

Thematic Review Series: Lipid Droplet Synthesis and Metabolism: from Yeast to Man

Lipid droplet-based storage fat metabolism in *Drosophila*

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Abstract The fruit fly *Drosophila melanogaster* is an emerging model system in lipid metabolism research. Lipid droplets are omnipresent and dynamically regulated organelles found in various cell types throughout the complex life cycle of this insect. The vital importance of lipid droplets as energy resources and storage compartments for lipoanabolic components has recently attracted research attention to the basic enzymatic machinery, which controls the delicate balance between triacylglycerol deposition and mobilization in flies. This review aims to present current insights in experimentally supported and inferred biological functions of lipogenic and lipolytic enzymes as well as regulatory proteins, which control the lipid droplet-based storage fat turnover in *Drosophila*.—Kühnlein, R. P. Lipid droplet-based storage fat metabolism in *Drosophila*. *J. Lipid Res.* 2012. 53: 1430–1436.

Supplementary key words lipolysis • triacylglycerol • synthesis

LIPID DROPLET TURNOVER DURING *DROSOPHILA* DEVELOPMENT

The fruit fly *Drosophila melanogaster* has become increasingly valued as a model organism in lipid metabolism studies (reviewed in Refs. 1–4). In this context, the lipid droplets (LD) of the fly have recently attracted significant research interest, which is echoed by current reviews on this topic (5–7).

Lipid droplets are present at all developmental stages of *Drosophila*. As in higher organisms, triacylglycerols (TG) represent the major storage lipids of LDs in the fly (8). *Drosophila* development is characterized by alternating TG synthesis and mobilization phases, which cause, for example, a dramatic increase of body fat content during larval development followed by a 3-fold reduction during metamorphosis (9). During oogenesis, fruit fly mothers synthesize numerous LDs in the so-called nurse cells of the egg

chambers. These LDs are eventually transferred to the oocyte to provide energy and membrane building blocks for the developing embryo. Understorage of the maternally provided lipids or an impairment of lipid mobilization causes developmental arrest and death of the embryo (10, 11). The small LDs of early embryos undergo a complex and tightly regulated migration pattern of currently unknown function (reviewed in Ref. 12). At this stage, the LD surface serves as a transient storage compartment for histones, which become integrated in the nuclear DNA during the rapid first mitotic cycles during fly embryogenesis (13). Oleic acid-fed cell lines derived from *Drosophila* embryos have been successfully employed in genome-wide RNAi-based screens for LD phenotypes (14, 15). After embryogenesis, the three larval stages are mainly dedicated to feeding and accumulation of body mass. During larval development, *Drosophila* accumulates large amounts of storage lipids in an organ called the fat body, which corresponds to adipose tissue and possesses some liver-like functions in the fly. Fat body cells contain numerous, variably sized LDs, which represent the calorically most important energy store of the developing organism. Next to the LDs of fat body cells, which can reach tens of micrometers in diameter, a number of other tissues or organs display smaller-sized LDs during the larval stages (reviewed in Ref. 6). Examples are particular regions of the *Drosophila* gut, the hindgut musculature, and the Malpighian tubules, which perform a kidney-like function in the fly. Notably, LDs are also present in larval imaginal disc cells, which give rise to adult body structures, such as eyes, legs, and wings after metamorphosis. During pupal development, the body plan of the fly is fundamentally restructured, and this is accompanied by the breakdown and histolysis of many

Abbreviations: AGPAT, 1-acyl-sn-glycerol-3-phosphate *O*-acyltransferase; CNS, central nervous system; DG, diacylglycerol; DGAT, diacylglycerol *O*-acyltransferase; G-3-P, glycerol-3-phosphate; GPAT, glycerol-3-phosphate acyltransferase; LD, lipid droplet; LPA, lysophosphatidic acid; MGAT, monoacylglycerol *O*-acyltransferase; PA, phosphatidic acid; PL, phospholipid; TG, triacylglycerol.

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tissues. As a result of the proliferation and differentiation of imaginal cells, adult counterparts subsequently replace the larval tissues. In the course of metamorphosis, the larval fat body disintegrates, and the cells are cleared from the adult organism during the first few days of imaginal life (16). From this time onwards, the vast majority of LDs are stored in the adult fat body and are subject to TG accumulation and mobilization in response to the discontinuous feeding behavior of the imaginal fly. However, similar to the larval stages, some other organs of the adult fruit fly, such as the midgut, also harbor LDs.

Given the omnipresence of LDs during the *Drosophila* life cycle and their evolutionarily conserved function as energy storage compartments, it is surprising that the basic enzymatic machinery, which controls the turnover of LD-based TGs, has only recently attracted research interest. This review aims to give an overview of both the experimentally supported and inferred TG biosynthesis and mobilization pathways associated with LD accumulation and depletion in the fruit fly.

TRIACYLGLYCEROL BIOSYNTHESIS

The main route of storage fat formation follows the glycerol phosphate pathway or Kennedy pathway of TG synthesis (Fig. 1). In a chain of four enzymatic steps, TG is synthesized from glycerol-3-phosphate (G-3-P) via lysophosphatidic acid (LPA), phosphatidic acid (PA), and diacylglycerol (DG) as reaction intermediates. Three out of these four reactions are catalyzed by acyl transferases using fatty acid CoA (FA-CoA) as donor groups.

The initial and first committed step in TG synthesis is the acylation of G-3-P to LPA catalyzed by glycerol-3-phosphate acyltransferases (GPAT; reviewed in Refs. 17, 18). The *Drosophila* genome encodes CG5508, the single

homolog of mammalian mitochondrial (m)GPATs, GPAT1 and GPAT2. CG5508 is highly expressed throughout *Drosophila* development (19). In the adult fly, the CG5508 gene expression is particularly enriched in the central organs of lipid metabolism, such as the fat body, parts of the gut, and the heart (20). The gene is transcriptionally upregulated in fly heads in response to starvation (21) and downregulated upon bacterial infection, which causes metabolic wasting of energy stores in flies (22). Overexpression of CG5508 causes ectopic LD accumulation in larval salivary glands (23), which is consistent with a central and possibly rate-limiting role of CG5508 in fly TG synthesis. However, currently there is neither phenotypic information on CG5508 mutant flies nor published biochemical data that characterize the encoded putative fly mGPAT.

In addition to CG5508, *Drosophila* encodes two functionally uncharacterized genes, which are sequence-related to the mammalian endoplasmic reticulum-localized GPAT3 and GPAT4. Although CG3209 is ubiquitously expressed, the CG15450 gene is testis-specific (20). Taken together, the biological functions of the three putative fly GPATs are largely unexplored. In particular, the contribution of these enzymes to the total GPAT activity in *Drosophila* deserves future research attention.

The second step of TG synthesis is the acylation of LPA to generate PA catalyzed by 1-acyl-sn-glycerol-3-phosphate *O*-acyltransferases (AGPAT; reviewed in Ref. 24). The *Drosophila* genome encodes two homologs of the mammalian AGPAT1 and AGPAT2 genes called CG3812 and *fu12* (sequence identities between fly and mouse proteins 28–44%). These genes have not yet been studied by in vivo mutational analysis nor are the encoded enzymes biochemically characterized. However, moderate to high *fu12* gene expression in the fat body and midgut (20) predicts the involvement of the gene in the bulk TG synthesis of fat storing

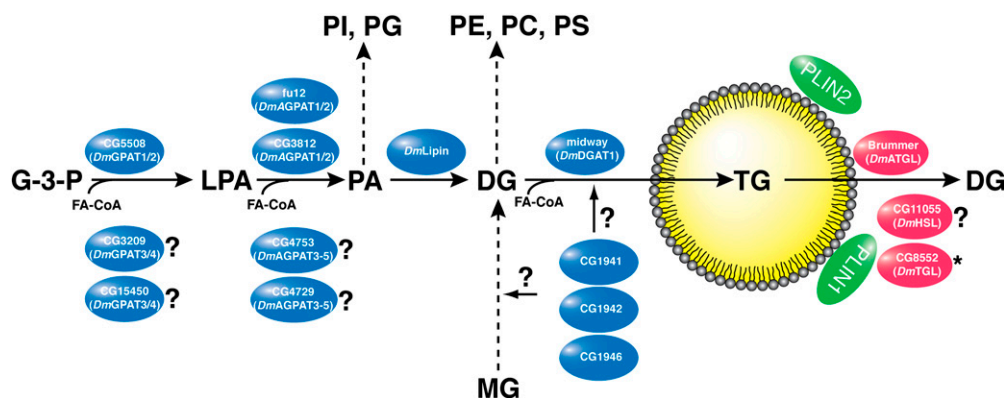


Fig. 1. Experimentally supported and inferred factors of *Drosophila* triacylglycerol synthesis and mobilization at lipid storage droplets. Represented are lipogenic enzymes of the glycerol-3-phosphate pathway (blue), lipases (red), and modulatory LD-associated proteins of the Perilipin family (green). The predicted function of proteins marked by a question mark (?) is largely based on sequence homology to functionally characterized mammalian relatives. Note that sequence similarity does not necessarily justify evolutionary orthology. An asterisk (*) indicates that in vitro evidence supports the involvement of the *Manduca sexta* CG8552 ortholog *M*sTGL in storage fat mobilization from LDs. For more details on all aspects of the pathways see text. ATGL: adipose triglyceride lipase; FA-CoA: fatty acid CoA ester; HSL: hormone sensitive lipase; MG: monoacylglycerol; PC: phosphatidylcholine; PE: phosphatidylethanolamine; PG: phosphatidylglycerol; PI: phosphatidylinositol; PLIN1, 2: Perilipin1, 2; PS: phosphatidylserine; TGL: triglyceride lipase.

tissues in flies. In contrast, the postembryonic expression of *CG3812* is largely restricted to the nervous system, the testis, and particularly, the ovaries (20). The latter expression suggests a function of the gene in lipid loading of the fly egg. Next to these putative fly AGPAT genes, the *Drosophila* genome encodes *CG4753* and *CG4729*, which are two proteins with high sequence-similarity to mammalian AGPAT3 and AGPAT4 (sequence identity between fly and mouse proteins 36–40%). Both of the corresponding fly genes are highly expressed in lipid storage organs, such as the fat body and the gut (20, 25), and transcriptionally downregulated during the global catabolic response to mycobacterial infection (22). Moreover, *CG4729* is transcriptionally repressed upon starvation (10). Although the transcriptional profiles and the gene regulation patterns of *CG4753* and *CG4729* are in agreement with a lipogenic function of the proteins, their possible contribution to AGPAT activity in the fly remains to be shown.

In the third step of TG synthesis, PA is the substrate for DG formation by Mg^{2+} -dependent PA phosphatases (PAP1 activity), which are encoded by three lipin genes in mammals (reviewed in Refs. 24, 26–28). *Drosophila* encodes a single lipin homolog called *Dmlipin* (*CG8709*). To date, the PA phosphatase activity of *DmLipin* has not been confirmed biochemically, and the contribution of *DmLipin* to the total PAP1 activity in *Drosophila* is unknown. However, *Dmlipin* encodes the N- and C-terminal lipin domain signatures (NLIPN and CLIPN), including the haloacid dehalogenase motif DXDXT, which is characteristic for Mg^{2+} -dependent phosphatases (29, 30). Consistent with a lipogenic function of fly *Lipin*, the gene is essential for adipose tissue development, TG storage, and control of LD size in *Drosophila* larvae (31). Fat body cells of hypomorphic *Dmlipin* mutants are increased in size and show ultrastructural defects in various cellular organelles, such as mitochondria, autophagosomes, and the nucleus (31). Consistent with these severe developmental defects, *Dmlipin* mutants exhibit reduced viability and fertility (31). Moreover, suppression of the ectopic lipid accumulation phenotype of *Drosophila Seipin* mutants by *Dmlipin* gene knockdown in the larval salivary gland (23) is in agreement with a function of *DmLipin* in TG accumulation. Consistent with this function, *Dmlipin* is expressed in various larval and adult tissues, which are central to the organismal fat storage in the fly (20). These tissues include the fat body, parts of the gut, the Malpighian tubules, and the neuroendocrine ring gland in larvae, as well as adult organs, such as the ovary. At least three different transcript and protein isoforms contribute to the complex expression pattern of *DmLipin* (30). *DmLipinA* is broadly expressed throughout development, whereas *DmLipinK* is enriched in the central nervous system (CNS) and *DmLipinJ* is testis-specific (30). The cytoplasmic or perinuclear localization of *DmLipin* in the fat body or CNS (30, 31) is consistent with a lipoanabolic function of the protein. Importantly, however, *DmLipins* also localize to the nucleus in some organs, such as the fat body or the Malpighian tubules (30, 31). Moreover, *Dmlipin* is transcriptionally upregulated under starvation (31), which argues against a

lipoanabolic function. Similarly, acute *Dmlipin* gene knockdown in the fat body of adult flies impairs their resistance to food deprivation, which suggests that *DmLipin* operates a starvation program independently of its role in TG synthesis. Given the nuclear localization of *DmLipin*, the protein might also act as a transcriptional coactivator or corepressor, as described for mammalian Lipins. Taken together the available data on *Dmlipin* support, but not prove, an evolutionarily ancestral, dual molecular role of lipins as lipogenesis genes and transcriptional cofactors (30, 31).

The final and only dedicated step in TG biosynthesis is catalyzed by diacylglycerol *O*-acyltransferases (DGAT; reviewed in Ref. 32). *Drosophila* DGAT1 is encoded by the *midway* (*mdy*) gene. Recombinant Midway has DGAT activity but does not acylate cholesterol (33). The gene is expressed during all stages of fly development with broad tissue-specificity (19, 20). Adult flies show pronounced *mdy* expression in the fat body, but the gene is also moderately expressed in various other adult organs, such as the ovaries. In line with a *mdy* gene function in storage fat deposition during oogenesis, hypomorphic mutants of the gene are female sterile due to lipid understorage in the developing oocyte and subsequent degeneration of the egg chamber (33). However, the central role of *mdy* in TG biosynthesis is not restricted to the germline. Consistent with a somatic function of the gene, knockdown of *mdy* in embryonic *Drosophila* tissue culture cells reduces lipid storage (14, 15). Moreover, adult flies with impaired *mdy* gene activity are lean (34). Conversely, larval salivary glands accumulate more lipid droplets in response to *mdy* overexpression (23). Taken together, it is clear that the *Drosophila* DGAT1 ortholog, Midway, plays a central role in TG synthesis from DG; however, the contribution of *mdy* to the total DGAT activity in flies is currently unknown. Mammalian genomes encode a second diacylglycerol *O*-acyltransferase, DGAT2, that forms a distinct protein family (DAGAT; pfam 03982) together with diacylglycerol *O*-acyltransferase 2-like 6 (DGAT2L6), three monoacylglycerol *O*-acyltransferases (MGAT1-3), and two acyl-CoA wax alcohol acyltransferases (AWAT1-2) (35, 36). The *D. melanogaster* genome encodes three members of the DAGAT family called *CG1941*, *CG1942*, and *CG1946*. Notably, the corresponding three genes are tightly clustered in a tandem array, spanning only 7 kbp of the fly genome. This genomic organization, a highly similar intron-exon structure, and the fact that the genomes of more primitive insects encode only a single DAGAT family member suggest that *D. melanogaster* DAGAT genes are the result of an evolutionarily recent gene radiation. In line with a concurrent functional diversification, the three DAGAT genes have only partially overlapping expression profiles (19, 20). The *CG1941* expression peaks at late embryonic and early larval developmental stages and is largely restricted to the gut. In contrast, *CG1942* has pronounced expression during mid-embryogenesis and pupal stages. Adult flies express moderate levels of this DAGAT family gene in the gut and fat body. Finally, *CG1946* is characterized by several activity peaks during fly development, including

specific expression in the adult midgut. Importantly, none of the *Drosophila* DAGAT family members has been functionally characterized by biochemical or mutant analysis. Therefore it is equally possible that one or more of these proteins has no DGAT but rather MGAT activity and accordingly catalyzes the first step of the monoacylglycerol pathway of TG synthesis (Fig. 1).

Cross-talk between triacylglycerol and phospholipid biosynthesis pathways

With PA and DG, two intermediates of the glycerol phosphate pathway of TG synthesis function as a nodal points of glycerolipid and phospholipid (PL) synthesis (Fig. 1). In particular, DG is a substrate for the CDP-ethanolamine phosphotransferase, encoded by the *Drosophila bb in a boxcar (bbc)* gene, in the PE synthesis pathway starting from ethanolamine. Global downregulation of all three enzymatic steps of this pathway, i.e., the ethanolamine kinase encoded by the fly *easter gene*, the phosphoethanolamine cytidyltransferase (Pect), and Bbc, increases fly body fat storage (37). Importantly, also organ-specific downregulation of PE synthesis causes lipid accumulation in the adult *Drosophila* heart, which leads to cardiac deficits (37). Lipid accumulation induced by dysfunction of PE homeostasis is driven by increased lipogenesis in the fly, which is mediated by activation of the sterol regulatory element binding protein HLH106 (or *DmSREBP*) (37). In general, studies on the pathophysiological consequences of lipid accumulation in the heart represent the currently most advanced *Drosophila* lipotoxicity model (reviewed in Ref. 38). Another example is the cardiac TG accumulation caused by high dietary fat, which leads to severe structural and functional changes in the fly heart, such as decrease in contractility, conduction block, and myofibrillar disorganization (39). Notably, tissue-specific knockdown of *CTP:phosphocholine cytidyltransferase*, the functional homolog of *Pect* in the PC synthesis, causes giant LD formation in larval fat body and increased body TG content (40). Collectively, these data demonstrate the importance of proper DG channeling between the TG and PL synthetic pathways to control the body fat storage in flies.

Phosphatidic acid is, next to DG, the second critical intermediate shared by the TG and PL synthesis pathways (Fig.1). Increase of PA in the *Drosophila* lipodystrophy model lacking the *Seipin* gene (*DmSeipin*) causes ectopic LD formation and TG storage increase in larval salivary glands (23) reminiscent of the action of seipin in mammalian tissue culture (41). Notably, human seipin can functionally replace its fly homolog in the *DmSeipin* mutant (23), which underscores the relevance of *Drosophila* as a valuable lipid metabolism model organism. The critical importance of PA homeostasis as a common TG and the PL synthesis precursor is supported by the phenotype of flies with impaired CDP diglyceride synthetase (*CdsA*) function. During the synthesis of PI and PG phospholipids, *CdsA* converts PA to CDP-DAG (Fig. 1). Downregulation of this PL pathway in *CdsA* mutant larvae causes ectopic LD accumulation in the salivary glands (23).

In summary, initial *Drosophila* studies have provided important insights into the function of central TG biosynthesis factors of the glycerol phosphate pathway. Certainly, the current knowledge covers only a small fraction of all lipoanabolic functions in this insect. However, the emerging picture highlights extensive similarities between the *Drosophila* and the mammalian anabolic TG metabolism, emphasizing the value of the fly as a model organism. This view is supported by the finding that glycerolipid homeostasis in both flies and mammals is responsive to changes in phospholipid biosynthesis.

TRIACYLGLYCEROL MOBILIZATION

The neutral lipid energy reserves, which are stored in LDs, become metabolically accessible through lipolysis (i.e., the successive hydrolytic cleavage of the three fatty acids from the glycerol backbone of TGs). Notably, DGs are the major lipid components of *Drosophila* lipoprotein particles, which supply peripheral organs with energy and lipid building blocks via the fly body fluid called hemolymph (42). This particularity of *Drosophila* lipid metabolism predicts that storage TGs are only partially hydrolyzed by TG lipases to DGs prior to their loading onto preformed lipoprotein particles, as described for the distantly related migratory locust (reviewed in Ref. 43). Alternatively, transport lipids could result from a more complete deacylation of TGs in the fat body followed by resynthesis of DGs. Insights into the lipolytic repertoire of *Drosophila* fat body cells are prerequisites for the understanding of TG mobilization in the fly.

Two modes of lipolysis can be differentiated within the fat storage tissue of the fly. On one hand, basal lipolysis is believed to balance steady-state lipogenesis in storage lipid homeostasis. In addition, stimulated lipolysis causes bulk TG mobilization during periods of negative energy balance or conditions of exceptional biosynthetic activity. The Brummer (BMM) lipase plays a central role in both basal and stimulated lipolysis (10, 44). Brummer and its paralog, Doppelgänger von brummer, are the only two Patatin-like domain-containing proteins in *Drosophila* (10). Accordingly, Brummer is a homolog of the adipose triglyceride lipase (ATGL or PNPLA2) (45, 46), which plays a central role in storage fat mobilization in mammalian tissues (reviewed in Refs. 47, 48). The *bmm* gene encodes a LD-associated TG lipase, which controls the systemic TG levels of the adult fly in a dose-dependent manner (10) (Fig. 1). Similarly, *bmm* knockdown increases lipid storage in *Drosophila* tissue culture cells (14, 15). Conversely, overexpression of *bmm* protects flies against high fat diet-induced TG accumulation and cardiac dysfunction (39). Consistent with the critical dose-dependency of the gene, *bmm* transcription is under tight nutritional control. Accordingly, *bmm* expression is induced under starvation (10), possibly by direct activation via the Forkhead box, subgroup O (Foxo) transcription factor (49) in response to downregulation of the insulin signaling pathway in the fly (reviewed in Ref. 50). Similarly, *bmm* transcription is repressed by the *Target of rapamycin*

gene function (51), which acts as a nutrient sensor in the fly (reviewed in Ref. 52). Additionally, the *bmm* gene is under antagonistic transcriptional control of the second, stimulated lipolysis pathway in *Drosophila* (44). The acute stimulated storage fat mobilization in flies is systemically controlled by the neuropeptide adipokinetic hormone (AKH), which binds to a fly G protein-coupled receptor called AKHR (or GRHR) on fat body cells. One branch of intracellular AKH/AKHR signaling operates via the second messenger cAMP and subsequent activation of protein kinase A (PKA) (53), analogous to β -adrenergic signaling in mammalian adipocytes. The effector TG lipase(s) of the AKH/AKHR pathway in *Drosophila* are currently unknown. Of the more than 50 predicted fly lipases (54), 2 enzymes qualify as candidates, which might execute acute lipolysis. One of them is CG8552, the *Drosophila* ortholog of the triglyceride lipase from the tobacco hornworm *Manduca sexta* (*MtTGL*) (55, 56; see below). The other is *DmHSL* (or CG11055), the single *Drosophila* homolog of mammalian hormone-sensitive lipase (HSL) (Fig. 1). *DmHSL* is a member of the embryonic LD proteome (13), consistent with a putative function in LD-based lipid metabolism. In fat body cells of fed larvae, however, tagged *DmHSL* fusion protein does not localize to LDs (57). However, starvation induces accumulation of this fusion protein on the surface of LDs of larval fat body cells (57). Starvation induces acute TG lipolysis in *Drosophila*, which is blunted in AKHR mutant fat body cells (44). Accordingly, translocation of *DmHSL* to LDs in response to fasting correlates well with a predicted function of the protein in AKHR-mediated storage lipid mobilization. Importantly, tagged *DmHSL* protein does not localize to fat body LDs of starved larva mutant for *Drosophila* *perilipin1* (*Dmplin1* or *Lsd-1*) (57). *DmPLIN1* is one of two *Drosophila* members of the evolutionarily conserved Perilipin family of LD-associated proteins (58; Fig. 1), which modulate storage lipid homeostasis in the fly (11, 34, 59). In vitro studies identified *DmPLIN1* as a PKA phosphorylation target (60), and in vivo mutant analysis demonstrated an essential role of *Dmplin1* as prolipolytic effector of the AKH/AKHR pathway on the LD surface (34). As PKA-dependent Perilipin phosphorylation and recruitment of HSL to LDs are hallmarks of stimulated lipolysis in mammalian adipocytes, it is tempting to speculate that this TG mobilization module is functionally conserved between flies and mammals.

The PKA-dependent phosphorylation of LD-bound *DmPLIN1* increases the lipolytic activity of the *Manduca sexta* CG8552 ortholog *MtTGL* in an in vitro assay (60). Moreover, *MtTGL* represents the major triglyceride hydrolase in the fat body of this insect species (56, 61), although the enzyme was shown not to localize to LDs (62). These two lines of evidence suggest that CG8552 is involved in TG mobilization in flies. However, final appreciation of the in vivo relevance of this enzyme for acute stimulated lipolysis in *Drosophila* has to await the phenotypic analysis of a CG8552 mutant fly.

In contrast to the prolipolytic *DmPLIN1*, the second Perilipin protein of the fly called *DmPLIN2* (or *LSD-2*) protects

TG stores in a dose-dependent manner. Accordingly, *Dmplin2* mutants are lean, whereas overexpression of the gene in the fat body increases fat accumulation in flies (59, 60, 63). A direct interaction of *DmPLIN2* with any of the aforementioned lipases is currently unknown.

PERSPECTIVES

An ever-growing number of publications on aspects of *Drosophila* lipid metabolism and lipid droplets testifies to the increasing interest in this research field. However, as a model organism with a rich tradition in forward genetics, fly studies on lipid metabolism often lack a broad biochemical basis. The experimentally supported and inferred steps of the glycerolipid turnover, which are outlined in this review, are prime examples of the currently very selective characterization of well-established biochemical pathways in the fly. The first in vivo studies of pathway members, such as *bmm*, *mdy*, and *Dmlipin*, not only emphasize a striking similarity between fly and mammalian lipid metabolism but also justify future reverse-genetic approaches in *Drosophila*. They should also encourage an unbiased systematic analysis of the fly lipid metabolism, which integrates genetic and biochemical approaches with lipidomic and proteomic technology.

Of particular interest are the presumably diverse functions of glycerolipid metabolism genes during the different stages of fly development. Another important research field is the understanding of the physiological and in particular the potential pathophysiological consequences of (ectopic) lipid accumulation in tissues outside the fly fat body. Organismal lipid metabolism is a highly integrated communication process, which involves various organs. All these organs continuously process environmental and intrinsic information on energy intake and expenditure to ensure proper storage fat homeostasis. The fruit fly *Drosophila* is uniquely suited to conditionally manipulate lipid metabolism regulators exclusively in specific organs in vivo. With this approach, the functional importance of gene activities at nodal points of this regulatory network can be explored.

Genome-wide RNAi screens in *Drosophila* tissue culture have identified numerous regulators of lipid droplet biogenesis and turnover, many of which are not yet mechanistically characterized. Accordingly, the fly model promises future contributions to the understanding of the complex cell biology of this highly dynamic organelle.

Finally, there is no doubt that future research will reveal distinctive features of fly lipid metabolism not shared by analogous processes in vertebrates. These differences will identify novel insecticide targets, which can be exploited to combat insect vector-borne diseases, such as malaria and dengue fever. ■■

The author apologizes for the omission of relevant publications in the *Drosophila* lipid droplet and lipid metabolism fields that were not included due to the focus of this review.

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