composition of each host. The host-specific fatty acid composition of *E. comstockii* remained unchanged throughout pupation and into adulthood, meaning that the parasitoid duplication phenomenon is not stage-specific. Similar findings were obtained for another ichneumonid parasitoid, *Itoplectis conquisitor*, when reared on the lepidopteran hosts *G. mellonella* and *Ostrinia nubilalis* (Thompson and Barlow 1970), and in two parasitoid tachinid flies (Delobel and Pageaux 1981).

To determine the generality of duplicated fatty acid compositions in parasitoids, Thompson and Barlow (1972a) tested several other parasitoid species at the larval stage, including aphidids and braconids, as well as species from the superfamily Chalcidoidea, including pteromalids and eulophids. All icheumonids tested ($n = 7$) had similar fatty acid compositions as their hosts, and the same was true for the pteromalid *Spalangia cameroni* and the eulophid *Dahlbominus fuscipennis.* A subsequent study with 30 species from 5 families of parasitic Hymenoptera revealed that while most ichneumonids had duplicated fatty acid compositions, this was not a general pattern for this group and duplication occurred also in species from other families (Thompson and Barlow 1974). Duplication of the fatty acid composition was suggested to be related to host range of the parasitoid, because most (although not all) species with duplicated compositions were generalists able to develop on a wide range of hosts. It should be noted, however, that in most experiments by Thompson and collaborators unparasitized hosts were compared to parasitoids. When fatty acid compositions differ between hosts and parasitoids, these changes could also result from manipulation of the host's fat metabolism by the parasitoid (see part 3 of this chapter). Furthermore, although in line with sampling expectations at the time, replication is rather low in the early works of Thompson and colleagues. Hence some caution is needed when interpreting their results.

The question arises how and why are some parasitoids duplicating the fatty acid composition of their hosts, but others are not? One explanation is that the parasitoids readily feed on the fat body

of the host and incorporate those fatty acids directly into their own fat stores without contributing de novo synthesized fatty acids themselves. Thompson and Barlow (1972b) tested this hypothesis using *E. comtockii* reared on the lepidopteran host *G. mellonella* and the dipteran host *L. sericata*. By injecting radiolabeled acetate (^{14}C-1-acetate) into the hosts, and rearing the parasitoid on both host species, it became apparent that *E. comstockii* larvae synthesized (as well as desaturated and elongated) fatty acids, with palmitate (C16:0) being the main synthetic product. While de novo fatty acid synthesis is clearly taking place in *E. comstockii,* fatty acids also originate from direct incorporation of host fat. This was demonstrated by the presence of eicosenoic acid (C20:1) that was synthesized de novo by *G. mellonella* only and was also present in the fatty acid fraction of *E. comstockii* (but without radioactivity and thus without fatty acid synthesis by the parasitoid).

If host fatty acid composition largely determines that of the parasitoid, what happens if the host is taken out of the equation altogether? Thompson and Barlow (1976) did the test: they reared larvae of another ichneumonid that also duplicates the fatty acid composition of its host, *Exeristes roborator*, on a fatty acid-free artificial medium. Without any host, the parasitoid larvae readily synthesized fatty acids de novo with a composition that did not mimic that of any of its hosts. The developmental environment is strikingly different for parasitoids reared on an artificially defined fatty acid-free medium compared to a natural, developing host insect that is rich in lipids. Triacylglycerols indeed appeared to be less toxic for *E. roborator* to consume than fatty acids (Thompson 1977), which makes sense considering that developing hosts typically contain substantial triacylglycerol quantities compared to free fatty acids. If host acylglycerols can be used by the parasitoid with relative ease, perhaps there is no need to invest in energetically costly triacylglycerol synthesis by the parasitoid itself. The study of Jones et al. (1982) compared triacylglycerol synthesis between ichneumonid species that duplicated the host's fatty acid composition, *E. roborator* and *I. conquisitor*, with species that have their own characteristic fatty acid composition irrespective of that of the host, i.e., the ichneumonids *Aphaereta pallipes*, *Hyposoter exigua,* and the chalcid *Brachymeria lasus.* What they found is that *E. roborator* and *I. conquisitor* did not incorporate glycerophosphate into acylglycerols, meaning that the de novo triacylglycerol pathway (also known as the Kennedy pathway) was not active. *Aphaereta pallipes* and *H. exigua*, that did not duplicate the host's fatty acid composition, readily incorporated glycerophosphate. Interestingly, all parasitoids were able to use the monoacylglycerol pathway, where monoacylglycerols are sequentially acylated by acyl-CoA to form di- and subsequently triacylglycerols (i.e., by monoacylglycerol transferase, and diacylglycerol acyltransferase, respectively; Fig. 1 in Visser et al. 2023). For *E. roborator*, 75% of triacylglycerols were formed from diacylglycerols, while this was 97% for *I. conquisitor*. The enzymes of the monoacylglycerol pathway further appeared to be substrate-specific in *E. roborator*, meaning that some fatty acid thioesters are more readily used to form triacylglycerols.

Overall, the work of Thompson and colleagues has shed an exceptional light on the mechanistic basis of the duplication of host fatty acid compositions in some parasitoids. When high levels of triacylglycerols are available in a fat-rich host, partial catabolism of triacylglycerols into diacylglycerols (the main form in which lipids are transported through the hemolymph; Soulages and Wells 1994; Turunen 1979) can then facilitate a fast and relatively inexpensive biochemical means to synthesize new triacylglycerols for storage in the parasitoid larvae. The parasitoid larvae thus do not use the de novo triacylglycerol pathway, but rather the monoacylglycerol pathway to accomplish this. The similarity in composition between host and parasitoid is thought to result from acyltransferase specificity favoring fatty acids that are similar to that of the host.

2.2 The Lack of Adult Triacylglycerol Accumulation in Adult Parasitoids

The storage of fat reserves in periods of food abundance is one of the most conserved metabolic responses across all domains of life (Birsoy et al. 2013). Fat is a key energy substrate fueling insect life, including behavior and other components of fitness (i.e., survival, reproduction; Box 1) (Arrese and Soulages 2010). Although adult parasitoids use dietary carbohydrates to meet short-term energetic demands, adult parasitoids show an extraordinary physiological response to sugar feeding, unlike other insects. During the 1990s and 2000s, adults of several parasitoid species were found to not appreciably convert excess carbohydrates into long-term storage in the form of fat. For example, the adult fat content of *Asobara tabida* (Ichneumonoidea) was highest at emergence and declined rapidly with age, despite continuous access to sugar (see Box 1; Ellers 1996). Similar findings were obtained also for other species of various superfamilies: Ichneumonoidea (*Ventura canescens* and *Diadegma insulare;* Casas et al. 2003; Lee et al. 2004), Cynipoidea (*Leptopilina heterotoma*; Eijs et al. 1998), and Chalcidoidea (*Nasonia vitripennis*; *Eupelmus vuilletti*; Giron and Casas 2003b; Rivero and West 2002), demonstrating that this extraordinary physiological phenotype was more common in parasitic Hymenoptera.

Lack of adult fat accumulation was proposed to be an evolutionary consequence of the parasitoid lifestyle (Visser and Ellers 2008). Efficiently utilizing a single host insect and manipulating host nutrient content (see part 3 on host manipulation) generally leads to a lipid-rich environment for developing parasitoid larvae. Under such conditions, where larval host fat content is high, adult fat accumulation is no longer necessary (leading to relaxed selection on adult fat accumulation; Lahti et al., 2009) or too costly to maintain (i.e., leading to selection against adult fat accumulation). Visser and Ellers (2008), therefore, hypothesized that parasitoids lost the ability for adult fat accumulation. A study using a comparative approach with more than 90 insect species indeed revealed that (1) loss of fat accumulation is ancestral in parasitic Hymenoptera; (2) the loss of adult fat accumulation coincided with or followed the evolution of the parasitoid lifestyle; and (3) there is parallel evolution, as the loss of fat accumulation evolved repeatedly and independently in parasitoid flies (Diptera), beetles (Coleoptera), and wasps (Hymenoptera; Visser et al. 2010). There were some exceptions, however, because several generalist parasitoid species did accumulate fat as adults, including *L. heterotoma*, *Pteromalus puparum,* and *Gelis agilis* (Visser et al. 2010). A reason why adult generalist synthesize fat is that manipulation of host fat content is difficult when many species can serve as potential hosts. When a generalist then develops on a fat-poor host, fat accumulation in adults is critical for survival and reproduction (Visser et al. 2010).

An important question is which mechanism (s) underlies the loss of fat accumulation in adult parasitoids? There can be several ways in which the fat accumulation phenotype was lost: (1) the gene (s) underlying fatty acid or triacylglycerol synthesis and accumulation were lost (i.e., not present in the genome anymore; as in the yeast *Malassezia globose*; Xu et al. 2007); (2) the gene(s) have accumulated mutations in the coding regions, leading to non-functionality; (3) the gene(s) remain present, but are silenced through regulatory processes or mutations in regulatory regions. Consequently, either insufficient quantities of fatty acids and triacylglycerols are produced by adult parasitoids or accumulation itself is hampered. The loss or non-functionality of key genes in the fatty acid and triacylglycerol metabolism pathways is unlikely, however, because many genes (e.g., fatty acid synthase *fas*, acetyl-CoA carboxylase *acc*, glycerol-3-phosphate-acyltransferase *gpat*) involved in the conversion of carbohydrates into triacylglycerols, are also essential for the synthesis of other lipid classes and are part of other key metabolic pathways (e.g., pyruvate metabolism, citrate cycle, phospholipids).

The first study on the molecular mechanisms and transcriptional profiles underlying the lack of adult fat accumulation in parasitoids was performed with the chalcid *N. vitripennis*.

Genome analysis indeed revealed that coding sequences of *fas* and *acc* did not contain any stop codons, mutations, or signs of genetic damage (Visser et al. 2012). But contrary to findings in other animals, no effect of continuous access to sugar was found on the transcription levels of *fas* or *acc* (Visser et al. 2012), suggesting that fatty acid synthesis is not taking place. The same was found for *gpat*, involved in the early steps of acylglycerol synthesis (and part of the de novo triacylglycerol synthesis pathway). Genes involved in the monoacylglycerol pathway, e.g., *dgat,* did not respond to continuous access to sugar either. Functionality of *fas* and *acc*, as well as other genes and their enzyme products, were also confirmed in several other parasitoid wasp species (Kraaijeveld et al. 2019; Lammers et al. 2019; Prager et al. 2019; Visser et al. 2021). Presence and functionality of fat-related genes suggest that changes in gene expression, rather than structural genetic changes are involved in the lack of adult fat accumulation (Visser et al. 2012).

For transcriptomic studies on fat metabolism, it is essential to know how fat metabolic phenotypes are affected. In the case of Visser et al. (2012), absence of fatty acid synthesis and fat accumulation in adult *N. vitripennis* were determined using stable isotope tracking methods (of deuterium into fatty acids of the neutral lipid fraction) and bulk fat extractions (comparing fat quantities between emerged and fed wasps), respectively. No incorporation of stable isotopes was found in fatty acids of the neutral lipid fraction, indicating that fatty acid synthesis did not take place in *N. vitripennis*. This was confirmed by quantitative PCR measurements of gene transcripts of key fatty acid synthesis genes, e.g., *fas*, *acc*, and *dgat*. In contrast, the honeybee *Apis mellifera* that readily synthesizes and stores fat as adult, did incorporate stable isotopes into the neutral fat fraction, illustrating that the method could indeed measure fatty acids that were synthesized and incorporated into stored triacylglycerols. In *N. vitripennis,* no adult fat accumulation was detected because fat quantities decreased significantly during life. Even though adult fat did not accumulate, intermediary metabolites involved in fat metabolism could still be synthesized. For example, Ruther et al. (2021) found that several parasitoid wasp species could synthesize fatty acids, and in the case of *N. vitripennis*, utilize these fatty acids in triacylglycerols and eggs (Multerer et al. 2022). However, no increase in bulk triacylglycerol stores was observed (Ruther et al. 2021). This means that even though fatty acids are synthesized and used to form some amount of triacylglycerols, *N. vitripennis* still lacks adult triacylglycerol accumulation.

To further understand the (lack of) fat accumulation phenotype observed in parasitoids, Visser et al. (2017) compared larval and adult fatty acid synthesis between *D. melanogaster*, showing typical and significant fat accumulation after feeding (Box Fig. 1b), a parasitoid that lacked fat accumulation, *E. vuilletti*, and two parasitoids that readily accumulate fat as adults, *Gelis areator* and *G. agilis.* In adults, fatty acid synthesis (of C16:0) was indeed very high for species that accumulate fat, while for *E. vuilletti* that does not accumulate fat, no fatty acid synthesis was detected. The same patterns were found when fatty acid synthesis was analyzed in the larvae of *D. melanogaster, E. vuilletti, G. agilis*, and *G. areator*. There thus seems to be concurrence in fatty acid synthesis phenotypes between larvae and adults.

Work on fat metabolism in parasitoids has had two distinct spurts in terms of studies, one between the 1960s and 1980s focused on the similarity of fatty acid compositions between hosts and parasitoid larvae; the other starting in the 2000s and still ongoing to understand why adult parasitoids do not accumulate fat. It may well be that despite the slightly different interests and focus, both phenomena result from the same underlying mechanism(s) and evolved in a similar way. Only one more recent study has so far compared fatty acid compositions and fat accumulation strategies, using adults of a rose gall wasp community, including the parasitoids *Orthopelma mediator* and *Pteromalus bedeguaris* (Visser et al. 2013). The gall wasp *Diplolepis rosae* is attacked by *O. mediator,* while *P. bedeguaris* can act as a primary parasitoid on *D. rosae* or as a secondary hyperparasitoid on other primary parasitoids of

D. rosae, including *O. mediator*. Both *O. mediator* and *P. bedeguaris* did not accumulate fat as adults, and only the fatty acid composition of *O. mediator* was considerably different from its main host *D. rosae*. *Orthopelma mediator* is an ichneumonid and *P. bedeguaris* a chalcid, both with a very limited host range. Fat accumulation strategy does thus not seem to be related to mimicking of the host's fatty acid composition, as *O. mediator* has a different fatty acid composition than its host *D. rosae*. The similar fatty acid composition of the more specialized *P. bedeguaris* suggests that copying of the host's fatty acid composition is not inherently linked to host breadth (as suggested in Barlow 1964; Bracken and Barlow 1967). The rose gall system may, however, not be ideal for evaluating the link between fat accumulation, host breadth, and fatty acid compositions due to this system's particular ecological niche. More work is thus needed to determine whether the lack of fat accumulation coincides with mimicking of the fatty acid composition of the host.

2.3 More Complex Adult Parasitoid Fatty Acid Synthesis and Fat Accumulation Phenotypes

While the majority of parasitoids do not accumulate fat as adults, for some parasitoid species repeated experiments hinted at more complicated patterns. For example, Moiroux et al. (2010) proposed that the ability of adult parasitoid wasps to accumulate fat was closely tied to geographic location and local environmental conditions. To test this, four geographically distinct *Leptopilina boulardi* populations were collected. Different adult fat accumulation phenotypes were found: two populations accumulated fat, while the two other populations did not (Moiroux et al. 2010). These observations could be related to genetic divergence between populations, as the two populations that accumulated fat were genetically closer to each other than to populations that did not (Seyahooei et al. 2011; Visser et al. 2017).

Like Moiroux et al. (2010), a large-scale study on the ability for fat accumulation of field-caught *L. heterotoma* populations and other *Leptopilina* species also revealed contrasting adult fat accumulation phenotypes (Visser et al. 2018). These differences were found to be related to the fat content of the *D. melanogaster* host strain used. Indeed, parasitoids emerging from a lean host contained a lower quantity of fat, leading to fat accumulation in adults, while no fat accumulation was observed for parasitoids emerging from a fatty host with a high amount of fat (Visser et al. 2018). A more recent study with several *L. heterotoma* populations confirmed that this species can switch fatty acid synthesis and fat accumulation on or off depending on the host's fat content: these wasps generally start synthesizing and accumulating fat on lean *Drosophila* larvae (Visser et al. 2021). Variation in fat accumulation strategies in adult *L. heterotoma* is plastic, meaning that a single genotype can generate different fatty acid synthesis and fat accumulation phenotypes depending on environmental conditions (Fig. 2). What is now needed is to test also other parasitoids for plasticity of fatty acid synthesis and fat accumulation, particularly considering consequences for adult life histories.

3 Lipid Metabolism in Parasitized Hosts

The parasitoid's unique lifestyle has led to the evolution of intricate mechanisms to manipulate host metabolism. A parasitoid relies on only a single host to complete development and to obtain sufficient nutrients to fuel adult life. There is thus an incredible advantage for the parasitoid to "hijack" the host's metabolism for its own benefit. Considering that many parasitoids do not accumulate substantial fat quantities as adults (see part 2) and fat is of key importance for parasitoid life histories and fitness (see Box 1), manipulating host lipid metabolism so that host lipids become more accessible or available for the parasitoid has a clear adaptive value.

Before exploring how host lipid metabolism can be manipulated by the parasitoid, there are some parasitoid-specific traits that have a large impact on host manipulation. Parasitoids show tremendous diversity related to their mode of

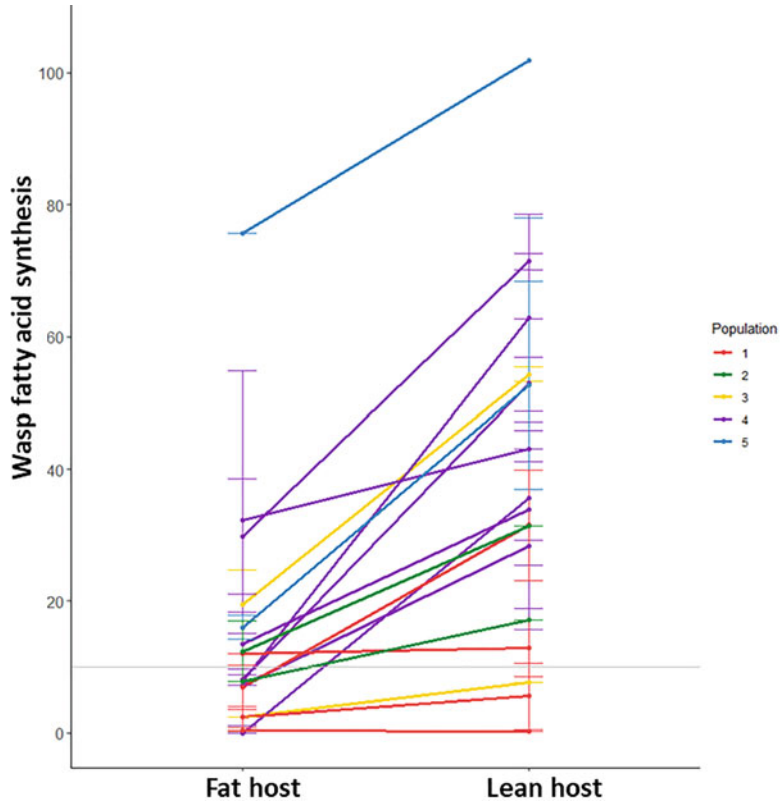


Fig. 2 Fatty acid synthesis (as % deuterium incorporation) of *Leptopilina heterotoma* families (sharing 75% of their genome) originating from different populations (1–5). Reaction norms reveal that some families show plasticity in fatty acid synthesis (synthesis on lean hosts, no synthesis on fat hosts), while other families constitutively synthesize fatty acids or lack fatty acid synthesis (under the gray line). Variation in the slope of the reaction norms suggests that there is genetic variation for plasticity of fatty acid synthesis, meaning that plasticity itself can evolve in response to selection. Redrawn from Visser et al. (2021)

life and general biology (Fig. 1; Godfray 1994; Quicke 1997). An important distinction can be made, for example, between parasitoid species that arrest host development, idiobionts, and species that allow the host to continue feeding and growing, koinobionts. For idiobionts, resource availability for the parasitoid is largely fixed close to the time of oviposition, while for koinobionts host resources generally keep on accumulating, at least for some time while the parasitoid is developing. Among koinobionts, a further distinction can be made between parasitoid species that stop host development prematurely, reducing final host body size, and parasitoid species that prolong host development, increasing final host body size (Cuny and Poelman 2022). Several studies have indeed reported that host food consumption is reduced following parasitism by koinobiont parasitoids (Kaeslin et al. 2005; Morales et al. 2007; Pruijssers et al. 2009; Shi et al. 2015; Thompson 1982a; Thompson 1983), while some parasitized hosts feed longer but remain smaller compared to unparasitized hosts (Thompson and Redak 2008). The extent to which a parasitoid can affect host development can also be dependent on the environment (i.e., phenotypic plasticity). The braconid *Meteorus pulchricornis*, for example, increases final size of the small lepidopteran host *Plutella xylostella* by 30%, while final size of the larger lepidopteran host *Mythimna separata* is increased by 95% (Harvey et al. 2010). The host species can thus have a major impact on resource levels and resource availability for koinobiont parasitoids, which in turn can have major consequences for fatty acid synthesis and fat accumulation of the parasitoid (see part 2.2; Visser et al. 2021).

Parasitoids are highly efficient in carrying over resources from the host, which for some species can mount to >90% of the host's body mass (Harvey et al. 2009). An increase in host fat availability and content can have a major impact on both parasitoid larval development and

survival, as well as adult fitness (Rivers et al. 1998). When more fat can be carried over from the host, the parasitoid has more energetic reserves available for allocation into fitness-related traits (see Box 1). For parasitoids in which complete consumption of host tissues is required, developing on larger hosts can be detrimental if it leads to overfeeding (Harvey 1996; Harvey and Strand 2002). Indeed, many parasitoids are so-called "tissue-feeders", where most or all host tissues are consumed during the parasitoid's development (Fig. 1). Within the superfamily Ichneumonoidea, all gregarious (i.e., with multiple offspring emerging from a single host) koinobiont endoparasitoids (e.g., *Microplitis* sp. and *Cotesia* sp., as well as the family Chelonidae) have, however, evolved the ability to feed mostly on host hemolymph (Harvey and Malcicka 2016). These "hemolymph-feeders" initially only feed on hemolymph and part of the fat body of the host but exit the host during the last larval stage to pupate externally (Fig. 1). The adaptive significance of hemolymph feeding is that a wider range of host developmental stages and sizes can be parasitized, including hosts that are much larger than the parasitoid itself.

An important question is whether hemolymph or tissue-feeding koinobionts have evolved different strategies to manipulate host metabolism. We could expect that for tissue-feeders, increasing host fat body lipid content is more important, while for hemolymph-feeders an increase or steady flow of hemolymph lipids can increase the efficiency of scavenging from the host. This could be tested using host-parasitoid systems where the same host species is attacked by multiple parasitoids that differ in feeding strategy. Koinobiont microgastrine braconids and campoplegine ichneumonids may be ideal systems for testing the evolution of host manipulation strategies in parasitoids, e.g., *P. xylostella* parasitized by *Diadegma semiclausum* (tissue-feeder) and *Cotesia vestalis* (hemolymph-feeder), *Pieris brassicae* parasitized by *Hyposoter ebeninus* (tissue-feeder) and *Cotesia glomerata* (hemolymph-feeder), *Spodoptera littoralis* parasitized by *Hyposoter didymator* (tissue-feeder) and *Cotesia marginiventris* (hemolymph-feeder). Comparing host manipulation strategies of hemolymph versus tissue-feeders developing on the same host offers a unique opportunity to increase our understanding of the mechanisms underlying host manipulation.

3.1 The Effects of Parasitism and the Developing Parasitoid(s) on Host Fat Metabolism

The easiest, and sometimes only, way to determine how host metabolism is affected by parasitism is to compare unparasitized with parasitized hosts. Overall, when parasitized, host lipid levels can increase, remain stable, or decrease for a variety of reasons (see Table 1). For example, parasitism of the locust *Chortoicetes terminifera* by the parasitoid fly *Trichopsidea oestracea* led to a steep increase in overall lipid content, although the mechanism has remained unclear (Horwood and Hales 1991). In another parasitoid fly, *Blepharipa sericariae*, the developing larvae were found to secrete a peptide that inhibits lipid transport in the host silkworm, *Philosamia cynthia prieri* (Hayakawa 1987). *Blepharipa sericariae* eggs are consumed by the host during larval feeding, and after parasitoid hatching the parasitoid larvae remain in the second instar until the following spring when the larvae molt and start feeding on the host's pupal tissues. Lipid release from the host fat body into the hemolymph was reduced by 50–70%, and lipid uptake by lipophorin (a blood protein used for lipid transport) was inhibited by ~60% through the action of a parasitoid-secreted peptide (Hayakawa 1986). Similar results were obtained when the locust *Locusta migratoria* was parasitized, with a 50% inhibition of diacylglycerol release (Hayakawa 1987). This finding supports the idea that lipid uptake and transport in the hemolymph, which typically entails the transport of diacylglycerols in insects, is inhibited (Turunen 1979; but see also Ford and van Heusden (1994) who identified a lipophorin transporting triacylglycerols in *Aedes aegypti*). Considering it takes about a year for *B. sericariae* to complete its development, inhibition of lipid transport by lipophorin conserves the triacylglycerol stores of

Table 1 Overview of studies looking at the effect of parasitism on host lipid levels (mainly triacylglycerols) in the whole body, fat body, and/or hemolymph. A distinction is made between the effects of parasitism in general, the venom (with or without the egg, i.e., envenomation), polydnaviruses (with or without the egg, i.e., pseudoparasitization or injection), and teratocytes (with or without the egg, i.e., injection)

Parasitoid species	Parasitoid family	G/S	I/K	Gen/Sp	Ecto/ Endo	Host stage attacked	H/T	Host species	Host order	Host treatment	Host whole body	Host fat body	Host hemolymph	References
Parasitism in general														
Apanteles galleriae	Braconidae	S	K	Gen	Endo	L	T	*Achoria grisella*	Lepidoptera	Par	Sim	–	–	Nurullahoğlu et al. (2004)
Cotesia congregata	Braconidae	G	K	Sp	Endo	L	H	*Manduca sexta*	Lepidoptera	Par	Low	–	–	Thompson and Redak (2008)
Cotesia flavipes	Braconidae	G	K	Sp	Endo	L	H	*Diatraea saccharalis*	Lepidoptera	Par	–	Sim	Low	Salvador and Cônsoli (2008)
								Diatraea flavipennella	Lepidoptera	Par	–	Sim	Low	dos Passos et al. (2019)
Glyptapanteles liparidis	Braconidae	G	K	Sp	Endo	L	H	*Lymantria dispar*	Lepidoptera	Par	Low	–	Sim	Bischof and Ortel (1996)
Cardiochiles nigriceps	Braconidae	S	K	Sp	Endo	L	H	*Heliothis virescens*	Lepidoptera	Par	Sim	–	Sim	Barras et al. (1970)
Hyposoter exigua	Ichneumonidae	G	K	Gen	Endo	L	H	*Trichoplusia ni*	Lepidoptera	Par	Low	–	–	Thompson (1982b)
Trichomalopsis apanteloctena	Pteromalidae	S	I	Gen	Ecto	P	T	*Cotesia kariyai*	Hymenoptera	Par	Low	–	–	Nakamatsu and Tanaka (2004a)
Trichopsidea oestracea	Nemestridae	S	K	Sp	Endo	N	T	*Chortoicetes terminifera*	Orthoptera	Par	Hig	–	–	Horwood and Hales (1991)
Venom														
Bracon nigricans	Braconidae	G	I	Gen	Ecto	L	T	*Spodoptera littoralis*	Lepidoptera	Env	–	Low	Low	Becchimanzi et al. (2017, 2020)
Habrobracon brevicornis	Braconidae	G	I	Gen	Ecto	L	T	*Galleria mellonella*	Lepidoptera	Env	–	Low	Hig	Kryukova et al. (2021)
Lysiphlebia japonica	Braconidae	S	K	Gen	Endo	A	T	*Aphis gossypii*	Hemiptera	Par	Hig	–	–	Xueke et al. (2017)
Euplectrus separatae	Eulophidae	G	K	Sp	Ecto	L	T	*Mythimna separata*	Lepidoptera	Par	–	Low	Hig	Nakamatsu and Tanaka (2003)

								Mythimna separata	Lepidoptera	Env	–	Low	Hig	Nakamatsu and Tanaka (2003), Nakamatsu and Tanaka (2004a, b)
Nasonia vitripennis	Pteromalidae	G	I	Gen	Ecto	P	T	*Sarcophaga bullata*	Diptera	Env	Hig	Hig	Hig	Rivers and Denlinger (1994, 1995)
								Sarcophaga bullata	Diptera	Env	–	–	Hig	Rivers et al. (1998)
								Sarcophaga bullata	Diptera	Par	–	Hig	–	Rivers and Denlinger (1995)
								Sarcophaga bullata	Diptera	Env	–	Hig	–	Rivers and Denlinger (1995)
								Sarcodexia sternodontus	Diptera	Env	–	Low	Low	Rivers and Denlinger (1995)
								Phormia regina	Diptera	Env	–	Low	Hig	Rivers and Denlinger (1995)
								Musca domestica	Diptera	Env	–	Sim	Hig	Rivers and Denlinger (1995)
								Sarcophaga bullata	Diptera	Par	–	Hig	Hig	Rivers and Yoder (1996)
Trichomalopsis apanteloctena	Pteromalidae	S	I	Gen	Ecto	P	T	*Cotesia kariyai*	Hymenoptera	Env	Sim	–	–	Nakamatsu and Tanaka (2004a)
Muscidifurax zaraptor	Pteromalidae	S	I	Gen	Ecto	P	T	*Sarcophaga bullata*	Diptera	Env	–	–	Hig	Rivers et al. (1998)
Trichomalopsis near Americana	Pteromalidae	G	I		Ecto	P	T	*Sarcophaga bullata*	Diptera	Env	–	Low	Hig	Rivers et al. (1998)
Pteromalus puparum	Pteromalidae	G	I	Gen	Endo	P	T	*Pieris rapae*	Lepidoptera	Par	–	Hig	Hig	Wang et al. (2020a)

(continued)

Table 1 (continued)

Parasitoid species	Parasitoid family	G/S	I/K	Gen/Sp	Ecto/ Endo	Host stage attacked	H/T	Host species	Host order	Host treatment	Host whole body	Host fat body	Host hemolymph	References
Scleroderma sichuanensis	Bethylidae	G	I	Gen	Ecto	P	T	*Tenebrio molitor*	Coleoptera	Par	–	Low	Low	Zhuo et al. (2016)
										Env	–	Sim	Low	Zhuo et al. (2016)
Teratocytes														
Meteorus pulchricornis	Braconidae	S	K	Gen	Endo	L	T	*Mythimna separata*	Lepidoptera	Par	–	Low	–	Suzuki and Tanaka (2007)
Cotesia kariyai	Braconidae	G	K	Sp	Endo	L	H	*Mythimna separata*	Lepidoptera	Par	–	Low	–	Nakamatsu et al. (2002)
Microplitis croceipes	Braconidae	S	K	Sp	Endo	L	H	*Heliothis virescens*	Lepidoptera	Par	–	Low	–	Zhang et al. (1997)
										Inj	–	Low	–	Zhang et al. (1997)
Dinocampus coccinellae	Braconidae	S	K	Gen	Endo	L/A	T	*Hippodamia convergens*	Coleoptera	Par	–	Low	–	Sluss (1968)
Dinocampus coccinellae	Braconidae	S	K	Gen	Endo	L/A	T	*Coccinella septempunctata*	Coleoptera	Par	–	Low	–	Gopalapillai et al. (2005)
Polydnavirus														
Microplitis demolitor	Braconidae	S	K	Gen	Endo	L	H	*Chrysodeixis includens*	Lepidoptera	Inj	Low	–	–	Pruijssers et al. (2009)
Cotesia vestalis	Braconidae	S	K	Sp	Endo	L	H	*Plutella xylostella*	Lepidoptera	Par	Low	Low	–	Wang et al. (2021)
		S	K	Sp	Endo	L	H			Ps	Low	Low	–	Wang et al. (2021)
Chelonus inanitus	Braconidae	S	K	Gen	Endo	E/L	H	*Spodoptera littoralis*	Lepidoptera	Par	Hig	–	–	Kaeslin et al. (2005)
										Ps	Hig	–	–	Kaeslin et al. (2005)

G Gregarious, *S* solitary, *I* Idiobiont, *K* Koinobiont, *Gen* Generalist, *Sp* Specialist, *Ecto* Ectoparasitoid, *Endo* Endoparasitoid, *A* Adult, *E* Egg, *L* Larva, *N* Nymph, *P* Pupa, *H* Hemolymph-feeder, *T* Tissue-feeder, *Env* Envenomation, *Inj* Injection, *Par* Parasitization, *Ps* Pseudoparasitization, *Hig* Higher, *Low* Lower, *Sim* Similar, NB: *Trichomalopsis apanteloctena* is a hyperparasitoid

the host's fat body. *Blepharipa sericariae* thus prevents the locust host from mobilizing and using lipids. Preventing lipid mobilization by the host is needed for the developing parasitoid to be able to complete its development in spring. The parasitoid fly *T. oestracea* takes a similar time to develop as *B. sericariae*; hence both parasitoid flies have optimized host use, either by increasing or conserving the lipid stores of their respective hosts.

So far, most work on host manipulation has been done on laboratory-reared hymenopteran parasitoids. Unlike the dipteran parasitoids described above, many hymenopteran parasitoids complete their development within several weeks. Major host physiological changes can already be brought about within a short timespan, including a decrease in lipid levels. There are two, not mutually exclusive, reasons why lipid levels are lower in parasitized compared to unparasitized hosts: the host is not able to develop its own fat body (Dahlman 1970) or host and parasitoid compete for lipid resources, with both species consuming and utilizing lipids.

The koinobiont parasitoid *H. exiguae* feeds mainly on lepidopteran host hemolymph (*Trichoplusia ni*) during the first 8 days of development (when the host molts into the third and fourth instar), after which the larvae exit the host to pupate externally (Thompson 1982b). Parasitized larvae had a lower total triacylglycerol content compared to unparasitized larvae near the end of parasitoid development. The reason that parasitized hosts do not get as fat as unparasitized hosts is that the parasitoid is consuming the host's fat or affecting the host's ability to feed and accumulate fat. When comparing unparasitized starved *T. ni* hosts with parasitized *T. ni* hosts, the physiological state in terms of fat content is very similar. In contrast to a starved host, however, a parasitized host still has access to food (at least in this system, where host development continues), which means that host and parasitoid are in direct competition for lipids (Dahlman and Greene 1981). Lipids of parasitized *T. ni* were, however, not depleted completely, suggesting that the parasitoid utilizes resources in such a way that the host does not die prematurely (which would also lead to death of the parasitoid). The above studies contribute to our general understanding of how lipid metabolism of the host is affected following parasitism, including the investigation of rare field-collected hosts that are typically more difficult to study (see Table 1). Experiments focusing solely on the effect of parasitism can, however, be confounded by other factors that can affect host metabolism, such as venom, teratocytes, and mutualistic viruses, which will be discussed in more detail in the following sections.

3.2 Venom-Induced Changes in Host Lipid Metabolism

All female Hymenoptera produce venom in a specialized venom-gland that is a part of the reproductive system (Pennacchio and Strand 2006; Poirié et al. 2014). The venom of parasitoids is injected into the host and consists of both proteinaceous and non-proteinacious compounds (Moreau and Asgari 2015). The venom of ecto and endoparasitoids seems to serve different functions, for the former mainly inducing host paralysis and for the latter mainly interfering with the host's immune system. For all parasitoids, nutrient acquisition during development is critical for survival, investment in costly metamorphosis, and to fuel (at least part of) adult life. In this subsection, we will focus solely on the effects of parasitoid venom on host lipid metabolism.

3.2.1 Venom-Induced Alterations in Host Lipid Metabolism

Venom generally leads to an increase in host lipid levels either in the whole body, the fat body, or the hemolymph (see Table 1). There are some exceptions, however, where host lipid levels were lower, or no changes were observed. For example, in parasitized *S. littoralis,* transmission electron microscopy revealed that the host fat body rapidly released its content (glycogen and lipids) through cell vacuolization and reabsorption (Becchimanzi et al. 2017). Lipid mobilization was aided by hemocytes surrounding the fat

body and increased cathepsin L activity. Hemolymph titers of glycerolipids decreased during 48 h after parasitization, probably because the host's tissues require fat for ongoing metabolic activities, albeit reduced. For the coleopteran *Tenebrio molitor* parasitized by the bethylid *Scleroderma sichuanensis,* fat body and hemolymph lipid content also decreased following envenomation and parasitism (Zhuo et al. 2016). This decrease could be due both to consumption of host resources by the parasitoid and the host's own requirement for lipids to stay alive. The host fat body was degraded following parasitism, but envenomation alone did not alter the appearance of the fat body. This suggests that rupture of the fat body cannot be brought about by venom alone.

Host manipulation requires fine-tuned physiological interactions between parasitoid and host that can be highly species-specific. For example, the parasitoid *N. vitripennis* is highly polyphagous, being able to parasitize more than 60 different host species (Desjardins et al. 2010). Yet, despite its wide host range, *N. vitripennis* prefers to oviposit on the fly *Sarcophaga bullata* (Desjardins et al. 2010). Rivers and Denlinger (1995) looked at the effects of parasitism by *N. vitripennis* on four distinct fly species, including *S. bullata, Phormia regina, Musca domestica,* and *Sarcodexia sternodontus.* Only in the host *S. bullata* were marked increases in both fat body and hemolymph lipids observed (Rivers and Denlinger 1995). For *P. regina* and *M. domestica* hemolymph lipids also increased following parasitism but lipid levels in the host fat body did not increase. For the host fly *S. sternodontus* both fat body and hemolymph lipids decreased. For the host *S. bullata* both envenomation and parasitism led to increased fat content, which could result from active fatty acid synthesis and fat accumulation by the host. Parasitism by the wasp *Lysiphlebus japonica* of the aphid *Aphis gossypii* led to upregulation of almost all genes in the glycerolipid pathway, including diacylglycerol acyltransferase that produces triacylglycerols from diacylglycerols, revealing that venom likely induces lipogenesis in hosts (Zhang et al. 2015).

Zooming in on the interaction between *N. vitripennis* and *S. bullata,* the elevation in host hemolymph lipids depended on the location where oviposition occurred on the host pupa. A posterior sting, where parasitism occurs under natural conditions, led to a steeper increase in lipids compared to an anterior sting (Rivers and Yoder 1996). *Nasonia vitripennis* larvae developing on posterior-oviposited hosts also contained more fat than anterior-oviposited hosts, suggesting indeed that lipid availability depends on the location of the parasitoid's sting. Elevation of host hemolymph lipids was also associated with the number of developing parasitoid larvae (Rivers and Yoder 1996). A higher number of eggs laid by the parasitoid led to a greater increase in host hemolymph lipid content. A similar finding was obtained for another gregarious parasitoid, *Trichomalopsis* near *americana* (Rivers et al. 1998). An increase in host hemolymph lipids when more eggs are laid suggests that parasitoid venom increases nutrient content of the host in such a manner that competition between multiple offspring and the host can be avoided. Resource availability is thought to be more restricted for idiobionts that arrest the host's development, where nutrients contained in the host are not altered. Overall, the body of work on *N. vitripennis* suggests that idiobiont parasitoids may not be limited in host lipid resources as substantial increases in host hemolymph and fat body lipid content is brought about by the parasitoid's venom (Rivers and Yoder 1996).

Only few researchers investigated both the composition of the venom and the effects of venom on host lipid metabolism. Wang et al. (2020b) characterized the lipases contained in *P. puparum* venom. Overall, parasitism led to a decrease of triacylglycerols and several phospholipids (e.g., sphingomyelin, phosphatidylcholine etc.) in the host fat body, whereas triacylglycerols and phospholipids increased in the hemolymph (see Table 1). The increase of triacylglycerols in the host hemolymph was concurrent with a decrease in diacylglycerols. In *P. pupurum* venom, diacylglycerol acyltransferase (DGAT2), catalyzing the last step of triacylglycerol synthesis

from diacylglycerols, is not present. The venom does, however, contain multiple lipases (some with missing catalytic triads, potentially involved in lipid binding and transport), which suggests that the host's enzymatic machinery facilitates the conversion of di- to triacylglycerols. In the fat body, increasing triacylglycerol levels were mainly observed for highly unsaturated triacylglycerols, while triacylglycerols with fewer double bonds decreased. An increase in unsaturation generally increases triacylglycerol solubility. There was, however, no difference in unsaturation levels of triacylglycerols in the hemolymph. Hence it is unclear what role the unsaturation plays in the fat body (i.e., higher solubility does not lead to increased transport and presence of unsaturated triacylglycerols in the hemolymph for use by the parasitoid larva). Desaturases were not found in the venom of *P. puparum,* but a desaturase was found to be upregulated in the venom glands (Wang et al. 2020a). It thus remains unclear whether the wasp's venom or the host is responsible for the observed changes in triacylglycerol saturation levels.

The decrease of some phospholipids in the fat body and increase in the hemolymph of the host *Pieris rapae* suggest that destruction of the fat body and fat body cell membranes ensues quickly after parasitism by *P. puparum* (Wang et al. 2020b). Parasitized hosts also had an increased cholesteryl ester content in the hemolymph, suggesting that cholesterol transport increased. Increased cholesteryl ester content was also observed in Dufour's gland (i.e., part of the anatomy of the ovipositor) suggesting that cholesteryl esters may be derived from the venom. Lipases with potential cholesteryl esterase function have been identified from the salivary glands of developing *P. puparum* larvae (Wang et al. 2020b). Cholesteryl esterase hydrolyzes cholesteryl esters to form cholesterol, which may allow the developing parasitoid to acquire essential sterols (that insects cannot synthesize). Sterols can subsequently serve important functions as hormone-precursors, signaling molecules, and components of cell membranes, and were found to increase egg viability at least in the wasp *E. vuilletti* (Mondy et al. 2006).

3.2.2 Lipid-Related Parasitoid Venom Components

Venom components related to lipid metabolism have been identified in 23 different parasitoid species (see Table 2). The function of venom enzymes regarding lipid metabolism can be divided into four different categories: lipid catabolism, transport, synthesis, and storage (see Table 2). When venom is injected, even the host's enzymes may participate in freeing lipids for the developing parasitoid(s). Cathepsin of the host *S. littoralis*, for example, contributes to degradation of the host's fat body following parasitization by *Bracon nigricans* (Becchimanzi et al. 2017). On a cellular level, phospholipases play a key role for increasing nutrient transfer from the cytosol to the hemolymph by disintegrating cells to release their content. Various phospholipases have been identified in parasitoid venom that differ in their specific site of action. Phospholipase A1, for example, disrupts phospholipid packaging of cell membranes, leading to cell lysis, while phospholipase A2 hydrolyzes glycerophospholipids in membranes to release free fatty acids and lysophospholipids (Perez-Riverol et al. 2019). Phospholipases can indeed be part of a complex pathway affecting the host's lipid metabolism. The venom of *N. vitripennis*, for example, modifies cell membrane permeability leading to an influx of Na^+ in the cell (Danneels et al. 2010; Rivers et al. 2002). An increase in Na^+ can subsequently activate phospholipase C, leading to an increase in inositol-3-phosphate (a signaling molecule) and the release of Ca^{2+} from the mitochondrion. Calcium in turn activates phospholipase A2, stimulating fatty acid synthesis (Rivers et al. 2002). Within parasitoid venom, phospholipases thus play an important role in making lipids available for parasitoid offspring (see Table 2).

Once lipids are released from the fat body, lipids need to be transported to the developing parasitoid through the hemolymph. Several hemolymph transport enzymes are contained within the venom, including apolipophorin (e.g., Liu et al. 2018; Scieuzo et al. 2021; see Table 2). In addition to this more typical enzyme involved

Table 2 Overview of genes and/or enzymes involved in lipid metabolism found in the venom of different parasitoid species. We did not distinguish between different homologs or orthologs. For each enzyme, a potential function is indicated based on functional studies in animals, including humans

Enzyme	Function	Species		
Lipid catabolism				
Carboxylesterase	Degradation of triacylglycerols, mainly long-chain triacylglycerols (Deng et al. 2021)	*Anisopteromalus calandrae*[1]	*Microplitis mediator*[13]	*Torymus sinensis*[24]
		Bracon nigricans[4]	*Ooencyrtus telenomicida*[16]	
		Hyposoter didymator[9]	*Psyttalia lounsburyi*[19]	
Cathepsin (D, L, J)	Digestive enzymes (e.g. degradation of the fat body) (Becchimanzi et al. 2017; Cristofoletti et al. 2003; Yang et al. 2020)	*B. nigricans*[3]	*Microctonus hyperodae*[12]	*Toxoneuron nigriceps*[25]
		Leptopilina heterotoma[11]	*M. mediator*[13]	*T. sinensis*[24]
		Microctonus aethiopoides[12]	*O. telenomicida*[16]	
Enolase	Mediates host tisue degradation (Falabella et al. 2009; Grossi et al. 2016)	*M. mediator*[13]	*Psyttalia concolor*[19]	*Tetrastichus brontispae*[23]
		O. telenomicida[16]	*P. lounsburyi*[19]	*T. nigriceps*[25]
Enoyl-CoA hydratase	Metabolizing fatty acids in beta-oxidation to produce both acetyl-CoA and ATP	*B. nigricans*[4]	*O. telenomicida*[16]	
Fatty acid binding protein	Fatty acid import, storage, and export (also cholesterol and phospholipids) (Furuhashi and Hotamisligil 2008)	*Diversinervus elegans*[7]	*M. mediator*[13]	
Lipase (3, A, H)	Digestion, transport, processing of dietary lipids (Wang et al. 2020b)	*B. nigricans*[4]	*O. telenomicida*[16]	*Pteromalus puparum*[22]
		Chelonus inanitus[5]	*M. aethiopoides*[12]	*P. lounsburyi*[19]
		Leptopilina boulardi[10]	*M. hyperodae*[12]	*T. sinensis*[24]
		L. heterotoma[11]	*Nasonia vitripennis*[14-15]	
		M. mediator[13]	*Pimpla hypochondriaca*[17]	
Low-density lipoprotein receptor	Low-density lipoprotein, mediating endocytosis of vitellogenin and lipophorin	*Aphidius ervi*[2]	*N. vitripennis*[14-15]	*P. puparum*[22]
		M. mediator[13]	*O. telenomicida*[16]	*T. sinensis*[24]
Low-density lipoprotein receptor-like venom protein	Central role in cholesterol and other lipoprotein metabolism (Scieuzo et al. 2021)	*A. calandrae*[1]	*N. vitripennis*[14-15]	*O. telenomicida*[16]
Phospholipase (A1, A2, B, C)	Hydrolyses phospholipid substrates at specific ester bonds (Richmond and Smith 2011)	*B. nigricans*[4]	*L. heterotoma*[11]	*P. concolor*[19]
		Cotesia chilonis[6]	*M. mediator*[13]	*P. lounsburyi*[19]
		Eupelmus orientalis[8]	*O. telenomicida*[16]	*T. nigriceps*[25]
		D. elegans[7]	*Pimpla turionellae*[17]	

(continued)

Table 2 (continued)

Enzyme	Function	Species		
Vitellogenin receptor	Low-density lipoprotein receptor that transports lipids into a recipient cell	*M. aethiopoides*[12]	*O. telenomicida*[16]	
Lipid transport (in the hemolymph)				
Annexin	Ca^{2+}-dependent lipid binding protein that could be involved in membrane transport processes	*L. heterotoma*[11]	*O. telenomicida*[16]	
		M. mediator[13]	*P. concolor*[19]	
Apolipophorin	Hemolymph lipid transport (Weers and Ryan 2006)	*B. nigricans*[4]	*O. telenomicida*[16]	*T. sinensis*[24]
		D. elegans[7]	*M. mediator*[13]	
		L. heterotoma[10]	*T. brontispae*[23]	
Apolipoprotein D-like	Lipid transport processes in the insect hemolymph (Scieuzo et al. 2021)	*M. mediator*[13]	*O. telenomicida*[16]	*T. sinensis*[24]
Calreticulin	Chaperoning and regulation of Ca^{2+} homeostasis in the endoplasmic reticulum lumen	*A. calandrae*[1]	*M. mediator*[13]	
		C. chilonis[6]	*N. vitripennis*[14-15]	*P. lounsburyi*[19]
		H. didymator[9]	*O. telenomicida*[16]	*T. brontispae*[23]
		M. hyperodae[12]	*P. puparum*[20,22]	*T. sinensis*[24]
		M. aethiopoides[12]	*P. concolor*[19]	*T. nigriceps*[25]
Odorant binding protein	Solubilizing and carrying free fatty acids released by lipases (Ishida et al. 2013; Pelosi et al. 2018)	*A. calandrae*[1]	*M. mediator*[13]	*T. brontispae*[23]
		B. nigricans[4]	*N. vitripennis*[14-15]	*T. sinensis*[24]
		C. inanitus[5]	*O. telenomicida*[16]	
		L. heterotoma[11]	*P. puparum*[21-22]	
Lipid synthesis				
3-oxoacyl-ACP reductase	Fatty acid synthesis and polyunsaturated fatty acid synthesis	*B. nigricans*[4]		
Fatty acid synthase	Catalyzing the de novo synthesis of fatty acids	*A. ervi*[2]	*M. mediator*[13]	*T. brontispae*[23]
		D. elegans[7]	*O. telenomicida*[16]	
n-acetyllactosaminide beta-n-acetylglucosaminyltransferase	Glycosphingolipid synthesis	*L. heterotoma*[11]	*O. telenomicida*[16]	*T. nigriceps*[25]
Phosphatidate phosphatase	Conversion of phosphatidate to diacylglycerols	*D. elegans*[7]	*O. telenomicida*[16]	*T. brontispae*[23]
Lipid storage				
Adipocyte plasma membrane-associated protein-like	Maturation of adipocytes and their capacity to store lipids (Sarjeant and Stephens 2012)	*O. telenomicida*[15]	*T. sinensis*[24]	
Insulin-like growth factor-binding protein	Regulation of lipid metabolism, lipid accumulation, adipocyte differentiation (Pan et al. 2021; Baxter 2023; Kim 2013)	*L. heterotoma*[10]	*O. telenomicida*[16]	
		M. mediator[12]	*T. sinensis*[24]	

(continued)

Table 2 (continued)

Enzyme	Function	Species		
Regucalcin	Ca^{2+} signaling, lipid accumulation in adipocytes (Doğan et al. 2021)	*B. nigricans*[3]	*M. mediator*[13]	*O. telenomicida*[16]

[1]Perkin et al. (2015), [2]Colinet et al. (2014), [3]Becchimanzi et al. (2017), [4]Becchimanzi et al. (2020), [5]Vincent et al. (2010), [6]Teng et al. (2017), [7]Liu et al. (2017), [8]Doury et al. (1997), [9]Dorémus et al. (2013), [10]Colinet et al. (2013), [11]Heavner et al. (2013), [12]Crawford et al. (2008), [13]Lin et al. (2019), [14]de Graaf et al. (2010), [15]Sim and Wheeler (2016), [16]Cusumano et al. (2018), [17]Dani et al. (2005), [18]Uçkan et al. (2006), [19]Mathé-Hubert et al. (2016), [20]Zhu et al. (2010), [21]Wang et al. (2015), [22]Yan et al. (2016), [23]Liu et al. (2018), [24]Scieuzo et al. (2021), [25]Laurino et al. (2016)

in lipid transport, there have been several reports of odorant binding proteins being part of the parasitoid venom (e.g., in *N. vitripennis, P. puparum*, and 8 other species; see Table 2). Most volatiles are lipophilic, and odorant-binding proteins typically serve for the transport of odorant molecules (e.g., pheromones) to olfactory receptors. In the parasitoid venom, odorant binding proteins are hypothesized to play a role as fatty acid and fatty acid ester carriers, as was found in several other insects (e.g., the ant *Camponotus japonicus*; Ishida et al. 2013; the blowfly *P. regina*; González et al. 2009). Existing odorant binding proteins thus seem to have acquired new functions.

The venom of some parasitoid species also contains enzymes that are involved in lipid synthesis, including fatty acids, glycosphingolipids, and diacylglycerols (e.g., Colinet et al. 2014; Heavner et al. 2013; see Table 2). So far, no clear explanation has been proposed as to why the venom would contain enzymes involved in lipogenesis. When hosts are lipid-poor, there could be an advantage for the parasitoid to increase the host's lipogenesis by injecting enzymes involved in lipid synthesis contained in the venom. The aphid *Acyrtosiphon pisum* and the scale insect *Parasaissetia nigra,* for example, are plant sap-sucking insects, a nutritional resource that is expected to contain substantial carbohydrate resources, but not many lipids. Lipid synthesis enzymes present in the venom can then utilize precursors, such as carbohydrates, from the host to increase lipid content and availability. The presence of fatty acid and diacylglycerol synthesizing enzymes in the parasitoid venom may aid the developing parasitoid in obtaining sufficient lipids to complete development and fuel adult life.

Three enzymes implicated in host adipocyte maturation and/or lipid storage were found in the venom of several parasitoid species (e.g., Scieuzo et al. 2021; Sim and Wheeler 2016; see Table 2). At the time of oviposition, the parasitoid is still in the egg or early larval stage, a time at which absorption of nutrients may be relatively little (compared to later developmental stages). For example, during the early stages of parasitism, the braconids *Aphidius ervi* and *Toxoneuron nigriceps* absorb nutrients through the epidermis (Caccia et al. 2005; Grimaldi et al. 2006). In parasitoid offspring in general, some time may be needed to develop a fully functioning gut and absorption of nutrients through the epidermis or the anal vesicle in early larval stages may be more common (Edson and Vinson 1977). Storage of large fat reserves by the parasitoids is also expected to take some time, with fat droplets becoming clearly visible only during later larval instars (e.g., in *E. vuilletti* and *Gelis* sp., Pers. Obs.). When fat precursors accumulate in the hemolymph of the host, initial fat storage in host adipocytes can provide a reserve to be consumed by the developing parasitoid at a later time. Increased fat storage in the preferred host *S. bullata* was indeed found following parasitism by *N. vitripennis* (Rivers and Denlinger 1994, 1995). Parasitoid venom thus contains many enzymes involved in releasing, transporting, synthesizing, and storing fat by the host. What is

still mostly lacking are studies identifying the specific functional role of identified venom components on host lipid metabolism.

3.3 Polydnaviruses Increase Host Lipid Availability for the Developing Parasitoid

Polydnaviruses are viruses associated with endoparasitoid wasps (i.e., the primary hosts), persisting as proviruses (i.e., DNA sequences integrated in the host genome) in every germ and somatic cell of the wasp. The proviral genome is composed of both core genes necessary for viral replication and virulence genes that, after amplification and excision from the wasp's genome, form viral particules (i.e., virions). Viral replication occurs only in calyx cells (that are part of the wasp's reproductive tract) during the parasitoid pupal and adult stage. The polydnavirus life cycle starts with virions that are first released from calyx cells to accumulate in the lumen of the parasitoid's reproductive tract where eggs are stored. Eggs, containing both the proviral genome and virions, are then laid by the parasitoid in the host during oviposition along with parasitoid venom (Strand and Burke 2013). After virion injection, the virus integrates into the host genome via a second domain present on the viral DNA termed the host integration motif. Virulence genes are then transcribed in host cells until wasp development is completed and the adult parasitoid has emerged from the host (see Fig. 1 from Strand and Burke 2012).

Polydnaviruses can be grouped into two distinct genera: Bracoviruses, associated with the braconid family, and Ichnoviruses, associated with the ichneumonid family (Strand and Burke 2013). Braco- and Ichnoviruses each have a distinct morphology of the virion (that enters the secondary host, which is the host of the parasitoid) and an independent evolutionary origin (Strand and Burke 2012). The virus participates in the parasitization process, affecting the host's immune system (i.e., to prevent the host from killing the wasp's offspring), host growth, and metabolism (Strand and Burke 2013). During parasitoid oviposition, the bracovirus of the wasp *T. nigriceps*, for example, releases several viral protein tyrosine phosphatases in the host *Heliothis virescens's* body that disrupt the prothoracic gland function of the host and inhibits host metamorphosis (Falabella et al. 2006; but see also Strand and Burke 2015 for other examples). The following subsection focuses on the effects polydnaviruses have on (secondary) host lipid metabolism.

The braconid *Chelonus inanitus* is an endoparasitoid that injects both venom and a bracovirus along with the egg. Kaeslin et al. (2005) disentangled the role of the *C. inanitus* venom, bracovirus, and developing parasitoid on the fat body of the host *S. littoralis*. Separating the effects of venom and bracovirus from developing parasitoids is possible when comparing parasitized hosts with unparasitized hosts, but also using pseudoparasitized hosts, where the eggs within the mother are killed using x-rays prior to oviposition. Pseudoparasitized hosts thus receive the venom and the bracovirus, but the parasitoid larva does not hatch. Venom proteins disappear within 1-2 days after parasitization, while the polydnavirus remains throughout parasitoid development. The parasitoid larva, along with polydnavirus, and potential early effects of venom cause an accumulation of whole-body lipids during development (see Table 1). During the last host larval instar, lipid content was significantly higher in parasitized hosts than in unparasitized larvae, meaning that the parasitoid larva itself also plays a major role in increasing host fat accumulation.

In a recent study, Wang et al. (2021) determined which *C. vestalis* parasitoid-associated factor led to the decrease of lipid levels in the host moth *P. xylostella. Cotesia vestalis* injects venom and bracoviruses and forms teratocytes derived from the embryonic membrane. Wang et al. (2021) used both parasitized and pseudoparasitized *P. xylostella* hosts, thereby removing the effect of teratocytes (as teratocytes are derived from developing parasitoid offspring) and the developing parasitoid. Following parasitization and pseudoparasitization, host whole-body triacylglycerol levels decreased, as did hemolymph fat levels.

Injection of venom alone did not result in any changes; yet a similar reduction in lipids was observed when only the bracovirus was injected. The reduction in host lipids can be due to alterations in lipid absorption and synthesis. Parasitized *P. xylostella* indeed showed reduced formation of neutral lipid droplets in the gut, suggesting that changes in host lipid absorption and synthesis underlie the decrease in whole-body lipids. Transcriptomics further led to the identification of several bracovirus genes that could be involved in manipulating host lipid metabolism (Wang et al. 2021). Expression of one of these genes, *CvBV 9-2*, was indeed found to be responsible for reducing triacylglycerol levels in parasitized larvae by increasing the expression of a tachykinin gene (*PxTk*) in the host gut, suppressing lipogenesis.

3.4 Parasitoid-Derived Teratocytes Increase Fat Availability for the Parasitoid

Teratocytes are specialized cells derived from the dissociation of the cellular membrane surrounding the parasitoid embryo during its development that are released in the host's hemolymph during parasitoid hatching (Strand 2014). Teratocytes are produced by some subfamilies within Braconidae (i.e., Microgastrinae, Meteorinae, Euphorinae, Aphidiinae) and Platygastridae (i.e., Scelioninae, Telenominae, Teleasinae), all of which are endoparasitoids (Dahlman 1990; Strand 2014). Teratocyte-like cells have also been reported in the Ichneumonidae (Rouleux-Bonnin et al. 1999) and Chalcidoidea (Pedata et al. 2003; Strand 1986). The number of teratocytes in parasitoids is species-specific, and can range from 10 (e.g., *Telenomus heliothidis*, Platygastridae; Strand et al. 1988) to more than 1,000 (e.g., *M. pulchricornis*, Braconidae; Suzuki and Tanaka 2007) (Strand 2014). Teratocytes help to disrupt host growth, inhibit host metamorphosis, and also seem to play a role in evading the host's immune system (Ali et al. 2013; Dahlman et al. 2003; Strand 2014). Teratocytes further aid in nutrient acquisition for the developing parasitoid(s), particularly lipids (Falabella et al. 2000, 2005; Nakamatsu et al. 2002; Qin et al. 2000; Suzuki and Tanaka 2007).

Ultrastructure studies revealed that once released in the host's hemolymph, teratocytes show both morphological and metabolic changes (Pennacchio et al. 1994; Strand et al. 1986; Volkoff and Colazza 1992; Zhang et al. 1994), e.g., teratocyte size greatly increases (de Buron and Beckage 1997; Strand and Wong 1991; Volkoff and Colazza 1992). To promote nutrient exchange between the teratocyte's intracellular and extracellular space, teratocytes exhibit long microvilli on their surface (to increase the surface for absorption/secretion), as well as large exosome-like spherical vesicles (containing lipids and other nutrients; Hotta et al. 2001; Salvia et al. 2019; Shelby et al. 2014; Sluss 1968). An abundant rough endoplasmic reticulum, numerous mitochondria, and an extensive vacuolization are observed in the teratocyte cytoplasm (de Buron and Beckage 1997; Gerling and Orion 1973; Sluss 1968; Volkoff and Colazza 1992). Teratocytes further do not divide after being released, but often become highly polyploid associated with an increase of the nuclear area. This polyploidization seems to stimulate the synthesis of proteins of the teratocytes (Gerling and Orion 1973; Hotta et al. 2001; Strand and Wong 1991). In the insect fat body, DNA polyploidy caused by juvenile hormone stimulation was indeed found to increase the transcription of vitellogenin (Dittmann et al. 1989; Nair et al. 1981; Hotta et al. 2001). These characteristics show that teratocytes are specialized cells, able to metabolically interact with other close cells (Dahlman and Bradleigh Vinson 1993; Salvia et al. 2019; Sluss 1968).

Teratocytes supply nutrients to the developing parasitoid by digesting the host's fat body during early parasitoid larval stages when mouth parts are not yet formed. In the host-parasitoid system *Pseudaletia separata-Cotesia kariyai*, triacylglycerol levels of the host fat body decreased 6 days after parasitism but increased in the parasitoid's second instar larva from the 7th day (Nakamatsu et al. 2002). The increased lipase activity in the gut parasitoid larva, as well as the

presence of lipid granules in the parasitoid midgut, confirmed the ingestion of host lipids by the parasitoid (Nakamatsu et al. 2002). Interestingly, teratocytes were attached to the host fat body and locally released collagenases (i.e., enzymes that break down the collagen sheath surrounding the host's fat body) to disrupt the host fat body matrix and release fat body cells (Nakamatsu et al. 2002). Teratocytes of other parasitoid species, such as the braconids *Microplitis mediator* or *Microplitis pulchricornis*, seem to play a similar role in disrupting and digesting the host fat body to secure parasitoid survival and development (Qin et al. 2000; Suzuki and Tanaka 2007).

Teratocytes release several other enzymes that can enhance host fat body digestion until complete consumption by the parasitoid larva: a teratocyte-specific carboxylesterase, assumed to be involved in the hydrolysis of host lipids (*Dinocampus coccinellae*; Gopalapillai et al. 2005), enolases and lipases (*A. ervi*, *Microplitis demolitor, D. coccinellae*; Burke and Strand 2014; Falabella et al. 2009; Kadono-Okuda et al. 1998), as well as cathepsin (Burke and Strand 2014). These lipid-catabolic enzymes have also been found in the venom of some parasitoid species (e.g., Dorémus et al. 2013; Perkin et al. 2015; see Table 2). In the parasitoid *T. nigriceps*, teratocytes produced a chitinase during the last larval stage of the parasitoid. This chitinase was hypothesized to be part of the enzymes that help the parasitoid larva's egression by breaking down the host cuticle (Cônsoli et al. 2005).

In addition to fat body disruption, teratocytes also facilitate the transport of lipids from the host hemolymph to the developing larvae. For example, teratocytes of *A. ervi* produce an extracellular fatty acid binding protein that transports fatty acids in the host's hemolymph (Falabella et al. 2000, 2005; Pennacchio et al. 1999). This protein showed a high affinity for C14-C18 saturated fatty acids, oleic acid (C18:1), and a longer chain polyunsaturated fatty acid (arachidonic acid; C20:4) (Falabella et al. 2005). Immunolocalization revealed that the fatty acid binding protein was distributed around lipid particles abundantly present in the hemolymph of the parasitized host, but also in the external epidermal layer and the midgut lumen of parasitoid larvae (Caccia et al. 2012; Falabella et al. 2005). Altogether these findings suggest that (1) fatty acids can be absorbed by the epidermal epithelium of the developing parasitoid, as had previously been found for amino acids and sugars (Caccia et al. 2012) and (2) fatty acid binding protein transports key fatty acids in the host hemolymph to the growing parasitoid larva, which can subsequently be absorbed by the parasitoid and stored as triacylglycerols (Caccia et al. 2012). Similar lipid transport proteins were found in parasitoid venom, such as annexin, apolipophorins, and calreticulin (Crawford et al. 2008; Lin et al. 2019; see Table 2) (Burke and Strand 2014).

A decrease in teratocyte number during later stages of parasitoid development has been observed in several parasitoid species (de Buron and Beckage 1997; Gopalapillai et al. 2005; Kadono-Okuda et al. 1995; Suzuki and Tanaka 2007; Volkoff and Colazza 1992). The number of teratocytes decreases due to the teratocyte undergoing programmed cell death, as evidenced by the appearance of multiple bleb structures (i.e., teratocyte anatomical deformations resulting from the enlargement or coalescence of microvilli; de Buron and Beckage 1997; Zhang et al. 1994) on the teratocycte membrane (de Buron and Beckage 1997; Hotta et al. 2001). Another factor contributing to the declining teratocyte numbers late in parasitoid development is that teratocytes are progressively consumed by the parasitoid larva (e) (Kadono-Okuda et al. 1995; Strand and Wong 1991). Teratocytes produce proteins that can be released in the host's hemolymph for disrupting the host fat body but can also store a high abundance of proteins (e.g., glycoproteins, vitellogenin, amino-acids) as well as lipids (i.e., lipid droplet) that can constitute an additional source of nutrients for successful parasitoid development (de Buron and Beckage 1997; Gopalapillai et al. 2005; Kadono-Okuda et al. 1998; Okuda and Kadono-Okuda 1995). On the contrary, no decrease in teratocyte number was observed during later stages of parasitism of other parasitoids, such as *C. kariyai*, suggesting that the teratocytes are not consumed immediately by the parasitoid and may have another potential role in host regulation or

parasitoid development at a later stage (Hotta et al. 2001; Suzuki and Tanaka 2007). Teratocytes produced by some parasitoid wasps are important specialized cells that use a variety of enzymes to disrupt the host's fat body. The release of host fat cells transported from the host to the parasitoid aids parasitoid development and survival.

4 Conclusions and Future Perspectives

Parasitoids are fascinating creatures, particularly regarding lipid metabolism. Parasitoid larvae can mimic the fatty acid composition of the host, because there is little to no de novo triacylglycerol synthesis. The adults of many parasitoid species do not accumulate fat at all, except for some polyphagous species that typically develop on fat-poor hosts. More studies are now needed to determine how host fatty acid composition, host breadth, and the ability to synthesize triacylglycerols are related in parasitoids. Such an endeavor should start with a replication of the work of Barlow and Jones (1981), and Jones et al. (1982), in larvae and adult parasitoids, using tracers to identify if and when the Kennedy pathway for de novo synthesis of triacylglycerols is activated or not. The number of host species a parasitoid can parasitize was found to play a role, where typically specialists mimic the host fatty acid composition, while generalists do not. Generalists were also found to accumulate fat in more recent studies (Visser et al. 2010). To test how host breadth and host fatty acid composition affect parasitoid fatty acid synthesis and fat accumulation, a comparative approach using specialists and generalists developing on the same hosts could be used. For example, the parasitoid guild associated with *Drosophila* contains both specialists and generalists developing on distinct hosts, including *D. melanogaster* and *D. simulans.* Another interesting system to use is the *Nasonia* species complex, with *N. vitripennis* being an extreme generalist (but preferring and manipulating lipid synthesis only of *S. bullata*), and *Nasonia giraulti* and *Nasonia longicornis* that are restricted to hosts in the genera *Protocalliphora* and *Sarcophaga.*

More recently, fatty acid synthesis and fat accumulation were found to vary in response to the fat content of the host and is thus plastic, in the wasp *L. heterotoma*. Plasticity of fatty acid synthesis and fat accumulation may be more common, also in other parasitoid species, but this remains to be explicitly tested on a large scale. More information about genotype-level responses to host fat content in diverse parasitoid species allows to make inferences about the evolution of plasticity and potential consequences for life histories. The latter is particularly relevant for species that are used as important natural enemies in agro-ecosystems. The finding that fat synthesis is plastic can lead to many other interesting avenues for future research. For example, gaining a deeper understanding of the ecological conditions favoring or selecting against more or less plastic phenotypes in natural populations in insects in general. We can further continue to dig into the mechanisms underlying fatty acid synthesis and fat accumulation (and the lack thereof) by experimentally manipulating parasitoid phenotypes (e.g., by changing host fat content; Enriquez et al. 2022). Several other research directions focus on parasitoid lipids, including symbiotic interactions with bacteria, such as *Wolbachia*, as well as the use of parasitoids as a model resisting obesity (being able to switch fat synthesis off when being fat and continuing to feed, as highlighted by Visser et al. 2023). The plethora of future research lines shows that, despite the considerable research effort into parasitoid lipid metabolism since the 1960s, there is still a great diversity of research opportunities that can and hopefully will be pursued.

Parasitoids are masters in host manipulation with the sheer number of mechanisms by which host lipid metabolism can be affected as proof. The diversity of parasitoids and thus host manipulation strategies may seem daunting to try and elucidate because most responses are host and parasitoid-species specific. Using hosts and parasitoids that share an evolutionary history is, therefore, essential to further our understanding of host manipulation in a biologically meaningful way. *Pteromalus puparum* is one of the few species with which complementary studies have been performed to understand the entire process of host

manipulation, from physiology to genes and gene diversification (Wang et al. 2020b, 2021). Extending such thorough investigation to other systems (i.e., hemolymph-feeders, koinobionts), also in a comparative context, will certainly enrich our understanding of host manipulation (see Sect. 3). There is also much to learn from parasitoid host manipulation strategies, even for our own benefit. For example, some venom components can be used in biological control of insect pests (Danneels et al. 2010; Moreau and Asgari 2015). Virulence factors associated with teratocytes and polydnaviruses have also been proposed for use in transgenic plants, where virulence genes involved in manipulation of the host are integrated in the plant genome to increase plant resistance to pest attack (Merlin et al. 2021; Kim et al. 2016). Parasitoid venom components were suggested as potential pharmaceuticals against allergies, blood clotting, and as an antibiotic against microbial infections (Moreau and Asgari 2015). Parasitoids can thus inspire the development of new technologies, perhaps even beyond insect pest control.

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