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Review

Lipid metabolism in *Drosophila*: development and disease

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Proteins, nucleic acids, and lipids are three major components of the cell. Despite a few basic metabolic pathways, we know very little about lipids, compared with the explosion of knowledge about proteins and nucleic acids. How many different forms of lipids are there? What are the *in vivo* functions of individual lipid? How does lipid metabolism contribute to normal development and human health? Many of these questions remain unanswered. For over a century, the fruit fly *Drosophila melanogaster* has been used as a model organism to study basic biological questions. In recent years, increasing evidences proved that *Drosophila* models are highly valuable for lipid metabolism and energy homeostasis researches. Some recent progresses of lipid metabolic regulation during *Drosophila* development and in *Drosophila* models of human diseases will be discussed in this review.

Keywords *Drosophila*; lipid metabolism; development; disease model

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Introduction

The fruit fly *Drosophila melanogaster* has been used frequently as a cost-effective model organism with completed genome, unparalleled collection of mutants, and extremely powerful genetic tools. It has been proved to be excellent in modeling human diseases, which has been supported by the fact that around 75% of human disease genes have orthologues in the fly genome [1]. Thus, the *Drosophila* system is currently being widely used in basic and applied researches on a broad spectrum of human diseases including cancers [2], infectious diseases [3], neurodegenerative diseases [4], and metabolic diseases [5]. In recent years, *Drosophila* has been emerged as a useful model organism for lipid metabolism and energy homeostasis studies [6].

Using *Drosophila* System to Study Lipid Metabolism

The major functions of lipids are storing energy, composing the cellular membranes, and serving as precursors of hormones and vitamins. Compared with mammals, *Drosophila* shares comparative anatomy of organs and cell types involved in lipid metabolism and homeostasis. In *Drosophila*, storage lipids in the form of triacylglycerol (TAG) and cholesterol ester are mainly accumulated in the adipose tissue-fat body. Similar to mammalian adipocytes, the *Drosophila* fat body cells are full of lipid droplets (LDs), which can be labeled by neutral lipid dye Nile red or BODIPY [7,8]. Besides that, the fat body, along with oenocytes located in the cuticle, has been demonstrated to fulfill the metabolic regulation and storage function of mammalian liver [9]. In mammals, insulin, produced by the β-cells of the pancreas, regulates carbohydrate and lipid metabolism [10]. In *Drosophila* there is no pancreas, but the corpora cardiaca cells located in the larval ring gland can secret glucagon-like adipokinetic hormone (AKH) and behave like pancreatic α-cells [11]. *Drosophila* genome encodes seven insulin-like peptides (DILPs) and the main insulin-producing cells (IPCs) analogous to the pancreatic β-cells are localized in the central brain [12]. In addition, DILPs are also expressed and function in other tissues, such as the fat body [13]. The lipotoxicity target cell types such as cardiomyocytes and body muscle cells are also comparable between *Drosophila* and human. The embryonic, larval, and adult hearts of *Drosophila* are good models to study human cardiovascular diseases, such as arrhythmia [14] and cardiomyopathy [15]. For example, mutants of *tafazzin*, which encodes a putative acyl transferase, showed greatly reduced level of cardiolipin associated with reduced locomotor activity and abnormal mitochondria, resembling a human skeletal muscle weakness Barth syndrome [16].

Besides organs/cells exhibiting similar metabolic functions, the basic metabolic pathways and signaling pathways involved in lipid metabolism are evolutionarily and

functionally conserved between *Drosophila* and mammals. For instance, *Drosophila* has a full set of lipogenic enzymes involved in TAG *de novo* biosynthesis from fatty acids, including glycerol-3-phosphate acyltransferase, acylglycerol phosphate acyltransferase, phosphatidate phosphatase (LIPIN), and diacylglycerol acyltransferase (DGAT) [17–19]. In mammals, the transcription factor SREBP promotes cholesterol and fatty acid synthesis and its activity is negatively regulated by cholesterol [20]. In the cholesterol auxotrophs *Drosophila*, dSREBP regulates fatty acid synthesis and instead of cholesterol, phosphatidylethanolamine made from fatty acids, negatively inhibits the activity of dSREBP [21]. Moreover, in general *Drosophila* has a less complex genome and less gene redundancy than vertebrates, which offers significant benefits in dissecting *in vivo* gene functions and identifying new pathway components.

Because of these facts and its genetic tractability, *Drosophila* provides an ideal model system for identifying key regulators of lipid metabolism and revealing vital functions of lipid metabolism in development and diseases (**Fig. 1**).

Lipids Function in *Drosophila* Early Development

Matured *Drosophila* oocytes accumulate large sum of lipids in the form of lipid droplets. Therefore, it is not surprised to find that lipids play important role in oogenesis and embryo development. In *midway* (*mdy*) mutants, just as the name refers to, oogenesis stops in the middle stage, leading to egg chamber degeneration. *mdy* encodes *Drosophila* DGAT, which converts diacylglycerol (DAG) into TAG and *mdy* mutants exhibit a strong reduction of neutral lipids in female germline [17]. During early embryogenesis, lipid droplets exhibit an interesting motion. Lipid droplets are spread throughout the periphery in syncytial blastoderm stage and move inward in cellularization stage. In gastrulation stage, lipid droplets shift back into the periphery. Although this is a microtubule-mediated lipid droplet trafficking process, the significance of such movement is not known. Blocking the movement by several mutants did not lead to an obvious embryogenesis defect [22,23]. Besides providing lipids, lipid droplets also serve as storage depots for maternally loaded histones based on proteomic study using purified embryonic lipid droplets [24]. Under the condition that histone expression is mildly compromised, the maternally loaded histones are essential for early mitoses during embryogenesis [25]. Other than that, the importance of lipid droplets in early embryogenesis is not known since there is no lipid droplet biogenesis mutant available.

Besides oogenesis and early embryogenesis, many recent studies showed that lipids, including fatty acids, phosphatidylinositol (PI), and cholesterol, play critical roles in various stages of the *Drosophila* spermatogenesis. Perturbing the levels of very-long-chain fatty acid (VLCFA) in the fatty acid elongases *noa* or *bond* mutants or in peroxisome biogenesis defective *pex* mutants caused severe defects in spermatogenesis including cytokinesis and spermatid differentiation [26–28]. Interestingly, the levels of VLCFAs are increased in *pex* mutants and are likely decreased in *noa* or *bond* mutants. These results suggest that a proper balance of VLCFA levels is essential for spermatogenesis. Conservatively, a recent genome-wide association study identified human peroxisome biogenesis gene *PEX10* as one of the three risk loci for non-obstructive azoospermia [29]. Similar to VLCFA, PI lipids are also critical for cytokinesis process and spermatid differentiation in *Drosophila* sperm development. *giotto/vibrator*, a PITP mutant, exhibits a cytokinesis failure phenotype in both meiotic spermatocytes and mitotic neuroblasts [30,31]. Depletion of phosphatidylinositol 4, 5-bisphosphate (PIP2) in spermatocytes by the expression of phosphoinositide phosphatase SigD revealed an essential role of PIP2 in sperm tail biogenesis. Depletion of PIP2 altered axoneme microtubule organization and axoneme-assembling protein distribution, resulting in an axoneme architecture defect [32]. Along with the defects in flagellar biogenesis, SigD overexpression or the PIP2 biosynthetic enzyme Sktl loss of function results in bipolar spermatid cysts which fail to fully elongate [33]. Compared with VLCFA and PI, cholesterol is required at a later stage during spermatogenesis. Cholesterol is important for membrane fluidity and a key component of lipid rafts. *Drosophila* is cholesterol auxotroph and the dietary supply of sterols is necessary for the development and viability in this organism [34]. Mutant phenotypic analysis revealed that sterol intracellular trafficking is important for the spermatid individualization, a rapid membrane remodeling process in which the interconnected fully elongated spermatids in a bundle are separated to individual sperms. Interestingly, both endosomal cholesterol trafficking defective *npc1* mutants and the non-vesicular-mediated intracellular sterols trafficking defective *Osbp* mutants exhibit similar individualization failure in *Drosophila* spermatogenesis [35,36]. *npc1* mutants showed abnormal sterol accumulation in aberrant multi-lamellar body-like organelles and *Osbp* mutants lost sterol accumulation in the leading edge of individualization complex. In addition, mutants of FAN, a VAMP-associated endoplasmic reticulum (ER) protein which interacts with OSBP, have defect in sterol distribution and individualization [35].

Sphingolipids and their metabolites play critical roles both as structural membrane components and as signaling molecules. The key sphingolipid metabolism enzymes are conserved in *Drosophila* [37,38]. Disruption of the sphingolipid metabolism such as mutations of sphingosine-1-phosphate (S1P) lysase (Sply) caused sphingolipid long-chain base

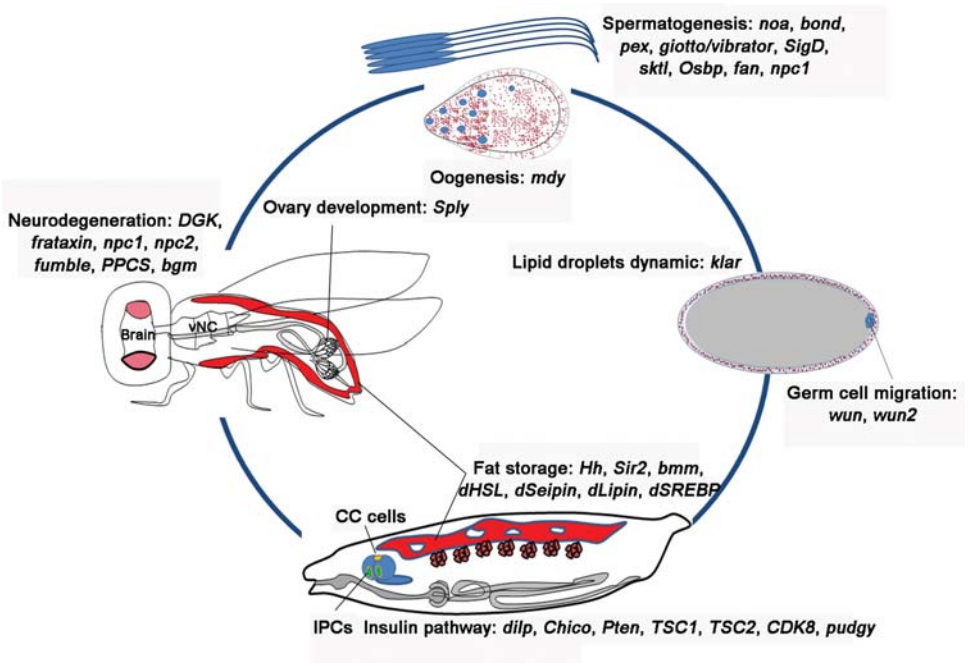

Figure 1 Lipid metabolic genes in *Drosophila* development and diseases The scheme depicts the life cycle of *Drosophila* from sperms and oocyte (with nurse cells) to adulthood. Lipid metabolism-related genes discussed in the text are subdivided into different functional groups.

metabolites accumulation and *Sply* mutants showed multiple abnormalities in both ovary and testis, including degenerative ovaries, supernumerary spermatocyte, and severely reduced testes [39]. On the other hand, blocking S1P biosynthesis by mutation of sphingosine kinase 2, a highly conserved enzyme that catalyzes the synthesis of S1P, impaired flight performance and diminished ovulation [40]. Lipid phosphate phosphatases (LPPs) are integral membrane enzymes that regulate the levels of bioactive lipids such as S1P and lysophosphatidic acid. The two *Drosophila* LPPs, Wunen (Wun) and Wunen-2 (Wun2), have a redundant role in regulating the survival and migration of germ cells [41–44]. *wun* and *wun2* are required in somatic tissues, in particular the central nervous system, to repel germ cells, probably through the generation of a lipid signal. *wun* and *wun2* also mediate germ cell–germ cell repulsion for germ cell dispersal to two embryonic gonads at the onset of germ cell migration. In addition, *wun2* is required in the germ cells for their survival and to perceive the signal. Besides the well-established role in germ cell migration, *wun* was found to regulate the function of septate junction. In *wun* mutants, the integrity of septate junction in the trachea and the blood–brain barrier is lost, indicating a role for phospholipids in septate junction function [45]. Together, sphingolipid and phospholipid metabolisms are critical for normal development and the subsequent integrity of adult tissues.

Despite the definite involvements in *Drosophila* early development, the exact roles of lipids during these developmental processes are largely unknown. It is possible that the lipid composition of the membrane affects the membrane curvature or fluidity, which subsequently influences the developmental processes. Alternatively, lipids may be involved in signal transduction. Lipids can function directly as signal molecules, such as ceramide, PIP2, DAG, and S1P, or indirectly by modifying proteins to affect their trafficking or localization. The best example of the latter is the modification of two conserved morphogens, Wnt and Hedgeog (Hh). Wnt and Hh are secreted signaling molecules with important functions during embryonic development and throughout adult life. Palmitoylation on a conserved cysteine is essential for Wnt signaling activity [46]. In the case of Hh, the N terminus of Hh is modified by palmitate and the C terminus of Hh is covalently modified by cholesterol [47]. Hh is the only known protein modified by cholesterol. Since the important roles of Wnt and Hh in development and diseases have been reviewed extensively, readers are referred to recent reviews and references therein [48,49].

Drosophila Models of Obesity, Lipodystrophy, and Diabetes

Obesity is a worldwide problem and about 500 million adults are considered obese in 2008 (World Health Organization). Investigating the origin of obesity is an important step to understand the mechanisms of obesity-associated diseases such as diabetes and cardiac diseases. A systematic genetic dissection of adiposity regulation using genome-wide RNAi screening in adult *Drosophila* identified ~500 candidate obese/lean genes, including several Hh

signaling pathway components. Further studies revealed an important role of Hh signaling pathway in regulating SREBP and fatty acid synthetase (FAS) expression during adipogenesis and in fat storage in *Drosophila* and mice [50]. Another larval buoyancy-based candidate screen identified fat overstorage mutants including *Sir2*, which encodes a protein deacetylase [51]. In *Sir2* RNAi flies, the expressions of several lipases including lipase 3 and Brummer (Bmm), which are important for fat mobilization through lipolysis, were reduced [52]. Consistently, mutants of lipases which are involved in intracellular lipolysis exhibit an obese phenotype. Bmm is the *Drosophila* homology of human adipocyte triglyceride lipase. *bmm* mutants are partially defective in fat mobilization with increased TAG storage and its obese phenotype is more obvious at mature adult stage [53]. Hormone-sensitive lipase (HSL) is another key lipase in mammalian lipolysis. Similar to *bmm*, *Drosophila HSL* (*dHSL*) mutants are also partially defective in fat mobilization, especially under starvation. Moreover, *dHSL;bmm* double mutant flies are extreme obese [54]. In contrast to obese phenotype observed in intracellular lipolysis defective lipase mutants, inhibition of lipases activity in the intestine exhibits an anti-obesity effect, apparently through affecting the uptake of digestive fat [55]. Opposite to obesity, lipodystrophy is characterized by the loss or absence of body fat. In human, the most severe lipodystrophy, Berardinelli–Seip congenital lipodystrophy 2 (BSCL2), is caused by mutations in the *Seipin* gene, although the exact function of Seipin remains unclear. *dSeipin* mutant is the *Drosophila* model of BSCL2 and mutant flies showed reduced lipid storage in the fat body, accumulated ectopic lipid droplets in the salivary gland and other non-adipose tissues. Further genetic and lipidomic analysis revealed that dSeipin may participate in phosphatidic acid metabolism and subsequently down-regulate lipogenesis to prevent ectopic lipid droplet formation [19]. *Lipin* is a lipodystrophy gene in mice. Similarly, mutation of *Drosophila Lipin* (*dLipin*) affects fat body morphology and leads to reduced fat body mass and total TAG content [18]. Together, these results suggest that *Drosophila* can provide a useful model of metabolic diseases including obesity and lipodystrophy.

Diabetes mellitus is a group of metabolic diseases in which the patient has high blood sugar, either because the patient's pancreas cannot produce enough insulin (type 1), or because cells cannot use insulin properly and do not respond to the insulin (type 2). A deep understanding of the insulin pathway is of extreme medical relevance, and the identification of novel proteins in this pathway is of great value in the quest for new therapeutic targets. *Drosophila* insulin pathway mutants manifest many of the same symptoms observed in diabetes, including reduced body weight, accumulating fat, and elevated circulating carbohydrate levels (hyperglycemia), supporting the usage of *Drosophila* to study diabetes [56]. In *Drosophila*, the seven DILPs are mainly released by the pancreatic β-cell like IPCs in the central brain. Ablation of IPCs causes increased blood sugar levels and reduction in cell size in *Drosophila* larvae, similar to that observed in *Drosophila* insulin receptor and IRS1–4 ortholog Chico mutants [12,56]. InR activates insulin receptor substrates (IRS), which interacts with phosphatidylinositol 3-kinase (PI3K), leading to the activation of Akt and finally resulting increased glucose uptake, fatty acid and protein synthesis [57]. Studies in *Drosophila* revealed several new regulators including PTEN, a tumor suppressor gene, as a functional antagonist to PI3K [58], and Tor pathway tuberous sclerosis genes, which act downstream of Akt [59,60]. Further genetic and biochemical studies revealed many fine-tune regulators of insulin pathway, including miRNA, mitogen-activated protein kinase, and small GTPase [61–64]. In mammals, insulin positively regulates SREBP-1c and promotes lipogenesis in hepatocytes [65]. Further studies showed that insulin rapidly down-regulates the levels of Cyclin-dependent kinase 8 (CDK8) and its partner cyclin C (CycC). CDK8 phosphorylates SREBP-1c and subsequently increases SREBP-1c ubiquitination and degradation. In fly and mouse models, knockdown of CDK8 or CycC increases the expression of lipogenic genes, such as FAS and acyl-CoA synthetase (ACS) [66]. In addition, in *Drosophila* and mammalian cells, insulin directly represses the expression of *pudgy/ACS*, which is involved in fatty acid β-oxidation [67]. These discoveries of novel regulators/targets of insulin signaling might provide new therapeutic targets towards alleviating the defects in diabetes and other metabolic syndromes.

Besides to study the genetic mutation-caused diabetes/obesity, *Drosophila* has also been used to study nutrient-related metabolic homeostasis, such as high-fat-diet (HFD)- or high-sugar-diet (HSD)-induced obesity and diabetes. In *Drosophila*, HFD feeding leads to increased TAG levels, impaired insulin and glucose homeostasis, along with heart dysfunctions mimicking human diabetic cardiomyopathy [68]. Interestingly, these HFD-induced defects can be effectively suppressed by inhibiting Tor signaling pathway or increasing lipase expression [68]. Similar to HFD treatment, HSD induces peripheral insulin resistance with increased expression of lipogenesis, gluconeogenesis, and β-oxidation genes [69]. Interestingly, mutation of a c-Jun N-terminal kinase pathway target, lipocalin Neural Lazarillo, exhibits protective effect of HSD-induced insulin resistance and growth inhibition [70].

Lipid Metabolism and *Drosophila* Neuronal Diseases

Lipids are highly enriched in the nervous system. A number of *Drosophila* neurodegeneration mutants have

been showed to be linked to lipid homeostasis. *Drosophila* models of many common human neurodegenerative diseases, including Huntington's disease (HD), Alzheimer's disease (AD), and Parkinson's disease, have been successfully established [4,71]. Genetic modifiers of these disease models have been screened extensively. Inhibition of lipid signaling enzyme DAG kinase ε (DGKε) significantly improves the motor dysfunction in a fly model of HD. Importantly, the same result is obtained in the mice HD model, supporting that DGKε is a potential therapeutic target for HD [72]. Surprisingly, mutation in *Drosophila rdgA*, which encodes another DGK, causes severe retinal degeneration [73]. Apolipoprotein D (ApoD) is a small, ubiquitous lipid carrier but its level is especially high in the glia of the nervous system. In *Drosophila*, ApoD reduces age-associated lipid peroxide accumulation and protect against Aβ-42-induced cytotoxicity in AD model [74]. Caused by a deficit in the mitochondrial protein frataxin, Friedreich's ataxia (FRDA) is a common neurodegenerative disease characterized by demyelination in the central and peripheral nervous systems. *Drosophila* model of FRDA showed increased free fatty acid levels and accumulated lipid droplets in glial cells. Interestingly, ApoD has a strong protective effect in this model as well. Therefore, lipid imbalance may be a critical event in FRDA progression [75].

The function of Coenzyme A (CoA) is to carry the acetyl groups in the process of fatty acid biogenesis. Mutants of two genes involved in *de novo* CoA biosynthesis showed altered lipid homeostasis and displayed neurodegeneration phenotype. *fumble* (*fbl*), encoding the first enzyme in the CoA synthesis route, is linked to pantothenate kinase-associated neurodegeneration, a hereditary progressive neurodegeneration disorder with brain iron accumulation [76]. The second enzyme is phosphopantothenoylcysteine synthetase, which is required for normal locomotor function during the development of the central nervous system [77]. It is not known why defective in CoA biosynthesis pathway elicits a neurodegenerative phenotype. The studies of *bubblegum* (*bgm*) mutants might provide a hint. *bgm* encodes a fatty acid CoA ligase that appears to be specific for the metabolism of VLCFAs. *bgm* mutant exhibits adult neurodegeneration and elevated level of VLCFAs. The neurodegeneration phenotype can be rescued by dietary supplement with a mixture of unsaturated fatty acids 'Lorenzo's oil', which has been used in treating other VLCFA accumulation diseases [78]. Niemann–Pick type C (NPC) disease is a fatal neurodegenerative disease caused by impaired endosomal cholesterol trafficking due to mutations in *NPC1* or *NPC2* genes. *Drosophila npc1* mutant brain showed elevated cholesterol levels and progressive neurodegeneration [79]. *NPC2* encode lysosomal sterol-binding protein and a family of eight *npc2* genes (*npc2a–h*) exists in *Drosophila*. *npc2a* and *npc2b* double mutants undergo apoptotic neurodegeneration [80].

Taken together, lipid metabolism defects are associated with various neurodegenerative diseases in *Drosophila*. For most of the diseases, the underlying mechanistic connections between lipid metabolism and neurodegeneration are not clear. To better understand the physiological causes of the diseases, it will be worth depicting the roles of lipid metabolism in neural development as well.

Conclusion and Future Perspectives

Drosophila is a powerful genetic model for uncovering the function of a particular gene as well as for unraveling the genetic pathways. Future studies of lipid metabolism in *Drosophila* will be focused on the regulation of lipid metabolism during normal developmental processes or under disease conditions. The main challenges are to identify specific lipid metabolites and understand their exact functions. Genetic analysis will certainly keep providing more insightful information and building network connections. However, to pinpoint the exact mechanisms, it is necessary to combine the genetic analysis with many other new techniques, such as proteomics and lipidomics. With that, lipid metabolism studies in *Drosophila* will no doubt shed significant lights on the basic mechanism of development and diseases.

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