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Review

The *Drosophila* model to interrogate triacylglycerol biology

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ABSTRACT

The deposition of storage fat in the form of triacylglycerol (TAG) is an evolutionarily conserved strategy to cope with fluctuations in energy availability and metabolic stress. Organismal TAG storage in specialized adipose tissues provides animals a metabolic reserve that sustains survival during development and starvation. On the other hand, excessive accumulation of adipose TAG, defined as obesity, is associated with an increasing prevalence of human metabolic diseases. During the past decade, the fruit fly *Drosophila melanogaster*, traditionally used in genetics and developmental biology, has been established as a versatile model system to study TAG metabolism and the etiology of lipid-associated metabolic diseases. Similar to humans, *Drosophila* TAG homeostasis relies on the interplay of organ systems specialized in lipid uptake, synthesis, and processing, which are integrated by an endocrine network of hormones and messenger molecules. Enzymatic formation of TAG from sugar or dietary lipid, its storage in lipid droplets, and its mobilization by lipolysis occur via mechanisms largely conserved between *Drosophila* and humans. Notably, dysfunctional *Drosophila* TAG homeostasis occurs in the context of aging, overnutrition, or defective gene function, and entails tissue-specific and organismal pathologies that resemble human disease. In this review, we summarize the physiology and biochemistry of TAG in *Drosophila* and outline the potential of this organism as a model system to understand the genetic and dietary basis of TAG storage and TAG-related metabolic disorders.

1. Introduction

Lipids fulfill essential functions as energy substrates, structural components, and signaling molecules. In eukaryotic cells, the successive esterification of glycerol with fatty acids (FAs) produces triacylglycerol (TAG), a major and universal storage lipid. TAGs are highly concentrated stores of metabolic energy because they are reduced and anhydrous and can be efficiently stored in discrete organelles termed lipid droplets (LDs) [1,2]. TAG formation sequesters excess FAs and limits their conversion to potentially toxic intermediates to prevent cell and tissue damage [1,3]. On the other hand, TAG hydrolysis provides an on-demand lipid source for energy production, transport, or synthesis of membrane constituents [4]. TAG homeostasis is crucial for healthy development and aging and both, impaired and excessive TAG formation are hallmarks of metabolic human diseases such as lipodystrophy, non-alcoholic fatty liver disease, and obesity [1–3].

During the past two decades, *Drosophila melanogaster* (hereafter referred to as "*Drosophila*") has been becoming increasingly popular as a model system to study mechanisms of TAG homeostasis and the development of lipid-associated diseases [5–7]. The fly shares central lipid metabolic pathways with vertebrates and requires a similar interplay between specialized organ systems to maintain organismal lipid homeostasis [5,7,8]. The genetic accessibility of the *Drosophila* model has inspired large-scale genetic approaches to characterize the molecular basis of TAG metabolism and storage [9–12]. These studies have uncovered a striking conservation in the basic molecular and physiological mechanisms controlling TAG metabolism in *Drosophila* and mammals [6]. More recently, *Drosophila* research has been extended to model the etiology of diet-induced metabolic diseases and to characterize hormonal communication pathways that integrate tissue-specific functions in TAG metabolism [5,7,8,13]. Collectively, these studies exemplify the potential of the *Drosophila* model to unravel basic mechanisms of TAG

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homeostasis as well as pathophysiological consequences of defective TAG metabolism at cellular and organismal scales.

The aim of this review is to provide an overview of the biochemistry and physiology of TAG metabolism in *Drosophila*. As other eukaryotic organisms *Drosophila* uses TAG storage as an essential energy reservoir to drive developmental processes and to survive food deprivation but also as a metabolic buffer to cope with overnutrition [14,15]. Ontogenetic transitions and changing nutrient availability, which characterize the *Drosophila* life cycle, are often associated with particular changes in TAG metabolism [16]. Similar to humans, TAG homeostasis in *Drosophila* results from the interaction of different tissues specialized in uptake, transport, storage, and processing of lipids. An elaborate neuroendocrine and hormonal system integrates lipid-metabolizing organs with each other [5–7,13]. This system ensures TAG homeostasis in the healthy animal but becomes dysfunctional when animals are challenged by overnutrition. In the first part of the review we outline the role of TAG in the life cycle of *Drosophila* and provide an overview of the organ systems implicated in organismal TAG homeostasis. In the second part we focus on the biochemistry of *Drosophila* TAG metabolism and describe the enzymatic and molecular mechanisms regulating TAG synthesis, storage and degradation, as well as lipid transport between tissues. Finally, we describe how major anabolic and catabolic hormonal pathways converge at the enzymatic control of TAG metabolism and close our review by highlighting advances in modeling diet-induced obesity and related pathologies in *Drosophila*.

2. Triacylglycerol function and metabolism during the *Drosophila* life cycle

TAG is a major energy reserve but serves also numerous other functions unrelated to energy metabolism. Although this review focuses on *Drosophila melanogaster* we include observations from other *Drosophila* species in this section to illustrate more specific biological functions of TAG. During its life cycle *Drosophila* undergoes several developmental transitions with characteristic stage-specific changes in TAG storage and breakdown [16]. This includes two “non-feeding” stages, metamorphosis and embryogenesis, which rely entirely on endogenous reserves. To meet the metabolic demands of embryogenesis, mature oocytes accumulate numerous TAG-rich LDs, which are deposited in the early embryos and are consumed during embryogenesis [17,18]. Maternal TAG deposition and embryonic TAG breakdown are both essential processes and strictly required for oocyte and embryo survival, respectively [19–21]. Embryo TAG breakdown correlates with an increase in heat dissipation rates indicating a vital contribution of TAG-derived FAs to combustion and energy production [18]. Whether embryo TAG breakdown serves lipid metabolic functions beyond energy metabolism including the provision of precursors for structural or signaling lipids is yet unclear. However, an important non-canonical function of embryo LDs is to sequester and store histones, which support early chromatin assembly and act as antimicrobial agents [22–24]. Larval stages are characterized by continuous feeding and growth and a drastic increase in organismal TAG mass. Larval TAG storage manifests as accumulation of LDs in the fat body, which acts as major fat storing organ in *Drosophila* functionally equivalent to mammalian adipose tissue and liver. By sequestering excess carbon units, fat body TAG formation acts as a metabolic buffer to prevent harmful accumulations of sugar or lipid intermediates [15,25]. Environmental factors including diet, temperature, commensal microbiota, and pathogenic microorganisms affect larval TAG storage [26–29]. Once formed, fat body TAG reserves provide an energy reservoir for periods of starvation [30,31]. TAG mobilization requires cross-talk between the larval fat body and oenocytes, which sequester fat-body derived FA and accumulate LDs upon starvation [32]. Metamorphosis is the second strictly non-feeding stage in the *Drosophila* life cycle characterized by histolysis of larval and growth of imaginal tissues. The commitment to pupation is associated with a metabolic shift that restricts starvation-induced TAG mobilization to spare energy reserves for metamorphosis and early adulthood [33]. Similar to embryogenesis, lipid consumption has been estimated to account for the majority of the energy budget of metamorphosis [34]. Nevertheless, substantial TAG reserves are maintained and transmitted to the imaginal state in the form of free-floating fat cells, which represent the remainder of the dissociated larval fat body [35–38]. The nutrient depots contained in larval fat cells contribute to starvation resistance of immature adults and early allocation of the developing ovary [39,40]. Moreover, larval fat cell TAG is an important precursor reservoir for the synthesis of cuticular hydrocarbons, which occurs in adult oenocytes and contributes to desiccation resistance of the animals [41]. After removal of larval fat body cells by programmed cell death within a few days organismal TAG storage depends on adult fat body tissue [40,42]. The imaginal stage is characterized by dynamic changes in TAG storage, which depend on sex, age, reproductive status, temperature, diet, and other environmental factors [43–48]. Sexually dimorphic TAG stores develop soon after eclosion when TAG levels drop dramatically in male flies but are maintained or even expanded in female flies [43,44]. Reproductive diapause in response to shortened photoperiod and low temperature leads to further accumulation of TAG in females of several *Drosophila* species [49]. This includes also *Drosophila melanogaster*, in which low temperature induces a shallow diapause phenotype [47]. Conversely, high temperature stress decreases adult TAG storage and eventually causes long-lasting impairments in fat body TAG storage due to adipocyte apoptosis [46]. Temperature also affects *Drosophila* food choice and thus impacts on dietary macronutrient intake, which is another major determinant of TAG storage [50]. Fat body TAG stores increase in flies challenged by overnutrition with fat or sugar but are comparatively low on high protein diets [45,51–54]. Lack of nutrients causes TAG mobilization, which is essential to sustain energy homeostasis and starvation resistance [30]. Depletion of organismal TAG occurs also upon infection with specific pathogenic microorganisms as a result of impaired anabolic signaling or sequestration of host lipids [55,56]. Despite the central TAG-storage role of the fat body TAG-rich LDs can be observed in several other tissues including intestine, salivary glands, nervous tissue, skeletal muscle, and heart. Excessive TAG storage in these tissues often accompanies organ dysfunction in *Drosophila* models of chronic overnutrition, aging, and neurodegeneration resembling aspects of lipid-associated human disorders [43,51,57–61]. TAG formation in non-adipose tissues often reflects biological functions unrelated to energy homeostasis. E.g. TAG formation in larval glia cells preserves neuroblast proliferation upon oxidative stress or hypoxia by diverting FAs into LDs, where they are less vulnerable to peroxidation [61]. In several species of the *Drosophila* subgenus (but not the *Sophophora* subgenus, which includes *Drosophila melanogaster*) TAG functions as a male-specific pheromone. Pheromone TAGs are rich in short-chain FAs, are transferred to females during mating, and function synergistically with other lipids as anti-aphrodisiac [62,63].

3. Regulation of triacylglycerol metabolism by *Drosophila* organ systems

Organismal TAG homeostasis requires interaction of multiple tissues such as gastrointestinal tract, adipose tissue, muscle, and nervous system, which compartmentalize core metabolic responses. The specific roles of *Drosophila* tissues in organismal TAG homeostasis are outlined in Fig. 1 and are discussed in further detail below.

3.1. Central nervous and neuroendocrine systems

Behaviors like food intake, activity, and sleep determine organismal energy balance and the accumulation and utilization of energy reserves. The nervous system processes chemosensory inputs and information about the internal milieu of the organism to coordinate complex behavioral responses and to maintain homeostasis. Several distinct

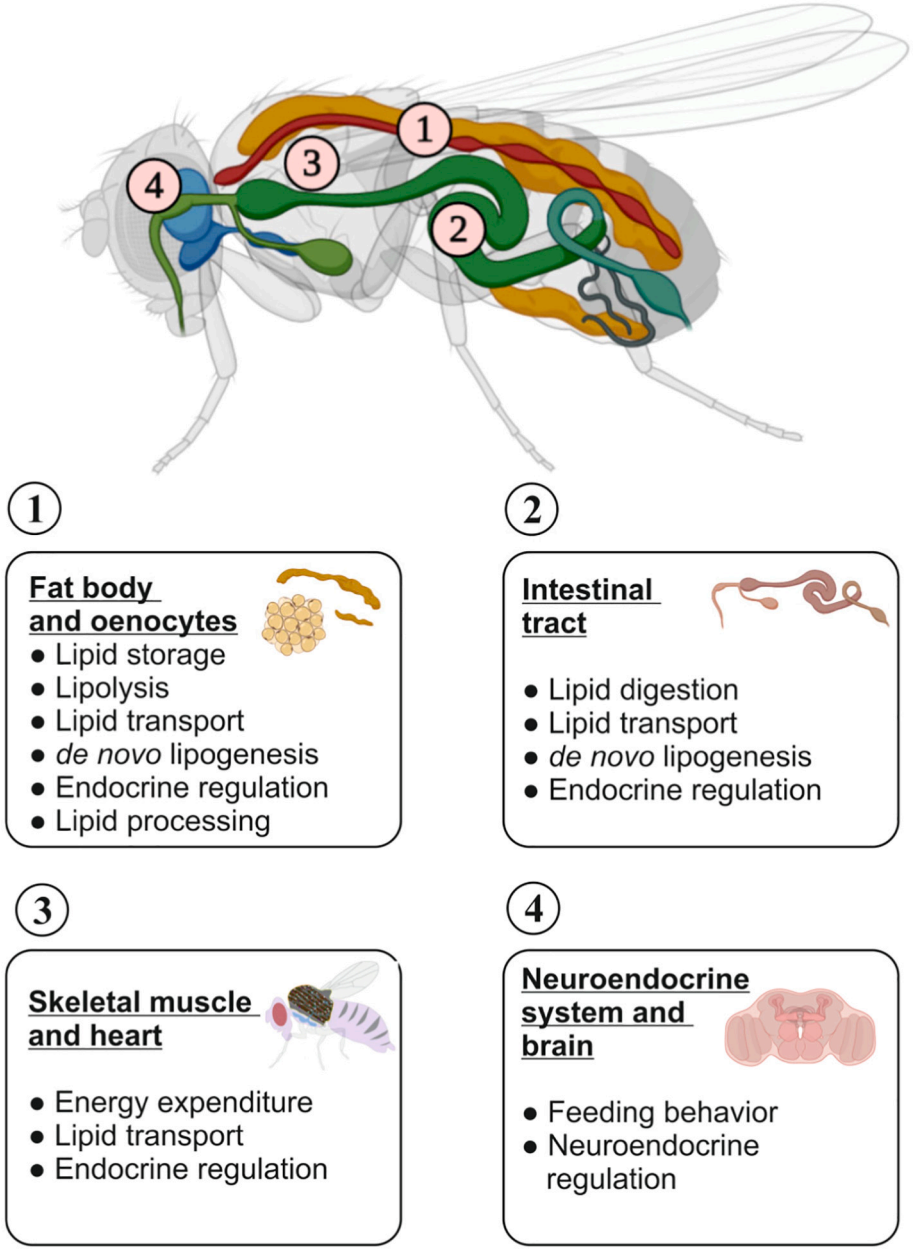

Fig. 1. Tissue-specific regulation of *Drosophila* TAG metabolism. Schematic overview of major organ systems involved in organismal TAG homeostasis and associated biochemical and physiological processes.

neuronal subpopulations have been linked to the control of feeding behavior and the accumulation of organismal TAG reserves [64–66]. Central to the neuronal control of energy metabolism are neuropeptides that are released by peptidergic neurons to convey information about the physiological state to other neurons or peripheral tissues (for review see [67]). Neuropeptides can act as potent orexigenic or anorexigenic factors. Anorexigenic Allatostatin A and Myoinhibitory peptide suppress feeding and reduce TAG storage [68–70]. Conversely, orexigenic Neuropeptide F (NPF) and the closely related short Neuropeptide F (sNPF) promote feeding and the expression of sNPF positively correlates with TAG storage in adult flies [10,71–73].

Two groups of neurosecretory cells produce circulating peptide hormones that directly regulate TAG metabolism in peripheral tissues (in particular fat body) by controlling expression and/or activity of metabolic enzymes: These hormones are *Drosophila* insulin-like peptides (Dilps), which are secreted by the insulin-producing cells (IPCs, also termed "median neurosecretory cells"), and the glucagon-like adipokinetic hormone (Akh), which is produced by corpora cardiaca cells [74,75]. IPCs are located bilaterally in the central brain and express Dilps 1, 2, 3 and 5. Binding of Dilps to the Insulin receptor (InR) on target tissues induces a conserved signaling cascade that controls growth, development, longevity, behavior, and metabolism (for review see [76,77]). Activation of insulin signaling in fat body cells inhibits breakdown of TAG reserves and promotes TAG storage by molecular mechanisms that are described in further detail below [78,79]. Insulin signaling is controlled at multiple levels by dietary nutrients, neurotransmitters, neuropeptides, and humoral factors. In particular, endocrine signals released by the fat body play a central role in coupling nutrient availability to alterations in systemic insulin signaling (for review see [77,80]). Akh acts antagonistically to insulin and promotes mobilization of fat body TAG reserves [14,36]. Akh is released by the neuroendocrine cells of the corpora cardiaca, which are part of the larval ring gland and associated with the proventriculus (also termed cardia) in adult animals [81]. Binding of Akh to the G-protein coupled Akh

receptor (AkhR) at fat body cells induces breakdown of TAG and limits lipogenesis [14]. Similar to insulin, Akh output is subjected to nutritional and hormonal regulation, which involves cross-talk with peripheral organs such as skeletal muscle and the midgut [82,83].

More recently, the *Drosophila* brain was identified as a site of active TAG metabolism with important implications for neuronal development and disease [61,84]. During the larval period cortical and subperineural glia accumulate substantial amounts of TAG-rich LDs [85]. Glial LD formation limits membrane lipid peroxidation by sequestering polyunsaturated FAs. This process is essential to sustain neuroblast proliferation under hypoxia [61]. Glial LD formation occurs also in adult *Drosophila* photoreceptors, in which LDs initially protect from reactive oxygen species-mediated cellular damage, but contribute to neurodegeneration later in life via the release of toxic peroxidated lipids [58,84,86,87]. In contrast to glia, information about the presence and relevance of LDs in neurons is scarce. LDs have not been detected in brain neurons but in peripheral motor neurons of *Drosophila* larvae [85,88]. Recently, LDs have also been identified in neurons of the adult brain and neuronal TAG metabolism has been implicated in sexually dimorphic regulation of organismal TAG breakdown [43]. Nevertheless, the emergence and (patho)physiological implications of neuronal LDs remain poorly understood and deserve future studies.

3.2. Fat body and oenocytes

The fat body is the major TAG storing tissue in *Drosophila* and a central site of lipid processing and transport (for review see [89]). The *Drosophila* fat body of larvae and adults differs in terms of morphology and ontogenetic origin. The larval fat body, which is derived from the embryonic mesoderm, dissociates during metamorphosis into free floating fat body cells, which persist up to three days post eclosion before being replaced by adult fat body tissue [35,38,90]. Larval and adult fat body tissue have common functions in TAG storage and metabolism. Upon nutrient intake the fat body converts excess dietary carbohydrates and lipids into TAG and generates abundant cytosolic TAG-rich LDs, which are a characteristic feature of this tissue [60,91]. As mentioned earlier, fat body TAG formation constitutes an important metabolic sink, which prevents harmful accumulations of sugar and lipid intermediates [15,25,26]. Once formed, fat body TAG serves as a central metabolic reserve to ensure energy homeostasis under diverse (patho)physiological conditions including starvation, reproduction, and infection [89]. The fat body is also an essential hub in lipid transport between tissues as it supplies apolipoprotein precursors, which circulate as reusable lipid shuttles in the hemolymph. Upon feeding, these lipoproteins mediate transfer of dietary lipids from the gut to the fat body and other tissues. During starvation, the same lipoproteins are used to mobilize lipids from the fat body for transport to other tissues [60,92]. Mobilization of fat body TAG requires enzymatic hydrolysis of TAG ester bonds, a process commonly referred to as lipolysis [4]. Fat body lipolysis generates diacylglycerol (DAG), which is the major circulating transport lipid in the hemolymph. Further hydrolysis of DAG provides FAs for oxidation and energy production [89]. Functional TAG storage and lipolysis strongly correlate with starvation resistance of *Drosophila* illustrating the central role of fat body TAG as metabolic fuel [14,20,30].

Fat body TAG homeostasis is tightly controlled by endocrine systems, which adjust the lipolytic output to changing organismal demands. As described above, two major endocrine regulators of fat storage are insulin and Akh, which suppress and stimulate TAG lipolysis, respectively [14,79]. In addition to receiving and processing hormonal information the fat body itself is an important endocrine organ. Dietary information is sensed by fat body Target of rapamycin (TOR) signaling and coupled to the secretion of peptides, which remotely control insulin release at IPCs [93–97]. One example is the leptin-like cytokine Unpaired 2 (Upd2), which is released in response to dietary sugar and fat and relieves tonal inhibition of insulin secretion by activating Janus kinase (JAK)/signal transducer and activator of transcription protein (STAT) signaling at specific γ-aminobutyric acidergic neurons. A dysfunction in Upd2-mediated amplification of insulin signaling results in impaired growth and decreased TAG storage [98,99]. Notably, the fat body produces its own insulin-like ligand, Dilp6, which is secreted from the larval fat body at the onset of metamorphosis to sustain tissue growth [100,101]. Fat body Dilp6 expression increases also in adult flies subjected to starvation and metabolically couples the fat body to another lipid processing cell-type termed oenocyte [102].

Oenocytes are specialized in the biosynthesis of cuticular lipids and pheromones (for review see [103]). Larval and adult oenocytes are organized as subepidermal cellular clusters and ribbons, respectively, and differ in size, number, and developmental origin [103]. Oenocytes acquire long chain FAs through de novo synthesis or lipoprotein-mediated transport and elongate them to very long chain FAs [91,104]. In larvae, oenocyte-derived very long chain FAs or related metabolites are required for tracheal waterproofing [91]. Adult oenocytes reduce very long chain FAs to hydrocarbons such as alkanes and alkenes, which are then deposited as barrier molecules and pheromones at the cuticle [104]. The fat body is an important nutrient-dependent regulator of oenocyte lipid metabolism. During starvation larval oenocytes acquire lipids via fat body TAG lipolysis and accumulate LDs [32]. It has been suggested that fat body-derived FA serve as precursors for very long chain FA synthesis in oenocytes [41,104]. Vice versa, oenocyte function is an important determinant of whole-body TAG metabolism: Proper synthesis of surface hydrocarbons in young adults depends on Hepatocyte nuclear factor 4 (Hnf4), which is required for transcriptional induction of very long chain FA and hydrocarbon synthesis genes. Oenocyte Hnf4 function is required to suppress oenocyte steatosis and organismal TAG over-storage [41]. A recent study implicated TOR signaling downstream of PDGF- and VEGF-related factor 1 (Pvf1) in developmental suppression of oenocyte steatosis and organismal lipogenesis during fly maturation [105]. Finally, cell ablation studies showed that both larval and adult oenocytes are also required for effective mobilization of fat body TAG [32,102]. In adult oenocytes, this response requires local increase in insulin-like signaling induced by fat body-derived Dilp6 [102].

3.3. Digestive system

As in other animals the *Drosophila* gut plays an essential role in the digestion and uptake of dietary macronutrients. The epithelium of the *Drosophila* gut actively participates in several aspects of TAG metabolism including lipid absorption, de novo lipogenesis, lipoprotein-mediated lipid transport and TAG storage [60,106,107]. In addition, the gut integrates inputs from diet, microbiota and humoral factors and, by secreting hormones and metabolites, transmits information to other tissues (for review see [108]). Inter-tissue communication between the gut and other organs is therefore a key determinant of organismal energy and TAG homeostasis and gut dysfunction as a result of aging or infection contributes to metabolic decay [82,109–111].

The intestinal tract of Drosophila consists of an epithelium, which is surrounded by muscles, nerves and tracheae. It is composed of foregut, midgut, and hindgut, and each segment can be further subdivided into functionally different sub-compartments [108]. The midgut epithelium consists of different cell types including intestinal stem cells, enteroendocrine cells and enterocytes [108]. Dietary macronutrients that enter the digestive tract are processed by digestive enzymes in the gut lumen before being absorbed by the enterocytes of the epithelium. The biochemistry of lipid digestion in *Drosophila* is poorly characterized. Studies in other insects suggest that complex dietary lipids including TAG and phospholipids are hydrolyzed into free FAs, monoacylglycerols and lysolipids by intestinal lipases [112]. A single intestinal TAG lipase, termed Magro, has been assigned a major function in intestinal TAG digestion in *Drosophila*. *Magro* expression is subject to extensive nutritional regulation and requires sterol-responsive hormone receptor 96 [106,113]. In addition to Magro, the *Drosophila* genome encodes several

other putative midgut lipases of unknown function that may contribute to lipid digestion [114]. Enterocytes acquire lipids not only from the diet but also from the conversion of dietary sugars via de novo lipogenesis. Lipids from both sources are converted to DAG and phospholipids, which are exported into the hemolymph and transported to other tissues [60,107]. This transport process depends on the supply of apolipoprotein precursors from the fat body and cardiomyocytes [60,115]. Enterocytes convert excess dietary lipid also to TAG for transient storage within cytosolic LDs [60]. Collectively, these aspects of intestinal lipid metabolism substantially contribute to the acquisition and maintenance of organismal TAG reserves. Genetic disruptions of dietary lipid digestion, enterocyte lipogenesis, or lipid transport limit organismal TAG storage. Conversely, a block in hemolymph lipid transport provokes midgut steatosis [106,107,116]. The midgut epithelium responds to hormones and itself serves as important source of humoral and paracrine factors, which can modulate local and systemic lipid metabolism. Intestinal hormones and neuropeptides are mainly secreted from enteroendocrine cells. Upon starvation, enteroendocrine cells secrete tachykinin, which signals locally to suppress enterocyte lipogenesis [107]. In response to nutrients enteroendocrine cells release Bursicon α into the hemolymph, which restricts production of the lipocatabolic Akh via a neuronal relay, thereby limiting breakdown of fat body TAG [109]. Notably, the number of enteroendocrine cells is sensitive to the lipid content of the diet, which alters progeny commitment of differentiating intestinal stem cells and thus exerts a long-lasting effect on midgut physiology [117,118].

The midgut epithelium is constantly exposed to microorganisms and serves as important site of interaction with commensal microbiota and pathogenic microorganisms. Commensal microbiota of laboratory *Drosophila* consist predominantly of *Lactobacillus* and *Acetobacter* species, which promote growth and development and modulate TAG metabolism [29]. Axenic flies exhibit excessive TAG storage under a wide range of nutritional conditions and a selective colonization with *Acetobacter* and/or *Lactobacillus* species lowers organismal TAG [119–121]. The absence of microbial acetate production has been identified as important factor contributing to developmental and metabolic defects associated with axenic conditions [29,122]. Enteric infection with pathogenic microorganisms elicits an immune response characterized by the synthesis and secretion of antimicrobial peptides and the enzymatic production of reactive oxygen species (for review see [123]). Depending on the pathogen, enteric infections cause diverse alterations in local or systemic TAG and energy metabolism including suppression of digestive enzyme expression, consumption of organismal TAG stores, and induction of intestinal TAG catabolism [114,124,125].

3.4. Muscle and heart

Although muscle contraction is highly energy-demanding the metabolic basis of this process in *Drosophila* has been poorly studied. Traditionally, lepidopteran and orthopteran species have been employed to characterize insect muscle energy metabolism. In *Locusta migratoria* sustained flight results in Akh-induced lipolysis of fat body TAG, increased circulation of hemolymph DAG, and utilization of this lipid as major metabolic fuel for muscle performance (for review see [126]). Early investigations of *Drosophila* energy reserve metabolism suggest preferential use of glycogen during flight [127]. This is further supported by the observation that glycogenolysis is required to maintain *Drosophila* flight performance [128]. Nevertheless, more recent studies indicate an important contribution of muscle metabolism and especially muscle-derived secreted factors to organismal TAG homeostasis. Genetically induced muscle mitochondrial dysfunction in *Drosophila* larvae increases deposition of fat body TAG, which relies on elevated transforming growth factor-β (TGF-β) signaling via muscle-derived Activin-β [82]. Conversely, specific muscle depots of adult *Drosophila* produce Pvf, which non-autonomously suppresses lipogenesis in oenocytes and the fat body [105]. Adult skeletal muscle limits TAG storage also by releasing Upd2, which promotes depletion of organismal TAG in adult *Drosophila* by increasing release of the lipocatabolic Akh from neurosecretory cells [83]. Skeletal muscle tissue itself is a target of hemocyte-derived Upd ligands, which maintain systemic TAG storage by suppressing excessive insulin signaling in muscle tissue [129]. Notably, muscle tissue displays age- and diet-dependent accumulations of intramuscular LDs often in association with mitochondrial deteriorations and organ dysfunction resembling ectopic fat depositions frequently observed in obese and diabetic patients [57,130–132].

Drosophila has an open circulatory system, in which hemolymph circulates in the hemocoel to supply organs with nutrients and hormones. The *Drosophila* heart (also called dorsal vessel) maintains hemolymph circulation by pumping it towards the anterior and posterior parts. Similar to skeletal muscle the heart has been identified as an important regulator of organismal TAG homeostasis. Cardiac-specific manipulations that decrease the function of MED13 (encoded by *Drosophila skuld*), a subunit of the Mediator complex, or Snail transcription factors (encoded by *snail*, *escargot* and *worniu*) non-autonomously increase fat body TAG storage [133,134]. While the secreted peptide Wingless has been identified as a downstream effector of MED13 the effectors of cardiac Snail transcription factors remain elusive [133,134]. In addition, the heart contributes to systemic lipid metabolism by supplying apolipoprotein precursors for hemolymph lipid transport. Upon a high fat diet, cardiac apolipoproteins promote lipid transfer of dietary lipid to the fat body and contribute to increased organismal TAG storage [115]. Interestingly, cardiac muscle tissue itself responds to a high-fat diet by an ectopic accumulation of TAG and the tissue-autonomous formation of LDs [51]. This is accompanied by altered lipid metabolic signatures and functional deteriorations reminiscent of cardiomyopathies observed in obese and diabetic human patients [51,135,136].

4. Biochemistry of *Drosophila* triacylglycerol metabolism

4.1. De novo lipogenesis and formation of triacylglycerol

The formation of TAG depends on the availability of FAs, which are either acquired from the diet or synthesized de novo from acetyl-CoA. Both sources contribute to TAG formation in *Drosophila* but available evidence suggests a predominant contribution of de novo synthesized FAs, which may simply reflect higher contents of carbohydrates relative to lipids in many laboratory foods [104,106]. The term “de novo lipogenesis” refers to the formation of TAG from de novo synthesized FAs. De novo FA synthesis requires the concerted enzymatic action of acetyl-CoA carboxylase (ACC) and FA synthase (FAS). First, ACC catalyzes the carboxylation of acetyl-CoA to malonyl-CoA. Then, FAS sequentially condensates acetyl-CoA units to malonyl-CoA to produce long-chain FAs [25,91]. The *Drosophila* genome encodes a single *ACC* gene and three *FAS* genes (encoded by *FASN1-3*). ACC is ubiquitously expressed with highest levels in fat body, midgut and oenocytes. *FASN1-3* show differential tissue expression patterns and FASN1 represents the major isoform in the fat body [25,91]. Loss of fat body *ACC* or *FASN1* function greatly reduces TAG storage even in the presence of supplemented dietary lipids [25,91,104]. Null mutants of *ACC*, *FASN1* and *FASN3* die or arrest at embryonic and early larval stages of development. These developmental deficits are likely not related to reduced TAG storage but due to defective formation of structural or signaling lipids [25,91]. Nevertheless, under specific dietary conditions de novo lipogenesis contributes to developmental success [15,25]. When *Drosophila* larvae are challenged with a high sugar diet de novo lipogenesis prevents formation of harmful advanced glycation end products by channeling excess sugar into TAG [25]. De novo lipogenesis is regulated by the basic helix-loop-helix-leucine zipper transcription factors carbohydrate element response binding protein (ChREBP, encoded by *Mondo* in *Drosophila*) and sterol-regulatory element binding protein (SREBP), which control expression of *ACC*, *FASN* and other lipogenic effector

genes [137,138]. ChREBP/Mondo is activated in response to sugar intake and coordinates a wide range of transcriptional programs related to nutrient metabolism including increased de novo lipogenesis [137]. SREBP resides in the endoplasmic reticulum (ER) membrane as an inactive precursor. A two-step proteolytic processing at the Golgi activates SREBP allowing entry of its N-terminal transcription factor domain into the nucleus [139]. This proteolytic processing is sensitive to membrane lipids: Whereas low cholesterol levels activate mammalian SREBP processing and transcriptional activity *Drosophila* SREBP is activated by reductions in phosphatidylethanolamine, the most abundant glycerophospholipid in *Drosophila* biomembranes [139,140]. Genetic interference with phosphatidylethanolamine synthesis results in ectopic SREBP activation and increased TAG levels [10,141]. Conversely, *Drosophila* mutants lacking SREBP or SREBP processing factors have low organismal TAG stores and require dietary FA supplementation for successful development [138,142].

The formation of TAG requires FA esterification to a glycerol backbone via several enzymatic steps. The enzymes mediating TAG synthesis in the *Drosophila* fat body are depicted in Fig. 2. First, FAs are converted to acyl-CoA thioesters by acyl-CoA synthetase (ACS). Then, acyl-CoAs

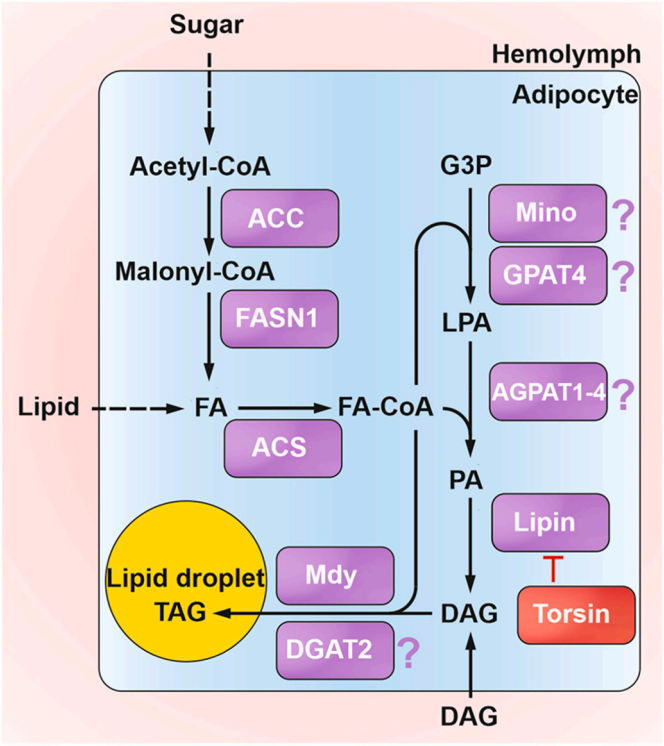

Fig. 2. Triacylglycerol synthesis in adipocytes of the fat body. Fatty acids (FAs) are derived from hemolymph lipids or are synthesized de novo by Acetyl-CoA-carboxylase (ACC) and the FA synthase complex (including FASN1). Acyl-CoA synthetase (ACS) enzymes convert FAs to Acyl-CoAs (FA-CoAs), which serve as acyl donors for the consecutive esterification of FAs with glycerol in the glycerol-3-phosphate (G3P) or Kennedy pathway of triacylglycerol (TAG) synthesis. G3P *O*-acyltransferases (GPATs, including possibly Mino and GPAT4) initiate the G3P pathway by acyl transfer from FA-CoA to G3P to form lysophosphatidic acid (LPA, also 1-acylglycerol-3-phosphate). Acylglycerol-3-phosphate *O*-acyltransferases (AGPATs, including possibly AGPAT1-4) convert LPA to phosphatidic acid (PA) by a second acyl transfer. Lipin dephosphorylates PA to diacylglycerol (DAG), which is further esterified to TAG by DAG *O*-acyltransferases (including Mdy and possibly DGAT2). Circulating hemolymph DAG may also be a substrate for TAG synthesis after transport into adipocytes. TAG is deposited in lipid droplets for storage. The AAA+ ATPase Torsin regulates G3P pathway activity by restricting Lipin activity. Adipocytes express several acyltransferase isoenzymes whose precise role in the G3P pathway remains to be elucidated (indicated by question marks).

are used as FA donors by two distinct acyltransferase enzymes, which transfer FAs in a consecutive manner to glycerol-3-phosphate (G3P) to generate phosphatidic acid (PA). Dephosphorylation of PA by PA phosphatases yields DAG, which is finally converted to TAG via a third acyl-CoA-dependent acyltransferase. This series of reactions is called G3P or Kennedy pathway of glycerolipid synthesis (for review see [143]). It is currently unclear if *Drosophila* TAG synthesis can alternatively commence with the esterification of monoacylglycerol or dihydroxyacetonephosphate as described for other organisms [2]. DAG esterification is the only committed step in TAG synthesis because PA and DAG can also undergo conversion to glycerophospholipids. Two phylogenetically unrelated DAG-*O*-acyltransferase (DGAT) isoenzymes termed DGAT1 and DGAT2 are responsible for TAG formation [143]. The *Drosophila* DGAT1 is encoded by the *midway* (*mdy*) gene. *Mdy* function is a major determinant of organismal TAG storage and contributes to the formation of TAG-rich LDs in fat body cells, glia, oenocytes, and nurse cells [19,61,144–146]. The inadequate buildup of oocyte TAG in *mdy* mutants is associated with premature egg chamber apoptosis and female sterility [19]. DGAT2 represents a second TAG synthesis enzyme, which differs from Mdy in terms of subcellular localization and tissue expression pattern. *Mdy* is ubiquitously expressed whereas *Dgat2* and its paralogs *CG1941* and *CG1946* are expressed in fat body and midgut [147]. DGAT2 exhibits dual localization at the ER and LDs whereas Mdy localizes exclusively to the ER [148]. Residual TAG storage in *mdy* mutants suggests a contribution of DGAT2 to *Drosophila* TAG formation in vivo although this assumption has not yet been confirmed by genetic approaches. The conversion of PA to DAG is the penultimate step in the G3P pathway of TAG synthesis. This reaction is catalyzed by PA phosphatases. The Lipin proteins are evolutionarily conserved magnesium-dependent PA phosphatases, which regulate TAG storage in diverse phyla [143]. The *Drosophila* genome encodes a single *Lipin* (*Lpin*) gene, which gives rise to at least three different isoforms [149]. *Lpin* mutant flies exhibit pupal semi-lethality, reduced fecundity and a lipodystrophy phenotype characterized by reductions in larval fat body mass, TAG content, and LD size [150]. The AAA+ ATPase Torsin acts as a suppressor of Lipin activity in the larval fat body. Defective fat body development in *Torsin* mutant flies can be partially rescued by genetic suppression of *Lpin* gene function arguing for a close correlation between fat body (dys)function and Lipin activity [151]. Mammalian Lipin proteins act as transcriptional coactivators independent of enzyme activity and regulate expression of FA oxidation genes [152]. Like its mammalian orthologs, *Drosophila* Lpin localizes to both, the cytosol and nucleus and harbors a conserved leucin-rich motif implicated in interactions with transcription factors [150,153]. *Drosophila* mutants specifically lacking the nuclear localization sequence of Lipin have unaltered TAG stores but display altered metabolic gene expression and are sensitive to starvation stress [154]. In addition to DGAT and PA phosphatase TAG formation relies on G3P *O*-acyltransferase (GPAT) and acylglycerol-3-phosphate *O*-acyltransferase (AGPAT) enzymes, which catalyze the first and second acyltransferase reactions of the G3P pathway, respectively. The *Drosophila* genome encodes three putative GPAT isoenzymes, which have been classified according to their homology to mammalian GPATs. Among them, *Gpat4* and *minotaur* (*mino*) are ubiquitously expressed whereas expression of *CG15450* is largely restricted to the testis [147]. GPAT4 localizes to the surface of a LD subset and contributes to LD growth in S2 cells. Depletion of GPAT4 reduces LD and TAG content in S2 cells and limits hypoxia-induced LD formation in larval glia cells [61,148]. *Gpat4* mutant flies are semi-lethal and developmentally delayed but have normal organismal TAG stores suggesting compensation by other GPAT isoforms [155]. Indeed, ectopic expression of *mino* is sufficient to induce LD formation in salivary glands suggesting a contribution of this GPAT isoenzyme to TAG formation [144]. Four different *Drosophila* proteins have been annotated as AGPATs based on their homology to mammalian AGPATs (encoded by *Agpat1-4*). Similar to GPAT4 the AGPAT3 isoenzyme contributes to LD formation in glia and S2 cells and localizes to the LD surface [61,148]. If

AGPAT isoenzymes have distinct, non-redundant roles in *Drosophila* TAG synthesis in vivo is currently unknown.

4.2. Triacylglycerol storage in lipid droplets

Intracellular TAG is stored in globular organelles termed LDs. LDs consist of a hydrophobic core of neutral lipids, which is covered by a phospholipid monolayer and proteins involved in lipid metabolism, signaling, and trafficking (for review see [156]). LDs are abundant in the fat body but present also in many non-adipose tissues including midgut, Malphigian tubules, imaginal discs, brain, salivary glands, and muscle [21,59,60,157,158]. Moreover, formation of LDs is a hallmark of vitellogenesis and essential for development and survival of mature oocytes and embryos [19,21]. The primary function of LDs is to store neutral lipid as an on-demand source of energy and lipid precursors. In addition, lipid sequestration in LDs prevents lipotoxicity and contributes to membrane homeostasis. Ectopic LD formation can thus be a signature of cellular stress and accompanies aging and neurodegeneration [3,57,84,130,156]. LDs are formed de novo in the ER by an incomprehensively understood mechanism. A common model suggests that TAG and other neutral lipids formed by ER-resident enzymes are initially deposited between the leaflets of the ER. These neutral lipid deposits eventually undergo phase separation into nascent LDs, which bud off the ER and expand in a protein-assisted maturation process [156]. An evolutionarily conserved protein implicated in the early steps of LD formation is the integral ER protein Seipin, which is dysfunctional in human patients with Berardinelli-Seip congenital lipodystrophy [156,159]. Seipin foci move along the ER and interact with early LDs in *Drosophila* S2 cells [160]. Absence of Seipin results in disordered LD formation and aberrant accumulation of numerous small and a few large LDs [144,160]. Cryo-electron microscopy indicates that *Drosophila* Seipin forms a barrel-shaped dodecamer with short N- and C-terminal segments oriented towards the cytoplasm and an assembly of folded domains oriented towards the ER lumen [161]. The molecular function of Seipin in LD biogenesis is not fully elucidated and may involve stabilization of TAG accumulations in the ER leaflet, recruitment and regulation of lipid synthesis enzymes, maintenance of ER-LD contact sites, and regulation of calcium homeostasis [162–165]. *Drosophila Seipin* null mutants have a lipodystrophy phenotype mimicking the pathophysiological manifestation of Seipin dysfunction in human patients [144]. The lipodystrophy phenotype of *Seipin* mutants is at least partly caused by impaired calcium homeostasis and concurrent mitochondrial dysfunction, which limit supply of citrate for de novo lipogenesis [165,166]. In addition, *Seipin* mutants exhibit ectopic accumulation of LDs in the midgut and salivary gland, which has been linked to an aberrant accumulation of the G3P pathway intermediate PA [144]. After initial steps of de novo formation specific LDs acquire distinct isoforms of TAG synthesis enzymes (such as GPAT4, AGPAT3 and DGAT2), which mediate LD expansion by localized TAG synthesis [148]. This process contributes to variations in LD size and function. Accordingly, the *Drosophila* fat body contains LD subpopulations with distinct size, subcellular localization and protein composition [167,168]. Large medial LDs are maintained largely by FASN1-mediated de novo lipogenesis and are distinct from small cortical LDs, which associate with ER-plasma membrane contact sites. Cortical LDs require a functional spectrin cytoskeleton and the syntaxin Snarzarus and are supplied mainly by hemolymph lipid transport rather than de novo lipogenesis [168,169]. LD coat proteins of the evolutionarily conserved perilipin (PLIN) family function as central regulators of LD structure and catabolism and contribute to the formation of LD subpopulations. The *Drosophila* genome encodes for two PLINs, termed PLIN1 and PLIN2 (also known as Lipid storage droplet-1 and -2). PLIN1 is highly expressed in the *Drosophila* fat body where it preferentially associates with large medial LDs [168,170]. Loss of *plin1* function compromises LD catabolism (see below) and promotes formation of aberrantly large LDs [145,170]. PLIN1-deficient LDs are prone to coalescence in vitro suggesting that PLIN1 stabilizes LD structure by decreasing surface tension and uncontrolled LD fusion [171]. Expression of *plin1* is limited by the transcription regulator martik (encoded by *mrt*) and nucleosome remodeling factors. It has been suggested that transcriptional repression of *plin1* may be a physiological mechanism to increased fat body LD size by facilitating LD coalescence [171]. PLIN2 preferentially associates with and maintains cortical LDs but is largely absent from large medial fat body LDs [168]. PLIN2 is broadly expressed and contributes to LD formation and/or maintenance in many non-adipose tissues including imaginal discs, ovaries, and skeletal muscle [130,172,173]. Loss of PLIN2 decreases LD size and fat storage due to unrestricted LD catabolism (see below) and impaired maintenance of cortical LDs [20,168]. Fig. 3 illustrates the association of PLIN2-EGFP with LDs in the fat body and posterior midgut of a mature female fly. In addition to LD-associated proteins like PLINs the phospholipid composition of the LD monolayer is a critical determinant of LD size and structure. In particular, impaired synthesis of phosphatidylcholine as a result of reduced phosphocholine cytidylyltransferase 1 (encoded by *Pcyt1*) or lysophosphatidylcholine acyltransferase (encoded by *LPCAT*) activities, favors formation of large LDs [174,175]. Elegant biophysical studies revealed that phosphatidylcholine acts as surfactant that decreases LD surface tension and limits LD coalescence [176].

4.3. Lipolysis and mobilization of triacylglycerol

The mobilization of TAG for lipid transport, energy production, or metabolic conversions requires enzymatic TAG hydrolysis, a process commonly referred to as lipolysis. In the *Drosophila* fat body, lipolysis is executed by Brummer (Bmm) lipase. TAG hydrolysis by Bmm generates DAG, which can be exported to the hemolymph or further hydrolyzed into FAs and glycerol by yet uncharacterized lipases [20]. After conversion to FA-CoA by ACS isoenzymes like Pudgy, FAs can be imported into mitochondria or peroxisomes and subjected to β-oxidation for energy production [177,178]. Bmm activity is complemented by a second enzymatic system that is activated by Akh signaling [14]. Mutant flies deficient in both Bmm activity and Akh signaling are incapable of accessing fat body TAG upon starvation and accumulate massive amounts of TAG under ad libitum fed conditions [14]. Although many components of the Akh signaling cascade have been identified (see below) the molecular identity of Akh-dependent lipase(s) is controversial. Two putative Akh effector lipases are phosphatidic acid phospholipase A1 (PAPLA1) and Hormone-sensitive lipase (Hsl). *Drosophila* Hsl contributes to TAG catabolism in the 3rd instar larval fat body and is recruited to the LD surface by PLIN1 [30]. A similar mechanism controls activity of mammalian HSL, which acts as a major adipose tissue lipase downstream of catabolic hormones including catecholamines and glucagon [179]. PAPLA1 is an ortholog of *Manduca sexta* TAG lipase (TGL), which has been assigned a major function in Akh-stimulated *Manduca sexta* fat body lipolysis [180]. Surprisingly, single deficiencies in either PAPLA1 or Hsl are largely compatible with starvation-induced TAG mobilization in adult flies suggesting that Hsl and PAPLA1 act in redundancy with each other or other lipases to execute adult fat body lipolysis [181,182] . Fat body lipolysis is regulated via transcriptional and post-transcriptional mechanisms, which are modulated by hormonal and nutrient-responsive signaling pathways (see below). *Bmm* expression depends on the Forkhead box subgroup O transcription factor (Foxo), whose transcriptional activity is suppressed by insulin signaling [79]. Hedgehog signaling positively regulates *bmm* transcription via the zinc finger transcription factor Cubitus interruptus, while juvenile hormone-responsive Kruppel homolog 1 (Kr-h1) and innate immune transcription factor nuclear factor κB (NF-κB)/Relish suppress *bmm* transcription [183–185]. Post-transcriptional regulation of lipolysis is executed by PLINs, which modulate access of lipases to the LD surface. PLIN1 restricts lipase access and activity under basal conditions but promotes lipolysis upon starvation [145,170]. Consequently, *plin1* mutant flies accumulate excessive TAG and exhibit impaired

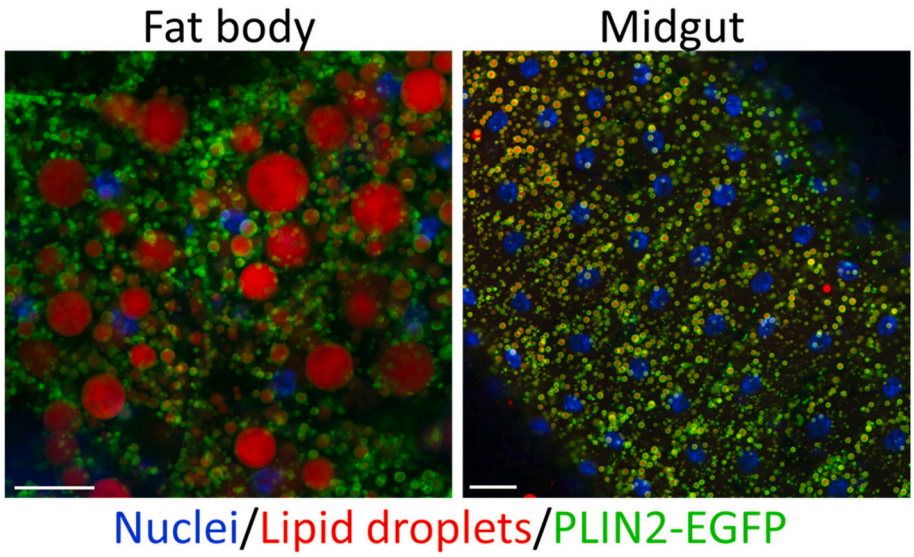

Fig. 3. Triacylglycerol storage in lipid droplets. Lipid droplets (LDs) harbor a distinct proteome, which includes members of the evolutionarily conserved perilipin (PLIN) family of proteins. A PLIN2-EGFP fusion protein localizes to the surface of LDs in fat body adipocytes and midgut enterocytes. Note that adipocytes maintain LD subsets of different size and protein composition, illustrated by the differential targeting of PLIN2-EGFP to small peripheral LDs and absence of PLIN2-EGFP from large median LDs. The *PLIN2-EGFP* transgene (described in [187]) was ubiquitously expressed in a w^{1118} female using an *Act5c-GAL4* driver and imaged by confocal fluorescence microscopy. LDs were stained with HCS LipidTOX™ Deep Red and cell nuclei were stained with Hoechst 33342. Scale bars represent 20 μm.

starvation-induced lipolysis [145,170]. Experiments in *Manduca sexta* and *Drosophila* suggest that Akh signaling impinges on PLIN1 to control the switch from a restrictive to a permissive lipolytic environment at the LD surface. This switch likely involves protein kinase A (PKA)-mediated phosphorylation of PLIN1 and recruitment of lipases including Hsl to the LD surface [145,170,186]. However, the molecular details of PLIN1-mediated lipolysis control in *Drosophila* and other insects are still poorly understood. In contrast to the TAG overstorage phenotype of *plin1* mutants, loss of *plin2* results in reduced organismal TAG [145,187]. Early studies suggest that PLIN2 acts mainly by restricting Bmm activity [20]. The presence of PLIN2 at a distinct cortical LD subpopulation close to the plasma membrane of the fat body indicates an additional function in lipid uptake, which possibly contributes to efficient TAG storage [168,169]. Fig. 4 summarizes the enzymes and regulatory proteins implicated in fat body TAG lipolysis. In contrast to the fat body much less is known about lipolysis in non-adipose tissues, which often maintain and process tissue-autonomous TAG pools. Non-adipose tissues may also hydrolyze hemolymph-derived DAG to FAs for energy production or integration into structural lipids. The broadly expressed Bmm lipase contributes to TAG homeostasis in several non-adipose tissues including midgut epithelium, skeletal muscle, nervous system, testis, and heart [43,57,60,135]. In addition, several putative midgut lipases with unknown substrate specificity have been implicated in TAG homeostasis including Lip3, CG8093 and CG6277 [188,189]. Lip3 shares homology with mammalian lysosomal acid lipase, which executes autophagy-dependent degradation of LDs. This process, commonly referred to as "lipophagy", acts in parallel with the cytosolic route of lipolysis in the liver and other tissues of mammals [4]. Evidence for lipophagy has been documented in *Drosophila* oenocytes, photoreceptors, and midgut indicating that both cytosolic lipolysis and lipophagy contribute to TAG degradation in *Drosophila* non-adipose tissues [124,158,190].

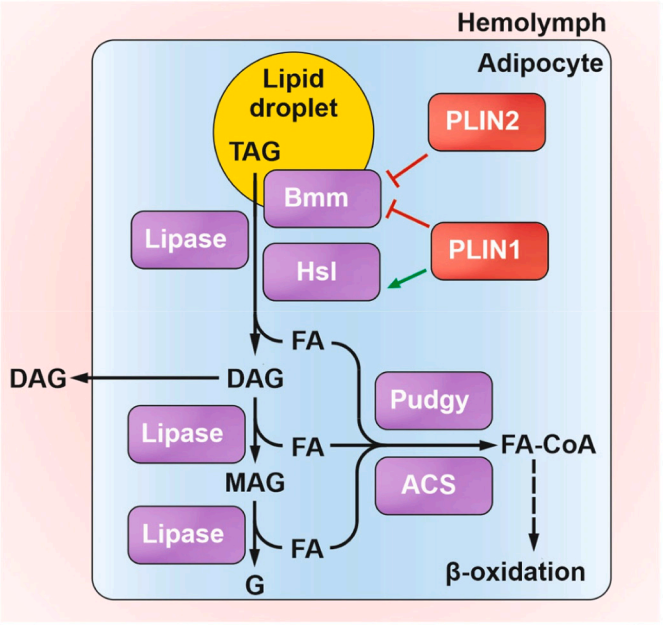

Fig. 4. Lipolysis and mobilization of triacylglycerol Mobilization of lipid droplet (LD) triacylglycerol (TAG) stores in adipocytes is initiated by hydrolysis of TAG to diacylglycerol (DAG) and fatty acid (FA) by Bmm, Hsl, and possibly additional lipase(s). DAG can be exported into the hemolymph for lipid transport to peripheral tissues. DAG may also be further hydrolyzed to fatty acids (FAs) and glycerol (G) via a monoacylglycerol (MAG) intermediate by yet uncharacterized lipases. FAs can be catabolized via β-oxidation after activation to acyl-CoA (FA-CoA) by Pudgy and possibly other acyl-CoA synthetase (ACS) enzymes. LD coat proteins PLIN1 and PLIN2 restrict Bmm activity. Upon starvation PLIN1 promotes activity of Hsl and possibly other lipases.

4.4. Lipid transport

Lipid transport between tissues requires a system of circulating hemolymph lipoproteins. Apolipoprotein precursors are synthesized and secreted by fat body cells and/or cardiomyocytes and act as reusable lipid shuttles in lipid exchange processes between hemolymph and tissues [60,115]. The *Drosophila* hemolymph contains several lipoproteins with different lipid and protein composition. Approximately 95% of all hemolymph lipids in 3rd instar larvae are associated with the lipoprotein Lipophorin (Lpp) [60]. Lpp particles contain mainly DAG, phospholipids, and free sterols with trace amounts of sphingolipids and hydrocarbons [60,191]. In feeding 3rd instar larvae Lpp is synthesized in fat body cells as a DAG-poor precursor particle, picks up dietary and de novo synthesized lipids at the midgut, and transfers it to target tissues. Upon starvation, Lpp delivers lipid from the fat body to other tissues [60,92]. Lpp has been implicated in lipid supply to imaginal discs, fat body, brain, oenocytes, and vitellogenic follicles although other tissues are also likely to access lipids via Lpp [21,60,91,168]. Lipid transfer

between Lpp and target tissues requires additional protein factors. Neuropeptide-like precursor 2 (Nplp2) is a small apolipoprotein produced in the fat body, which promotes lipid loading of Lpp at the midgut. Biochemical studies indicate that Nplp2 acts as exchangeable apolipoprotein to maximizes lipid transfer capacity of Lpp [116]. Efficient lipid loading of Lpp requires also Lipid transfer particle (LTP), which forms a distinct lipoprotein with higher density than Lpp and typically associates with only ~1% of total hemolymph lipids [60]. Nevertheless, LTP is essential for bulk lipid transport and required for Lpp loading at the midgut and efficient lipid delivery to imaginal discs and oocytes [60,192]. Biochemical and genetic studies in *Manduca sexta* and *Drosophila* indicate that LTP acts as lipid shuttle between Lpp and target tissues [193,194]. The interaction of LTP with target tissues is promoted by members of the low-density lipoprotein receptor family. Two members of this family, termed Lipoprotein receptors 1 and 2 (LpR1 and LpR2), are required for efficient margination of LTP particles at imaginal discs and oocytes. Direct associations between LpRs and LTP stabilize Lpp particles in the extracellular space of these tissues and promote lipid transfer [21,192]. How hemolymph lipids cross cellular membranes and if this process involves lipid processing is poorly understood. Although endocytosis of Lpp and LTP particles has been observed in imaginal discs and cultured cells ovaries acquire Lpp lipids also in the absence of functional endocytosis [21,192,195,196].

5. Hormonal regulation of lipid metabolism

5.1. Insulin and target of rapamycin signaling

Insulin/insulin-related growth factor signaling has a central role in growth, development, aging, stress resistance, and metabolism (for review see [77,80]). *Drosophila* insulin signaling is initiated by binding of Dilps to InR on target tissues. Multiple Dilps are capable of binding and activating InR. A primary source of circulating Dilps are IPCs, which produce context-specific mixtures of Dilp1, 2, 3, and 5. Specific Dilps, such as fat body-derived Dilp6, are produces outside of the IPCs [77,80]. Activation of InR relays the insulin signal via adapter proteins (including Chico) and a conserved cascade of molecular events to altered activities of kinases, transcription factors, and metabolic enzymes [76]. The protein kinase Akt1 and the transcription factor Foxo are central nodes in this cascade. Akt1 is activated in response to insulin-induced increases in the second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP3), which is catalyzed by phosphatidylinositol 3-kinase (PI3K, encoded by *Drosophila Pi3K92E*). This leads to the recruitment of Akt1 to the plasma membrane and allows its activation by Phosphoinositide-dependent kinase 1 (Pdk1)-mediated phosphorylation [76,197,198]. Akt1 promotes Foxo phosphorylation and cytoplasmic retention leading to a reduction in Foxo transcriptional activity. This decreases Foxo-dependent expression of lipid catabolic genes such as the lipase genes *bmm* and *Lip4* and the mitochondrial acyl-CoA synthetase gene *pudgy* [79,177,199,200]. Accordingly, insulin-mediated suppression of Foxo promotes TAG storage by inhibiting TAG catabolism. Upon starvation, when insulin signaling is low, Foxo translocates to the nucleus to activate expression of lipocatabolic genes and TAG mobilization [79]. Foxo activity is regulated by additional inputs from kinases, deacetylases, and interactions with other transcription factors. Histone deacetylase 4 (Hdac4) promotes Foxo transcriptional activity by decreasing its acetylation status. The nuclear abundance of Hdac4 is negatively regulated via phosphorylation by salt-inducible kinase 3 (Sik3), which limits Foxo deacetylation and transcriptional output [79,201]. This regulatory cascade is engaged by insulin-responsive Akt1 and by Liver kinase B1, both of which phosphorylate and activate Sik3 [79,201]. In addition, the *Drosophila* NF-κB homolog Relish and the juvenile hormone-responsive transcription factor Kr-h1 antagonize Foxo-induced *bmm* expression illustrating how Foxo integrates inputs from diverse hormonal and stress-responsive pathways to adjust TAG lipolysis rates to specific developmental or environmental cues [184,185]. While suppression of lipolysis is an important outcome of insulin signaling, efficient TAG storage requires also TAG synthesis via the G3P pathway. Genetic evidence indicates that insulin signaling supports G3P pathway activity at the level of the PA phosphatase Lipin [153]. Collectively, the molecular events induced by insulin signaling autonomously promote TAG storage in the *Drosophila* fat body and adult oenocytes and induce the formation of large LDs in the nurse cells of ovaries [78,79,102,202]. Paradoxically, systemic reductions in *Drosophila* insulin signaling also lead to elevated organismal TAG levels [203–205]. However, this phenotype may be the complex result of alterations in growth, development, and other metabolic pathways, which occur in response to systemic and chronic reductions in insulin signaling.

Enzymes of the G3P pathway are not only downstream effectors but also important regulators of insulin signaling. Genetic downregulation of GPAT4, AGPAT3, or Lipin expression blunts insulin signaling in the larval fat body and global loss of GPAT4 causes semi-lethality and delays larval growth, which resembles the phenotype of insulin pathway mutants [76,153,155]. Reduced membrane PIP3 levels and decreased Akt1 phosphorylation have been identified in Lipin-deficient larval fat body cells suggesting that impaired second messenger formation compromises insulin signaling in these animals [153]. A similar molecular phenotype occurs upon loss of the cytidine diphosphate-DAG synthase CdsA, an enzyme that generates cytidine diphosphate-DAG intermediates from PA for further conversion to phosphatidylinositol, phosphatidylglycerol, and cardiolipin [206]. Reduced membrane PIP3 levels and reduced insulin pathway activity in *CdsA* mutant salivary glands have been attributed to inefficient formation of PI and phosphatidylinositol 4,5-bisposphate (PIP2) precursors [206]. However, scarcity of membrane PIP2 has not been detected in Lipin-deficient fat body cells [153]. Thus, how exactly G3P pathway activity associates with membrane PIP3 levels remains to be elucidated.

Drosophila insulin signaling closely intersects with another nutrient sensing pathway, which relies on the activity of TOR kinase. TOR kinase can associate with distinct regulatory proteins that give rise to two functionally distinct TOR complexes, referred to as TOR complex 1 (TORC1) and TOR complex 2 (TORC2). The TOR pathway mediates cell autonomous nutrient sensing and growth control [207,208]. TOR kinase activity phosphorylates effector proteins to promote translation initiation and ribosome biogenesis, or to inhibit autophagy [208–210]. Collectively, these events promote cell growth and replication and are essential for successful development. The TOR pathway intersects with insulin/insulin-like growth factor signaling at multiple levels. In particular, insulin can activate TOR signaling via Akt1-dependent phosphorylation of the negative TOR regulators Tuberous sclerosis complex 1 and 2 (Tsc1/Tsc2) [211]. Tsc1/Tsc2 inhibit Ras homolog enriched in brain (Rheb), an activator of TOR kinase [212]. Vice versa, nutrient-responsive TOR signaling in the fat body acts as important non-autonomous regulator of Dilp release from IPCs and systemic insulin signaling [213]. This fat body-IPC axis is maintained by several secreted factors, which are differentially activated by macronutrients that are sensed and processed in the fat body [94–97]. In line with the central role of TOR in cellular and organismal growth and metabolism, alterations in TOR signaling have been associated with changes in TAG storage. Ectopic activation of TOR elevates TAG storage in the fat body and causes formation of large LDs in *Drosophila* nurse cells [214–216]. The outcome of TOR inhibition is more complex. Pharmacological inhibition of TOR activity by rapamycin has been associated with increased organismal TAG levels [215,217]. Conversely, reduced TAG storage and protection against high fat diet-induced obesity have been observed in hypomorphic *TOR* mutants. Increased *bmm* transcript concentrations in these mutants support the notion that TOR activity limits lipolysis under physiological conditions by suppressing *bmm* expression [51,218]. TOR signaling may also activate lipogenic gene expression via the transcription factor SREBP, which has been implicated as effector of cell growth downstream of Akt1 and TOR [219]. Moreover, TOR activity promotes expression and cytoplasmic localization of the PA phosphatase

Lipin, a central enzyme in the TAG synthesis pathway [153]. While these studies are consistent with the lipoanabolic function of TOR signaling individual TOR effectors differentially regulate TAG storage. E.g. 4E-BP, which suppresses translation initiation upon low TOR signaling, promotes TAG storage and decelerates TAG consumption upon starvation [215]. Similarly, Repressed by TOR (REPTOR), a transcription factor that is suppressed by TOR activity, is required for normal TAG storage and its loss reduces organismal TAG levels [220]. A recent study indicates that TOR activity in oenocytes is required to adequately suppress organismal de novo lipogenesis during fly maturation further illustrating that TOR-mediated regulation of lipid metabolism is highly context-specific [105]. An overview of the relationship between insulin, TOR, and enzymatic effectors of TAG metabolism is presented in Fig. 5.

5.2. Adipokinetic hormone

After secretion from corpora cardiaca cells, Akh circulates in the hemolymph and signals via binding to the G-protein coupled AkhR on target cells [221,222]. *Drosophila AkhR* expression is restricted to the fat body and a subset of gustatory and octopaminergic neurons [14,223,224]. Akh modulates different aspects of insect physiology including mating behavior, locomotion, food intake, and stress resistance [36,225–227]. However, its primary function in a multitude of model insects is the mobilization of energy stores, in particular TAG [228,229]. As a consequence, disruption of Akh signaling in adult *Drosophila* manifests in impaired TAG mobilization and excessive TAG accumulation [14,36]. The Akh signal is transmitted via 3′,5′-cyclic

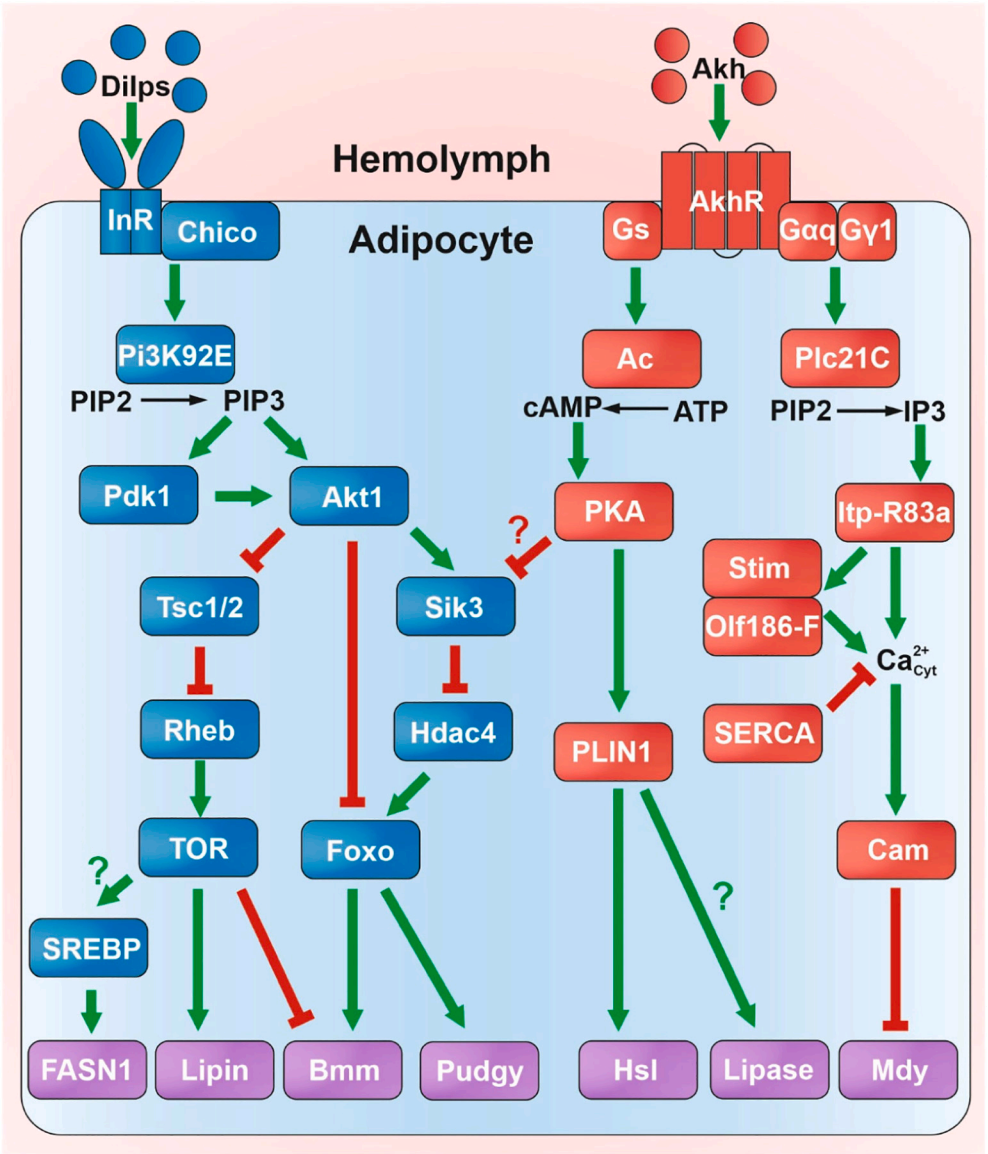

Fig. 5. Hormonal regulation of triacylglycerol storage and lipolysis by insulin-like and adipokinetic hormone signaling. Binding of *Drosophila* insulin-like peptides (Dilps) to insulin receptor (InR) triggers intracellular formation of the second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP3) from phosphatidylinositol 4,5-bisphosphate (PIP2) via adapter proteins (including Chico) and activation of phosphatidylinositol-3-kinase (Pi3K92E). PIP3 recruits and activates protein kinases including Pdk1 and Akt1. Akt1 suppresses nuclear translocation and transcriptional activity of the transcription factor Foxo and its co-factor Hdac4. Akt1 activates the kinase Sik3, which prevents nuclear translocation of Hdac4 and subsequent deacetylation of Foxo. Upon low insulin signaling Foxo activates transcription of lipocatablic effectors including the lipase Bmm and the acyl-CoA synthetase Pudgy. Akt1 may also promote TOR pathway activity by inhibition of the negative TOR regulator Tsc1/2. TOR promotes FASN1 expression possibly via the transcription factor SREBP and favors expression and cytoplasmic localization of the PA phosphatase Lipin. Conversely, TOR restricts expression of the lipase Bmm. Binding of Akh to AkhR activates G proteins (including Gαq, Gγ1 and a Gs protein), which relay the Akh signal to adenylate cyclase (Ac) and phospholipase C (including Plc21C) resulting in the enzymatic formation of the second messengers 3′,5′-cyclic adenosine monophosphate (cAMP) and inositol-1,4,5-trisphosphate (IP3). cAMP is an allosteric activator of the protein kinase PKA, which phosphorylates several downstream targets including kinases, transcription factors, and the lipid droplet protein PLIN1. PKA-mediated phosphorylation of PLIN1 may promote lipolysis by facilitating activity of Hsl and other lipases. PKA may also mediate increased Bmm expression via inhibition of Sik3 and the resultant de-repression of Foxo transcriptional activity. IP3 activates the IP3-sensitive ER calcium channel Itp-R83a, which releases ER calcium stores into the cytosol. Depletion of ER calcium favors interaction of the ER calcium sensor Stim with the plasma membrane calcium channel Olf186-F and influx of extracellular calcium into the cytosol. The ER calcium pump SERCA terminates calcium signaling by recycling calcium into the ER lumen. Elevated cytosolic calcium (Ca^{2+}_{Cyt}) favors increased lipolytic and decreased lipogenic gene expression (including Mdy) likely via the calcium binding protein Cam. Note that arrows/blocks can but do not necessarily represent direct interactions.

adenosine monophosphate (cAMP) and calcium second messenger systems [228,230]. Akh-mediated activation of adenylate cyclase (Ac) increases intracellular cAMP, which acts as allosteric activator of kinases and transcription factors [82,230]. In Akh-stimulated *Manduca sexta* fat body cells cAMP-activated PKA phosphorylates the lipid droplet protein PLIN1. This event promotes lipase access to the LD surface and increases lipolytic output in an in vitro reconstituted system [186,231]. In consistence with these observations, analyses of *plin1* and *AkhR* mutant *Drosophila* imply an interaction between PLIN1 and Akh-dependent lipases as central event in Akh-induced lipolysis [14,145]. However, the molecular details of this process are poorly understood. It is currently unclear as to which extent PLIN1 phosphorylation is necessary and sufficient for Akh induction of lipolysis because a *Drosophila* PLIN1 mutant variant lacking known and putative phosphorylation sites remains largely functional in vivo [145]. Ambiguity also exists with regard to the molecular identity of Akh-dependent lipase(s). As discussed above PAPLA1 and Hsl are possible candidate effectors of Akh-induced lipolysis. It has been reported that PLIN1 recruits Hsl to fat body LDs of 3rd instar larvae [170]. If this event is sufficient to activate TAG lipolysis downstream of Akh and PKA or if other lipases including PAPLA1 are involved has not been fully elucidated. The cAMP/PKA branch of Akh signaling has also been implicated in the regulation of transcription factors [82,201]. Upon acute starvation Akh suppresses Sik3 and supports Foxo-dependent transcription of *bmm* [201]. Although not directly shown for *Drosophila*, PKA-mediated phosphorylation and inactivation of SIK has been observed in mammals implying cAMP/PKA as causal link between Akh and Sik3 [201]. The second signaling system activated by Akh is initiated by phospholipase C (encoded by *Drosophila Plc21C*), which catalyzes the conversion of PIP2 to inositol-1,4,5-trisphosphate (IP3). The binding of IP3 to an ER-resident IP3-sensitive calcium channel (encoded by *Drosophila Itp-R83a*) triggers discharge of ER calcium stores into the cytosol. The concurrent depletion of ER calcium stores leads to interactions between the calcium sensor Stromal interaction molecule (Stim) and calcium channel subunits at the plasma membrane (*Drosophila Olf186-F*), which in turn triggers influx of extracellular calcium, a phenomenon referred to as store-operated calcium entry [10,228,232]. Collectively, these events elevate cytosolic calcium concentrations in the fat body cell. Depletion of genes that increase or maintain cytosolic calcium levels (e.g. Stim) cause an Akh resistance phenotype and a gene expression signature that favors progressive TAG accumulation [10,232–234]. Conversely, organismal TAG storage decreases upon interference with factors that counteract cytosolic calcium, e.g. the Sarco/ER calcium-ATPase, which terminates cytosolic calcium signaling by recycling calcium into the ER lumen [10,165]. Experiments in *Manduca sexta* and other non-dipteran insects suggest that increased cellular calcium is required for acute Akh stimulation of fat body lipolysis [230]. Depletion of fat body cytosolic calcium or of the calcium binding protein calmodulin in *Drosophila* cause elevated *mdy* and decreased *bmm* transcript levels. This observation argues that calcium signaling controls fat storage also via transcriptional control, e.g. by suppressing *mdy* expression [10,232]. However, how the calcium signal is transmitted to acute or chronic alterations of lipolytic and lipogenic effectors is not known. Importantly, *Drosophila* fat body calcium signaling controls TAG storage also indirectly by modulating feeding behavior and adipokine secretion [10,99]. Fig. 5 summarizes the regulation of fat body TAG by Akh signaling including interactions with insulin and TOR.

6. Pathophysiological complications of diet-induced obesity in flies

In humans, obesity, defined as an excessive accumulation of body fat, is associated with an elevated risk of developing insulin resistance, diabetes, cardiovascular disease, and non-alcoholic fatty liver disease [235]. Obesity arises as the result of a positive energy balance, i.e. the calories consumed exceed the calories expended. The global prevalence of obesity is the result of profound social and economic changes including growing availability of energy-rich food and reduced need for physical activity. Yet, at an individual basis the risk of developing obesity and associated co-morbidities results from a complex interaction of dietary, environmental, and hereditary factors [235,236]. *Drosophila* has been used to model both the genetic as well as the dietary basis of obesity. The genetic toolkit of the *Drosophila* system and its unique amenability for high-throughput studies inspired genetic screens aimed at identifying genes that prevent or favor obesity at genome-wide scales [10,11,237]. These genetic studies have been recently complemented by research elucidating the dietary basis of obesity. The most common obesogenic diets in *Drosophila* research include an excess of sugar or fat [5,15,51]. Feeding *Drosophila* larvae a high sugar diet containing excess sucrose results in increased TAG storage, hyperglycemia, hyperinsulinemia and insulin resistance, which manifests in delayed development and reduced body size [26,238]. Similar metabolic alterations including TAG over-storage, hyperglycemia, and reduced insulin signaling, are induced in high sugar-fed *Drosophila* adults, which are short-lived and display cardiac and nephrocyte dysfunctions reminiscent of diabetic cardiomyopathy and nephropathy [239,240]. Interestingly, organ dysfunction and decreased lifespan in high sugar-fed adults can be attributed to increased tissue hexosamine flux and water imbalance rather than TAG over-storage per se, illustrating that care must be taken in assuming causal relationships between excess TAG storage and diet-induced disease [239–241]. Metabolic abnormalities and organ dysfunction are also a hallmark of *Drosophila* chronically feeding on high fat diets that typically include coconut oil or lard [51,242]. High fat feeding results in elevated TAG storage, insulin resistance, and a reduction in life span. TGF-β signaling in the fat body has been causally linked to the development of insulin resistance in high fat diet-fed *Drosophila* [243]. In addition, systemic activation of JAK/STAT signaling by hemocyte-derived Upd3 has been identified as important trigger of high fat diet-induced insulin resistance and lifespan reduction [242]. Chronic high fat diet also causes ectopic TAG deposition in non-adipose tissues including cardiac and skeletal muscle [51,57]. Although the formation of ectopic TAG per se is not considered harmful it reflects an imbalance between lipid influx and usage, which has been commonly associated with tissue damage in obese and diabetic patients [3]. The "spillover" of lipids into non-adipose tissue, which is reflected by ectopic TAG deposition, often entails chronic elevations of other lipids including DAG or ceramides, which are potent signaling molecules and may directly or indirectly interfere with cellular signaling pathways or cause cellular stress [244,245]. This concept is referred to as "lipotoxicity" and is thought to contribute to organ dysfunction in obese and diabetic patients and animal models [3,246]. High fat diet-induced "lipotoxic cardiomyopathy" in *Drosophila* manifests in reduced fractional shortening, reduced heart period, dysfunctional ostia and increased incidence of non-contractile cells [51]. Genetic experiments identified TOR signaling as early event in high fat diet-induced lipotoxic cardiomyopathy [51]. TOR activity suppresses a protective epistatic interaction between Bmm lipase activity and the transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1)/Spargel, both of which are necessary for normal cardiac function even in the absence of dietary challenge [135]. Interestingly, high fat diet-induced decreases in *bmm* and *spargel* expression and the associated symptoms of cardiac lipotoxicity persist for a subsequent generation irrespective of the diet [247]. Inter- and transgenerational inheritance of obesity phenotypes have also been reported for *Drosophila* fed high sugar diets and have been linked to distinct epigenetic markers [248,249].

7. Conclusions and perspectives

The increasing prevalence of human disorders associated with TAG over-storage such as diabetes, obesity, and non-alcoholic fatty liver disease has inspired TAG metabolism research in genetically tractable model organisms. The genetic amenability of the *Drosophila* model

system has been exploited in several large-scale screens to identify genetic regulators of TAG storage and LD biology. These studies have strengthened the view that molecular processes of TAG formation, degradation, and storage are remarkably similar between *Drosophila* and higher organisms. In the past decade *Drosophila* research has been successfully extended to model the etiology and consequences of overnutrition and diet-induced metabolic diseases. While these examples underscore the value and versatility of *Drosophila* as a research tool to investigate TAG metabolism and TAG-associated disorders, several gaps of knowledge hinder a more profound understanding of the relationship between *Drosophila* genetics and TAG biochemistry. One example is the incomplete characterization of the enzymology of *Drosophila* TAG metabolism and of the signaling events that confer acute or chronic alterations in TAG storage. Annotations of isoenzymes in the *Drosophila* TAG synthesis pathway are often simply based on homology to human or yeast proteins but not on experimental evidence. Such isoenzymes may have non-redundant functions in the synthesis of TAG species and other glycerolipids or contribute differentially to TAG synthesis in various cell or tissue types. Open questions remain also with regard to enzymes mediating TAG breakdown. Candidate lipolytic effectors of the Akh pathway have been identified in *Manduca sexta* and *Drosophila* but the contribution of these enzymes to Akh-induced lipolysis is still unclear. Likewise, while immunohistochemical evidence suggests the occurrence of lysosomal TAG degradation ("lipophagy") in *Drosophila* the lipolytic effectors of this process are essentially unknown making it difficult to truly assess the contribution of this process to TAG homeostasis. A comprehensive functional characterization of candidate TAG metabolic enzymes will thus close an important gap in *Drosophila* lipid research and may also unravel novel aspects of TAG metabolism relevant for basic and translational research.

The integration of organ systems specialized in specific aspects of TAG metabolism requires a sophisticated endocrine system coordinating inter-tissue communication. *Drosophila* research has substantially advanced our understanding of how tissues sense alterations in energy intake and communicate this information to other central or peripheral organs. Humoral factors are secreted by essentially all organ systems involved in energy homeostasis and help to adjust TAG homeostasis to alterations in the nutritional status, often via cross-talk with insulin or Akh signaling. Nevertheless, how these endocrine factors are connected at the molecular level to lipogenic and lipolytic pathways is often poorly understood. Among the organ systems implicated in TAG metabolism the fat body deserves specific attention due to its central role in TAG storage, lipid processing, and lipid transport. The fat body acts as nutrient sensor, provides substrates for vitellogenesis, contributes to immunity, and acts as central endocrine organ in energy homeostasis and growth control. Understanding the cross-talk between those functions is an area of active research, which will certainly result in more advanced and integrated concepts of fat body biology in the near future. The *Drosophila* fat body is a plastic organ that expands upon elevated TAG storage mainly by an increase in cell size [35]. Expandability of adipose tissue is an important concept in human obesity research, and believed to be inversely related to detrimental ectopic fat depositions and lipotoxicity in obese patients. While there is evidence that excessive expansion of *Drosophila* fat body TAG stores entails detrimental lipid "spillover" to peripheral tissues little is known about environmental and genetic factors that define the storage capacity of *Drosophila* fat body. Moreover, fat body tissue exists as distinct depots in segments or associated with other tissues. Whether these depots are functionally equivalent or play distinct (patho)physiological roles in organismal TAG metabolism remains to be elucidated.

Declaration of competing interest

The authors declare no competing interest.

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References

[1] N. Krahmer, R.V. Farese, T.C. Walther, Balancing the fat: lipid droplets and human disease, EMBO Mol. Med. 5 (2013) 973–983.
[2] R.A. Coleman, D.G. Mashek, Mammalian triacylglycerol metabolism: synthesis, lipolysis, and signaling, Chem. Rev. 111 (2011) 6359–6386.
[3] J.E. Schaffer, Lipotoxicity: many roads to cell dysfunction and cell death: introduction to a thematic review series, J. Lipid Res. 57 (2016) 1327–1328.
[4] R. Zechner, F. Madeo, D. Kratky, Cytosolic lipolysis and lipophagy: two sides of the same coin, Nat. Rev. Mol. Cell Biol. 18 (2017) 671–684.
[5] L.P. Musselman, R.P. Kühnlein, Drosophila as a model to study obesity and metabolic disease, J. Exp. Biol. 121 (2018), jeb163881.
[6] C. Heier, R.P. Kühnlein, Triacylglycerol metabolism in Drosophila melanogaster, Genetics 210 (2018) 1163–1184.
[7] M. Gáliková, P. Klepsatel, Obesity and aging in the Drosophila model, Int. J. Mol. Sci. 19 (2018) 1–24.
[8] E. Owusu-Ansah, N. Perrimon, Modeling metabolic homeostasis and nutrient sensing in Drosophila: implications for aging and metabolic diseases, DMM Dis. Model. Mech. 7 (2014) 343–350.
[9] M. Beller, C. Sztalryd, N. Southall, M. Bell, H. Jäckle, D.S. Auld, B. Oliver, COPI complex is a regulator of lipid homeostasis, PLoS Biol. 6 (2008), e292.
[10] J. Baumbach, P. Hummel, I. Bickmeyer, K.M. Kowalczyk, M. Frank, K. Knorr, A. Hildebrandt, D. Riedel, H. Jäckle, R.P. Kühnlein, A Drosophila in vivo screen identifies store-operated calcium entry as a key regulator of adiposity, Cell Metab. 19 (2014) 331–343.
[11] J.A. Pospisilik, D. Schramek, H. Schnidar, S.J.F. Cronin, N.T. Nehme, X. Zhang, C. Knauf, P.D. Cani, K. Aumayr, J. Todoric, M. Bayer, A. Haschemi, V. Puviindran, K. Tar, M. Orthofer, G.G. Neely, G. Dietzl, A. Manoukian, M. Funovics, G. Prager, et al., Drosophila genome-wide obesity screen reveals hedgehog as a determinant of brown versus white adipose cell fate, Cell 140 (2010) 148–160.
[12] Y. Guo, T.C. Walther, M. Rao, N. Stuurman, G. Goshima, K. Terayama, J.S. Wong, R.D. Vale, P. Walter, R.V. Farese, Functional genomic screen reveals genes involved in lipid-droplet formation and utilization, Nature 453 (2008) 657–661.
[13] I.A. Droujinine, N. Perrimon, Interorgan communication pathways in physiology: focus on Drosophila, Annu. Rev. Genet. 50 (2016) 539–570.
[14] S. Grönke, G. Müller, J. Hirsch, S. Fellert, A. Andreou, T. Haase, H. Jäckle, R. P. Kühnlein, Dual lipolytic control of body fat storage and mobilization in Drosophila, PLoS Biol. 5 (2007), e137.
[15] L.P. Musselman, J.L. Fink, P.V. Ramachandran, B.W. Patterson, A.L. Okunade, E. Maier, M.R. Brent, J. Turk, T.J. Baranski, Role of fat body lipogenesis in protection against the effects of caloric overload in drosophila, J. Biol. Chem. 288 (2013) 8028–8042.
[16] H. Li, J.M. Tennessen, Methods for studying the metabolic basis of Drosophila development, Wiley Interdiscip. Rev. Dev. Biol. 6 (2017), 10.1002/wdev.280.
[17] J.M. Tennessen, W.E. Barry, J. Cox, C.S. Thummel, Methods for studying metabolism in Drosophila, Methods 68 (2014) 105–115.
[18] Y. Song, J.O. Park, L. Tanner, Y. Nagano, J.D. Rabinowitz, S.Y. Shvartsman, Energy budget of Drosophila embryogenesis, Curr. Biol. 29 (2019) R566–R567.
[19] M. Buszczak, X. Lu, W.A. Segraves, T.Y. Chang, L. Cooley, Mutations in the midway gene disrupt a Drosophila acyl coenzyme A, Genetics 160 (2002) 1511–1518.
[20] S. Grönke, A. Mildner, S. Fellert, N. Tennagels, S. Petry, G. Müller, H. Jäckle, R. P. Kühnlein, Brummer lipase is an evolutionary conserved fat storage regulator in Drosophila, Cell Metab. 1 (2005) 323–330.
[21] E. Parra-Peralbo, J. Culi, Drosophila lipophorin receptors mediate the uptake of neutral lipids in oocytes and imaginal disc cells by an endocytosis-independent mechanism, PLoS Genet. 7 (2011), e1001297.
[22] Z. Li, K. Thiel, P.J. Thul, M. Beller, R.P. Kühnlein, M.A. Welte, Lipid droplets control the maternal histone supply of Drosophila embryos, Curr. Biol. 22 (2012) 2104–2113.
[23] Z. Li, M.R. Johnson, Z. Ke, L. Chen, M.A. Welte, Drosophila lipid droplets buffer the H2Av supply to protect early embryonic development, Curr. Biol. 24 (2014) 1485–1491.
[24] P. Anand, S. Cermelli, Z. Li, A. Kassan, M. Bosch, R. Sigua, L. Huang, A. J. Ouellette, A. Pol, M.A. Welte, S.P. Gross, A novel role for lipid droplets in the organismal antibacterial response, Elife 1 (2012), e00003.
[25] D. Garrido, T. Rubin, M. Poidevin, B. Maroni, A. Le Rouzic, J.P. Parvy, J. Montagne, Fatty acid synthase cooperates with glyoxalase 1 to protect against sugar toxicity, PLoS Genet. 11 (2015) 1–26.
[26] L.P. Musselman, J.L. Fink, K. Narzinski, P.V. Ramachandran, S.S. Hathiramani, R. L. Cagan, T.J. Baranski, A high-sugar diet produces obesity and insulin resistance in wild-type Drosophila, DMM Dis. Model. Mech. 4 (2011) 842–849.
[27] P. Klepsatel, D. Knoblochová, T.N. Girish, H. Dircksen, M. Gáliková, The influence of developmental diet on reproduction and metabolism in Drosophila, BMC Evol. Biol. 20 (2020), 93.

[28] B.A. Martínez, R.G. Hoyle, S. Yeudall, M.E. Granade, T.E. Harris, J. David Castle, N. Leitinger, M.L. Bland, Innate Immune Signaling in Drosophila Shifts Anabolic Lipid Metabolism From Triglyceride Storage to Phospholipid Synthesis to Support Immune Function 16, PLoS Genet., 2020, e1009192.

[29] S.C. Shin, S.H. Kim, H. You, B. Kim, A.C. Kim, K.A. Lee, J.H. Yoon, J.H. Ryu, W. J. Lee, Drosophila microbiome modulates host developmental and metabolic homeostasis via insulin signaling, Science 334 (2011) 670–674 (80-.).

[30] J. Bi, Y. Xiang, H. Chen, Z. Liu, S. Grönke, R.P. Kühnlein, X. Huang, Opposite and redundant roles of the two Drosophila: perilipins in lipid mobilization, J. Cell Sci. 125 (2012) 3568–3577.

[31] J. Rodenfels, O. Lavrynenko, S. Ayciriex, J.L. Sampaio, M. Carvalho, A. Shevchenko, S. Eaton, Production of systemically circulating hedgehog by the intestine couples nutrition to growth and development, Genes Dev. 28 (2014) 2636–2651.

[32] E. Gutierrez, D. Wiggins, B. Fielding, A.P. Gould, Specialized hepatocyte-like cells regulate Drosophila lipid metabolism, Nature 445 (2007) 275–280.

[33] T. Yamada, K. ichi Hironaka, O. Habara, Y. Morishita, T. Nishimura, A developmental checkpoint directs metabolic remodelling as a strategy against starvation in Drosophila, Nat. Metab. 2 (2020) 1096–1112.

[34] A.B. Merkey, C.K. Wong, D.K. Hoshizaki, A.G. Gibbs, Energetics of metamorphosis in drosophila melanogaster, J. Insect Physiol. 57 (2011) 1437–1445.

[35] M.B. Johnson, F.M. Butterworth, Maturation and aging of adult fat body and oenocytes in Drosophila as revealed by light microscopic morphometry, J. Morphol. 184 (1985) 51–59.

[36] M. Gáliková, M. Diesner, P. Klepsatel, P. Hehlert, Y. Xu, I. Bickmeyer, R. Predel, R.P. Kühnlein, Energy homeostasis control in Drosophila adipokinetic hormone mutants, Genetics 201 (2015) 665–683.

[37] M. Carvalho, J.L. Sampaio, W. Palm, M. Brankatschk, S. Eaton, A. Shevchenko, Effects of diet and development on the Drosophila lipidome, Mol. Syst. Biol. 8 (2012), 600.

[38] A. Nelliot, N. Bond, D.K. Hoshizaki, Fat-body remodeling in Drosophila melanogaster, Genesis 44 (2006) 396–400.

[39] K.J. Min, M.F. Hogan, M. Tatar, D.M. O'Brien, Resource allocation to reproduction and soma in Drosophila: a stable isotope analysis of carbon from dietary sugar, J. Insect Physiol. 52 (2006) 763–770.

[40] J.R. Aguila, D.K. Hoshizaki, A.G. Gibbs, Contribution of larval nutrition to adult reproduction in Drosophila melanogaster, J. Exp. Biol. 216 (2013) 399–406.

[41] G. Storelli, H.J. Nam, J. Simcox, C.J. Villanueva, C.S. Thummel, Drosophila HNF4 directs a switch in lipid metabolism that supports the transition to adulthood, Dev. Cell 48 (2019) 200–214 (e6).

[42] J.R. Aguila, J. Suszko, A.G. Gibbs, D.K. Hoshizaki, The role of larval fat cells in adult Drosophila melanogaster, J. Exp. Biol. 210 (2007) 956–963.

[43] L.W. Wat, C. Chao, R. Bartlett, J.L. Buchanan, J.W. Millington, H.J. Chih, Z. S. Chowdhury, P. Biswas, V. Huang, L.J. Shin, L.C. Wang, M.P.L. Gauthier, M. C. Barone, K.L. Montooth, M.A. Welte, E.J. Rideout, A Role for Triglyceride Lipase Brummer in the Regulation of Sex Differences in Drosophila Fat Storage and Breakdown, 2020.

[44] M.H. Sieber, A.C. Spradling, Steroid signaling establishes a female metabolic state and regulates SREBP to control oocyte lipid accumulation, Curr. Biol. 25 (2015) 993–1004.

[45] D.A. Skorupa, A. Dervisefendic, J. Zwiener, S.D. Pletcher, Dietary composition specifies consumption, obesity, and lifespan in Drosophila melanogaster, Aging Cell 7 (2008) 478–490.

[46] P. Klepsatel, M. Gáliková, Y. Xu, R.P. Kühnlein, Thermal stress depletes energy reserves in Drosophila, Sci. Rep. 6 (2016), 33667.

[47] O.I. Kubrak, L. Kučerová, U. Theopold, D.R. Nässel, The sleeping beauty: how reproductive diapause affects hormone signaling, metabolism, immune response and somatic maintenance in Drosophila melanogaster, PLoS One 9 (2014), e113051.

[48] H.F. Hofbauer, C. Heier, A.K. Sen Saji, R.P. Kühnlein, Lipidome remodeling in aging normal and genetically obese Drosophila males, Insect Biochem. Mol. Biol. (2020), 103498.

[49] T. Ohtsu, M.T. Kimura, S.H. Hori, Energy storage during reproductive diapause in the Drosophila melanogaster species group, J. Comp. Physiol. B. 162 (1992) 203–208.

[50] M. Brankatschk, T. Gutmann, O. Knittelfelder, A. Palladini, E. Prince, M. Grzybek, B. Brankatschk, A. Shevchenko, Ü. Coskun, S. Eaton, A temperature-dependent switch in feeding preference improves Drosophila development and survival in the cold, Dev. Cell 46 (2018) 781–793 (e4).

[51] R.T. Birse, J. Choi, K. Reardon, J. Rodriguez, S. Graham, S. Diop, K. Ocorr, R. Bodmer, S. Oldham, High-fat-diet-induced obesity and heart dysfunction are regulated by the TOR pathway in Drosophila, Cell Metab. 12 (2010) 533–544.

[52] C.E. May, A. Vaziri, Y.Q. Lin, O. Grushko, M. Khabiri, Q.P. Wang, K.J. Holme, S. D. Pletcher, P.L. Freddolino, G.G. Neely, M. Dus, High dietary sugar reshapes sweet taste to promote feeding behavior in Drosophila melanogaster, Cell Rep. 27 (2019) 1675–1685 (e7).

[53] B.M. Rovenko, O.I. Kubrak, D.V. Gospodaryov, N.V. Perkhulyn, I.S. Yurkevych, A. Sanz, O.V. Lushchak, V.I. Lushchak, High sucrose consumption promotes obesity whereas its low consumption induces oxidative stress in Drosophila melanogaster, J. Insect Physiol. 79 (2015) 42–54.

[54] B.M. Rovenko, N.V. Perkhulyn, D.V. Gospodaryov, A. Sanz, O.V. Lushchak, V. I. Lushchak, High consumption of fructose rather than glucose promotes a diet-induced obese phenotype in Drosophila melanogaster, Comp. Biochem. Physiol. -Part A Mol. Integr. Physiol. 180 (2015) 75–85.

[55] A. Franchet, S. Niehus, G. Caravello, D. Ferrandon, Phosphatidic acid as a limiting host metabolite for the proliferation of the microsporidium Tubulinosema ratisbonensis in Drosophila flies, Nat. Microbiol. 4 (2019) 645–655.

[56] J.R. DiAngelo, M.L. Bland, S. Bambina, S. Cherry, M.J. Birnbaum, The immune response attenuates growth and nutrient storage in Drosophila by reducing insulin signaling, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 20853–20858.

[57] J.E. Villanueva, C. Livelo, A.S. Trujillo, S. Chandran, B. Woodworth, L. Andrade, H.D. Le, U. Manor, S. Panda, G.C. Melkani, Time-restricted feeding restores muscle function in Drosophila models of obesity and circadian-rhythm disruption, Nat. Commun. 10 (2019) 1–17.

[58] S. Muliyil, C. Levet, S. Düsterhöft, I. Dulloo, S.A. Cowley, M. Freeman, ADAM 17-triggered TNF signalling protects the ageing Drosophila retina from lipid droplet-mediated degeneration, EMBO J. 39 (2020), e104415.

[59] K. Thiel, C. Heier, V. Haberl, P.J. Thul, M. Oberer, A. Lass, H. Jäckle, M. Beller, The evolutionarily conserved protein CG9186 is associated with lipid droplets, required for their positioning and for fat storage, J. Cell Sci. 126 (2013) 2198–2212.

[60] W. Palm, J.L. Sampaio, M. Brankatschk, M. Carvalho, A. Mahmoud, A. Shevchenko, S. Eaton, Lipoproteins in Drosophila melanogaster-assembly, function, and influence on tissue lipid composition, PLoS Genet. 8 (2012), e1002828.

[61] A.P. Bailey, G. Koster, C. Guillermier, E.M.A. Hirst, J.I. MacRae, C.P. Lechene, A. D. Postle, A.P. Gould, Antioxidant role for lipid droplets in a stem cell niche of Drosophila, Cell 163 (2015) 340–353.

[62] J.Y. Yew, K. Dreiseweard, C.C. de Oliveira, W.J. Etges, Male-specific transfer and fine scale spatial differences of newly identified cuticular hydrocarbons and triacylglycerides in a Drosophila species pair, PLoS One 6 (2011), e16898.

[63] J.S.R. Chin, S.R. Ellis, H.T. Pham, S.J. Blanksby, K. Mori, Q.L. Koh, W.J. Etges, J. Y. Yew, Sex-specific triacylglycerides are widely conserved in Drosophila and mediate mating behavior, Elife 3 (2014), e01751.

[64] S.D. Albin, K.R. Kaun, J.M. Knapp, P. Chung, U. Heberlein, J.H. Simpson, A subset of serotonergic neurons evokes hunger in adult Drosophila, Curr. Biol. 25 (2015) 2435–2440.

[65] B. Al-Anzi, V. Sapin, C. Waters, K. Zinn, R.J. Wyman, S. Benzer, Obesity-blocking neurons in Drosophila, Neuron 63 (2009) 329–341.

[66] B. Al-Anzi, K. Zinn, Identification and characterization of mushroom body neurons that regulate fat storage in Drosophila, Neural Dev. 13 (2018), 18.

[67] D.R. Nässel, M. Zandawala, Recent advances in neuropeptide signaling in Drosophila, from genes to physiology and behavior, Prog. Neurobiol. 179 (2019), 101607.

[68] J.L. Hentze, M.A. Carlsson, S. Kondo, D.R. Nässel, K.F. Rewitz, The neuropeptide allatostatin a regulates metabolism and feeding decisions in drosophila, Sci. Rep. 5 (2015), 11680.

[69] S. Min, H.S. Chae, Y.H. Jang, S. Choi, S. Lee, Y.T. Jeong, W.D. Jones, S.J. Moon, Y. J. Kim, J. Chung, Identification of a peptidergic pathway critical to satiety responses in Drosophila, Curr. Biol. 26 (2016) 814–820.

[70] J. Chen, W. Reiher, C. Hermann-Luibl, A. Sellami, P. Cognigni, S. Kondo, C. Helfrich-Förster, J.A. Veenstra, C. Wegener, Allatostatin A signalling in Drosophila regulates feeding and sleep and is modulated by PDF, PLoS Genet. 12 (2016), e1006492.

[71] B.Y. Chung, J. Ro, S.A. Hutter, K.M. Miller, L.S. Guduguntla, S. Kondo, S. D. Pletcher, Drosophila neuropeptide F signaling independently regulates feeding and sleep-wake behavior, Cell Rep. 19 (2017) 2441–2450.

[72] D.H. Kim, M. Shin, S.H. Jung, Y.J. Kim, W.D. Jones, A fat-derived metabolite regulates a peptidergic feeding circuit in Drosophila, PLoS Biol. 15 (2017), e2000532.

[73] K.S. Lee, K.H. You, J.K. Choo, Y.M. Han, K. Yu, Drosophila short neuropeptide F regulates food intake and body size, J. Biol. Chem. 279 (2004) 50781–50789.

[74] E.J. Rulifson, S.K. Kim, R. Nusse, Ablation of insulin-producing neurons in files: growth and diabetic phenotypes, Science 296 (2002) 1118–1120 (80-.).

[75] S.K. Kim, E.J. Rulifson, Conserved mechanisms of glucose sensing and regulation by Drosophila corpora cardiaca cells, Nature 431 (2004) 316–320.

[76] A.A. Teleman, Molecular mechanisms of metabolic regulation by insulin in Drosophila, Biochem. J. 425 (2010) 13–26.

[77] D.R. Nässel, J. Vanden Broeck, Insulin/IGF signaling in Drosophila and other insects: factors that regulate production, release and post-release action of the insulin-like peptides, Cell. Mol. Life Sci. 73 (2016) 271–290.

[78] J.R. DiAngelo, M.J. Birnbaum, Regulation of fat cell mass by insulin in Drosophila melanogaster, Mol. Cell. Biol. 29 (2009) 6341–6352.

[79] B. Wang, N. Moya, S. Niessen, H. Hoover, M.M. Mihaylova, R.J. Shaw, J.R. Yates, W.H. Fischer, J.B. Thomas, M. Montminy, A hormone-dependent module regulating energy balance, Cell 145 (2011) 596–606.

[80] D.R. Nässel, Y. Liu, J. Luo, Insulin/IGF signaling and its regulation in Drosophila, Gen. Comp. Endocrinol. 221 (2015) 255–266.

[81] G. Lee, J.H. Park, Hemolymph sugar homeostasis and starvation-induced hyperactivity affected by genetic manipulations of the adipokinetic hormone-encoding gene in Drosophila melanogaster, Genetics 167 (2004) 311–323.

[82] W. Song, D. Cheng, S. Hong, B. Sappe, Y. Hu, N. Wei, C. Zhu, M.B. O'Connor, P. Pissios, N. Perrimon, Midgut-derived activin regulates glucagon-like action in the fat body and glycemic control, Cell Metab. 25 (2017) 386–399.

[83] X. Zhao, J. Karpac, Muscle directs diurnal energy homeostasis through a myokine-dependent hormone module in Drosophila, Curr. Biol. 27 (2017) 1941–1955 (e6).

[84] L. Liu, K. Zhang, H. Sandoval, S. Yamamoto, M. Jaiswal, E. Sanz, Z. Li, J. Hui, B. H. Graham, A. Quintana, H.J. Bellen, Glial lipid droplets and ROS induced by mitochondrial defects promote neurodegeneration, Cell 160 (2015) 177–190.

[85] V. Kis, B. Barti, M. Lippai, M. Sass, Specialized cortex glial cells accumulate lipid droplets in drosophila melanogaster, PLoS One 10 (2015), e0131250.
[86] L. Liu, K.R. MacKenzie, N. Putluri, M. Maletić-Savatić, H.J. Bellen, The glia-neuron lactate shuttle and elevated ROS promote lipid synthesis in neurons and lipid droplet accumulation in glia via APOE/D, Cell Metab. 26 (2017) 719–737 (e6).
[87] D.M. Van Den Brink, A. Cubizolle, G. Chatelain, N. Davoust, V. Girard, S. Johansen, F. Napoletano, P. Dourlen, L. Guillou, C. Angebault-Prouteau, N. Bernoud-Hubac, M. Guichardant, P. Brabet, B. Mollereau, Physiological and pathological roles of FATP-mediated lipid droplets in Drosophila and mice retina, PLoS Genet. 14 (2018), e1007627.
[88] C. Papadopoulos, G. Orso, G. Mancuso, M. Herholz, S. Gumeni, N. Tadepalle, C. Jüngst, A. Tzschichholz, A. Schauss, S. Höning, A. Trifunovic, A. Daga, E. I. Rugarli, Spastin binds to lipid droplets and affects lipid metabolism, PLoS Genet. 11 (2015), e1005149.
[89] E.L. Arrese, J.L. Soulages, Insect fat body: energy, metabolism, and regulation, Annu. Rev. Entomol. 55 (2010) 207–225.
[90] D.K. Hoshizaki, R. Lunz, M. Ghosh, W. Johnson, Identification of fat-cell enhancer activity in Drosophila melanogaster using P-element enhancer traps, Genome 38 (1995) 497–506.
[91] J.P. Parvy, L. Napal, T. Rubin, M. Poidevin, L. Perrin, C. Wicker-Thomas, J. Montagne, Drosophila melanogaster acetyl-CoA-carboxylase sustains a fatty acid-dependent remote signal to waterproof the respiratory system, PLoS Genet. 8 (2012), e1002925.
[92] D.J. van der Horst, D. van Hoof, W.J.A. van Marrewijk, K.W. Rodenburg, Alternative lipid mobilization: the insect shuttle system, Mol. Cell. Biochem. 239 (2002) 113–119.
[93] J. Colombani, S. Raisin, S. Pantalacci, T. Radimerski, J. Montagne, P. Léopold, A nutrient sensor mechanism controls Drosophila growth, Cell 114 (2003) 739–749.
[94] H. Sano, A. Nakamura, M.J. Texada, J.W. Truman, H. Ishimoto, A. Kamikouchi, Y. Nibu, K. Kume, T. Ida, M. Kojima, The nutrient-responsive hormone CCHamide-2 controls growth by regulating insulin-like peptides in the brain of Drosophila melanogaster, PLoS Genet. 11 (2015), e1005209.
[95] R. Delanoue, E. Meschi, N. Agrawal, A. Mauri, Y. Tsatskis, H. McNeill, P. Léopold, Drosophila insulin release is triggered by adipose stunted ligand to brain Methuselah receptor, Science 353 (2016) 1553–1556 (80-.).
[96] E. Meschi, P. Léopold, R. Delanoue, An EGF-responsive neural circuit couples insulin secretion with nutrition in Drosophila, Dev. Cell 48 (2019) 76–86 (e5).
[97] N. Agrawal, R. Delanoue, A. Mauri, D. Basco, M. Pasco, B. Thorens, P. Léopold, The Drosophila TNF Eiger is an adipokine that acts on insulin-producing cells to mediate nutrient response, Cell Metab. 23 (2016) 675–684.
[98] A. Rajan, N. Perrimon, Drosophila cytokine unpaired 2 regulates physiological homeostasis by remotely controlling insulin secretion, Cell 151 (2012) 123–137.
[99] A. Rajan, B.E. Housden, F. Wirtz-Peitz, L. Holderbaum, N. Perrimon, A mechanism coupling systemic energy sensing to adipokine secretion, Dev. Cell 43 (2017) 83–98 (e6).
[100] M. Slaidina, R. Delanoue, S. Gronke, L. Partridge, P. Léopold, A Drosophila insulin-like peptide promotes growth during nonfeeding states, Dev. Cell 17 (2009) 874–884.
[101] N. Okamoto, N. Yamanaka, Y. Yagi, Y. Nishida, H. Kataoka, M.B. O'Connor, A. Mizoguchi, A fat body-derived IGF-like peptide regulates postfeeding growth in Drosophila, Dev. Cell 17 (2009) 885–891.
[102] D. Chatterjee, S.D. Katewa, Y. Qi, S.A. Jackson, P. Kapahi, H. Jasper, Control of metabolic adaptation to fasting by dILP6-induced insulin signaling in Drosophila oenocytes, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 17959–17964.
[103] R. Makki, E. Cinnamon, A.P. Gould, The development and functions of oenocytes, Annu. Rev. Entomol. 59 (2014) 405–425.
[104] C. Wicker-Thomas, D. Garrido, G. Bontonou, L. Napal, N. Mazuras, B. Denis, T. Rubin, J.P. Parvy, J. Montagne, Flexible origin of hydrocarbon/pheromone precursors in Drosophila melanogaster, J. Lipid Res. 56 (2015) 2094–2101.
[105] A.C. Ghosh, S.G. Tattikota, Y. Liu, A. Comjean, Y. Hu, V. Barrera, S.J. Ho Sui, N. Perrimon, Drosophila PDGF/VEGF signaling from muscles to hepatocyte-like cells protects against obesity, Elife 9 (2020), e56969.
[106] M.H. Sieber, C.S. Thummel, The DHR96 nuclear receptor controls triacylglycerol homeostasis in Drosophila, Cell Metab. 10 (2009) 481–490.
[107] W. Song, J.A. Veenstra, N. Perrimon, Control of lipid metabolism by tachykinin in Drosophila, Cell Rep. 9 (2014) 40–47.
[108] I. Miguel-Aliaga, H. Jasper, B. Lemaitre, Anatomy and physiology of the digestive tract of drosophila melanogaster, Genetics 210 (2018) 357–396.
[109] A. Scopelliti, C. Bauer, Y. Yu, T. Zhang, B. Kruspig, D.J. Murphy, M. Vidal, O.D. K. Maddocks, J.B. Cordero, A neuronal relay mediates a nutrient responsive gut/fat body axis regulating energy homeostasis in adult Drosophila, Cell Metab. 29 (2019) 269–284 (e10).
[110] B. Biteau, J. Karpac, S. Supoyo, M. DeGennaro, R. Lehmann, H. Jasper, Lifespan extension by preserving proliferative homeostasis in Drosophila, PLoS Genet. 6 (2010), e1001159.
[111] J. Karpac, B. Biteau, H. Jasper, Misregulation of an adaptive metabolic response contributes to the age-related disruption of lipid homeostasis in Drosophila, Cell Rep. 4 (2013) 1250–1261.
[112] M. Holtof, C. Lenaerts, D. Cullen, J. Vanden Broeck, Extracellular nutrient digestion and absorption in the insect gut, Cell Tissue Res. 377 (2019) 397–414.
[113] M.H. Sieber, C.S. Thummel, Coordination of triacylglycerol and cholesterol homeostasis by DHR96 and the Drosophila LipA homolog magro, Cell Metab. 15 (2012) 122–127.
[114] N. Buchon, N.A. Broderick, M. Poidevin, S. Pradervand, B. Lemaitre, Drosophila intestinal response to bacterial infection: activation of host defense and stem cell proliferation, Cell Host Microbe 5 (2009) 200–211.
[115] S. Lee, H. Bao, Z. Ishikawa, W. Wang, H.Y. Lim, Cardiomyocyte regulation of systemic lipid metabolism by the apolipoprotein B-containing lipoproteins in Drosophila, PLoS Genet. 13 (2017), e1006555.
[116] S. Rommelaere, J.P. Boquete, J. Piton, S. Kondo, B. Lemaitre, The exchangeable apolipoprotein Nplp2 sustains lipid flow and heat acclimation in Drosophila, Cell Rep. 27 (2019) 886–899 (e6).
[117] R. Obniski, M. Sieber, A.C. Spradling, Dietary lipids modulate notch signaling and influence adult intestinal development and metabolism in Drosophila, Dev. Cell 47 (2018) 98–111 (e5).
[118] J. von Frieling, M.N. Faisal, F. Sporn, R. Pfefferkorn, S.S. Nolte, F. Sommer, P. Rosenstiel, T. Roeder, A high-fat diet induces a microbiota-dependent increase in stem cell activity in the Drosophila intestine, PLoS Genet. 16 (2020), e1008789.
[119] A.J. Sommer, P.D. Newell, Metabolic basis for mutualism between gut bacteria and its impact on the Drosophila melanogaster host, Appl. Environ. Microbiol. 85 (2019), e01882-18.
[120] A.C.N. Wong, A.J. Dobson, A.E. Douglas, Gut microbiota dictates the metabolic response of Drosophila to diet, J. Exp. Biol. 217 (2014) 1894–1901.
[121] J.M. Chaston, A.J. Dobson, P.D. Newell, A.E. Douglas, Host genetic control of the microbiota mediates the Drosophila nutritional phenotype, Appl. Environ. Microbiol. 82 (2016) 671–679.
[122] L. Kamareddine, W.P. Robins, C.D. Berkey, J.J. Mekalanos, P.I. Watnick, The Drosophila immune deficiency pathway modulates enteroendocrine function and host metabolism, Cell Metab. 28 (2018) 449–462 (e5).
[123] N. Buchon, N.A. Broderick, B. Lemaitre, Gut homeostasis in a microbial world: insights from Drosophila melanogaster, Nat. Rev. Microbiol. 11 (2013) 615–626.
[124] K.A. Lee, K.C. Cho, B. Kim, I.H. Jang, K. Nam, Y.E. Kwon, M. Kim, D.Y. Hyeon, D. Hwang, J.H. Seol, W.J. Lee, Inflammation-modulated metabolic reprogramming is required for DUOX-dependent gut immunity in Drosophila, Cell Host Microbe 23 (2018) 338–352 (e5).
[125] S. Hang, A.E. Purdy, W.P. Robins, Z. Wang, M. Mandal, S. Chang, J.J. Mekalanos, P.I. Watnick, The acetate switch of an intestinal pathogen disrupts host insulin signaling and lipid metabolism, Cell Host Microbe 16 (2014) 592–604.
[126] D.J. Van der Horst, K.W. Rodenburg, Locust flight activity as a model for hormonal regulation of lipid mobilization and transport, J. Insect Physiol. 56 (2010) 844–853.
[127] V.B. Wigglesworth, The utilization of reserve substances in Drosophila during flight, J. Exp. Biol. 26 (1949) 150–163.
[128] W.F. Eanes, T.J.S. Merritt, J.M. Flowers, S. Kumagai, E. Sezgin, C.T. Zhu, Flux control and excess capacity in the enzymes of glycolysis and their relationship to flight metabolism in Drosophila melanogaster, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 19413–19418.
[129] K. Kierdorf, F. Hersperger, J. Sharrock, C.M. Vincent, P. Ustaoglu, J. Dou, A. Gyoergy, O. Groß, D.E. Siekhaus, M.S. Dionne, Muscle function and homeostasis require cytokine inhibition of AKT activity in Drosophila, Elife 9 (2020), e51595.
[130] Y. Yan, H. Wang, M. Hu, L. Jiang, Y. Wang, P. Liu, X. Liang, J. Liu, C. Li, A. Lindström-Battle, S.M. Lam, G. Shui, W.M. Deng, R. Jiao, HDAC6 suppresses age-dependent ectopic fat accumulation by maintaining the proteostasis of PLIN2 in Drosophila, Dev. Cell 43 (2017) 99–111 (e5).
[131] X. Zhao, X. Li, X. Shi, J. Karpac, Diet-MEF2 interactions shape lipid droplet diversification in muscle to influence Drosophila lifespan, Aging Cell 19 (2020), e13172.
[132] M. Bosma, S. Kersten, M.K.C. Hesselink, P. Schrauwen, Re-evaluating lipotoxic triggers in skeletal muscle: relating intramyocellular lipid metabolism to insulin sensitivity, Prog. Lipid Res. 51 (2012) 36–49.
[133] Y. Liu, H. Bao, W. Wang, H.Y. Lim, Cardiac Snail family of transcription factors directs systemic lipid metabolism in Drosophila, PLoS Genet. 15 (2019), e1008487.
[134] J.H. Lee, R. Bassel-Duby, E.N. Olson, Heart- and muscle-derived signaling system dependent on MED13 and Wingless controls obesity in Drosophila, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 9491–9496.
[135] S.B. Diop, J. Bisharat-Kernizan, R.T. Birse, S. Oldham, K. Ocorr, R. Bodmer, PGC-1/spargel counteracts high-fat-diet-induced obesity and cardiac lipotoxicity downstream of TOR and brummer ATGL lipase, Cell Rep. 10 (2015) 1572–1584.
[136] I. Zlobine, K. Gopal, J.R. Ussher, Lipotoxicity in obesity and diabetes-related cardiac dysfunction, Biochim. Biophys. Acta - Mol. Cell Biol. Lipids 1861 (2016) 1555–1568.
[137] J. Mattila, E. Havula, E. Suominen, M. Teesalu, I. Surakka, R. Hynynen, H. Kilpinen, J. Väänänen, I. Hovatta, R. Käkelä, S. Ripatti, T. Sandmann, V. Hietakangas, Mondo-mlx mediates organismal sugar sensing through the Gli-similar transcription factor sugarbabe, Cell Rep. 13 (2015) 350–364.
[138] A.S. Kunte, K.A. Matthews, R.B. Rawson, Fatty acid auxotrophy in Drosophila larvae lacking SREBP, Cell Metab. 3 (2006) 439–448.
[139] R.A. DeBose-Boyd, J. Ye, SREBPs in lipid metabolism, insulin signaling, and beyond, Trends Biochem. Sci. 43 (2018) 358–368.
[140] I.Y. Dobrosotskaya, A.C. Seegmiller, M.S. Brown, J.L. Goldstein, R.B. Rawson, Regulation of SREBP processing and membrane lipid production by phospholipids in Drosophila, Science 296 (2002) 879–883 (80-.).
[141] H.Y. Lim, W. Wang, R.J. Wessells, K. Ocorr, R. Bodmer, Phospholipid homeostasis regulates lipid metabolism and cardiac function through SREBP signaling in Drosophila, Genes Dev. 25 (2011) 189–200.

[142] C. Ozdemir, R.B. Rawson, Other ways to skin a cat: activating SREBP without Scap, Fly (Austin) 5 (2011) 3–6.
[143] H. Wang, M.V. Airola, K. Reue, How lipid droplets, "TAG" along: glycerolipid synthetic enzymes and lipid storage, Biochim. Biophys. Acta - Mol. Cell Biol. Lipids 1862 (2017) 1131–1145.
[144] Y. Tian, J. Bi, G. Shui, Z. Liu, Y. Xiang, Y. Liu, M.R. Wenk, H. Yang, X. Huang, Tissue-autonomous function of Drosophila seipin in preventing ectopic lipid droplet formation, PLoS Genet. 7 (2011), e1001364.
[145] M. Beller, A.V. Bulankina, H.H. Hsiao, H. Urlaub, H. Jäckle, R.P. Kühnlein, PERILIPIN-dependent control of lipid droplet structure and fat storage in Drosophila, Cell Metab. 12 (2010) 521–532.
[146] E. Cinnamon, R. Makki, A. Sawala, L.P. Wickenberg, G.J. Blomquist, C. Tittiger, Z. Paroush, A.P. Gould, Drosophila Spidey/Kar regulates oenocyte growth via PI3-kinase signaling, PLoS Genet. 12 (2016), e1006154.
[147] V.R. Chintapalli, J. Wang, J.A.T. Dow, Using FlyAtlas to identify better Drosophila melanogaster models of human disease, Nat. Genet. 39 (2007) 715–720.
[148] F. Wilfling, H. Wang, J.T. Haas, N. Krahmer, T.J. Gould, A. Uchida, J.X. Cheng, M. Graham, R. Christiano, F. Fröhlich, X. Liu, K.K. Buhman, R.A. Coleman, J. Bewersdorf, R.V. Farese, T.C. Walther, Triacylglycerol synthesis enzymes mediate lipid droplet growth by relocalizing from the ER to lipid droplets, Dev. Cell 24 (2013) 384–399.
[149] V. Valente, R.M. Maia, M.C.B. Vianna, M.L. Paçó-Larson, Drosophila melanogaster lipins are tissue-regulated and developmentally regulated and present specific subcellular distributions, FEBS J. 277 (2010) 4775–4788.
[150] R. Ugrankar, Y. Liu, J. Provaznik, S. Schmitt, M. Lehmann, Lipin is a central regulator of adipose tissue development and function in Drosophila melanogaster, Mol. Cell. Biol. 31 (2011) 1646–1656.
[151] M. Grillet, B. Dominguez Gonzalez, A. Sicart, M. Pöttler, A. Cascalho, K. Billion, S. Hernandez Diaz, J. Swerts, T.V. Naismith, N.V. Gounko, P. Verstreken, P. I. Hanson, R.E. Goodchild, Torsins are essential regulators of cellular lipid metabolism, Dev. Cell 38 (2016) 235–247.
[152] T.E. Harris, B.N. Finck, Dual function lipin proteins and glycerolipid metabolism, Trends Endocrinol. Metab. 22 (2011) 226–233.
[153] S. Schmitt, R. Ugrankar, S.E. Greene, M. Prajapati, M. Lehmann, Drosophila Lipin interacts with insulin and TOR signaling pathways in the control of growth and lipid metabolism, J. Cell Sci. 128 (2015) 4395–4406.
[154] S.E. Hood, X.V. Kofler, Q. Chen, J. Scott, J. Ortega, M. Lehmann, Nuclear translocation ability of Lipin differentially affects gene expression and survival in fed and fasting Drosophila, J. Lipid Res. 61 (2020) 1720–1732.
[155] Y. Yan, H. Wang, H. Chen, A. Lindström-Battle, R. Jiao, Ecdysone and insulin signaling play essential roles in readjusting the altered body size caused by the dGPAT4 mutation in Drosophila, J. Genet. Genomics 42 (2015) 487–494.
[156] T.C. Walther, R.V. Farese, Lipid droplets and cellular lipid metabolism, Annu. Rev. Biochem. 81 (2012) 687–714.
[157] P. Hehlert, V. Hofferek, C. Heier, T.O. Eichmann, D. Riedel, J. Rosenberg, A. Takacs, H.M. Nagy, M. Oberer, R. Zimmermann, R.P. Kühnlein, The α/β-hydrolase domain-containing 4- and 5-related phospholipase Pummelig controls energy storage in Drosophila, J. Lipid Res. 60 (2019) 1365–1378.
[158] Y. Yan, H. Wang, C. Wei, Y. Xiang, X. Liang, C.W. Phang, R. Jiao, HDAC6 regulates lipid droplet turnover in response to nutrient deprivation via p62-mediated selective autophagy, J. Genet. Genomics 46 (2019) 221–229.
[159] J. Magré, M. Delépine, E. Khallouf, T. Gedde-Dahl, L. Van Maldergem, E. Sobel, J. Papp, M. Meier, A. Mégarbané, A. Bachy, A. Verloes, F.H. D'Abronzo, E. Seemanova, R. Assan, N. Baudic, C. Bourut, P. Czernichow, F. Huet, F. Grigorescu, M. De Kerdanet, et al., Identification of the gene altered in Berardinelli-Seip congenital lipodystrophy on chromosome 11q13, Nat. Genet. 28 (2001) 365–370.
[160] H. Wang, M. Becuwe, B.E. Housden, C. Chitraju, A.J. Porras, M.M. Graham, X. N. Liu, A.R. Thiam, D.B. Savage, A.K. Agarwal, A. Garg, M.J. Olarte, Q. Lin, F. Frohlich, H.K. Hannibal-Bach, S. Upadhyayula, N. Perrimon, T. Kirchhausen, C. S. Ejsing, T.C. Walther, et al., Seipin is required for converting nascent to mature lipid droplets, Elife 5 (2016), e16582.
[161] X. Sui, H. Arlt, K.P. Brock, Z.W. Lai, F. DiMaio, D.S. Marks, M. Liao, R.V. Farese, T. C. Walther, Cryo–electron microscopy structure of the lipid droplet–formation protein seipin, J. Cell Biol. 217 (2018) 4080–4091.
[162] J. Chung, X. Wu, T.J. Lambert, Z.W. Lai, T.C. Walther, R.V. Farese, LDAF1 and seipin form a lipid droplet assembly complex, Dev. Cell 51 (2019) 551–563 (e7).
[163] M. Pagac, D.E. Cooper, Y. Qi, I.E. Lukmantara, H.Y. Mak, Z. Wu, Y. Tian, Z. Liu, M. Lei, X. Du, C. Ferguson, D. Kotevski, P. Sadowski, W. Chen, S. Boroda, T. E. Harris, G. Liu, R.G. Parton, X. Huang, R.A. Coleman, et al., SEIPIN regulates lipid droplet expansion and adipocyte development by modulating the activity of glycerol-3-phosphate acyltransferase, Cell Rep. 17 (2016) 1546–1559.
[164] V.T. Salo, I. Belevich, S. Li, L. Karhinen, H. Vihinen, C. Vigouroux, J. Magré, C. Thiele, M. Hölttä-Vuori, E. Jokitalo, E. Ikonen, Seipin regulates ER–lipid droplet contacts and cargo delivery, EMBO J. 35 (2016) 2699–2716.
[165] J. Bi, W. Wang, Z. Liu, X. Hueng, Q. Jiang, G. Liu, Y. Wang, X. Huang, Seipin promotes adipose tissue fat storage through the ER Ca 2+-ATPase SERCA, Cell Metab. 19 (2014) 861–871.
[166] L. Ding, X. Yang, H. Tian, J. Liang, F. Zhang, G. Wang, Y. Wang, M. Ding, G. Shui, X. Huang, Seipin regulates lipid homeostasis by ensuring calcium-dependent mitochondrial metabolism, EMBO J. 37 (2018) 1–17.
[167] P.J. Thul, K. Tschapalda, P. Kolkhof, A.R. Thiam, M. Oberer, M. Beller, Targeting of the Drosophila protein CG2254/Ldsdh1 to a subset of lipid droplets, J. Cell Sci. 130 (2017) 3141–3157.
[168] R. Ugrankar, J. Bowerman, H. Hariri, M. Chandra, K. Chen, M.F. Bossanyi, S. Datta, S. Rogers, K.M. Eckert, G. Vale, A. Victoria, J. Fresquez, J.G. McDonald, S. Jean, B.M. Collins, W.M. Henne, Drosophila Snazarus regulates a lipid droplet population at plasma membrane-droplet contacts in adipocytes, Dev. Cell 50 (2019) 557–572 (e5).
[169] B. Diaconeasa, G. Harper Mazock, A.P. Mahowald, R.R. Dubreuil, Genetic studies of spectrin in the larval fat body of Drosophila melanogaster: evidence for a novel lipid uptake apparatus, Genetics 195 (2013) 871–881.
[170] J. Bi, Y. Xiang, H. Chen, Z. Liu, S. Grönke, R.P. Kühnlein, X. Huang, Opposite and redundant roles of the two Drosophila perilipins in lipid mobilization, J. Cell Sci. 125 (2012) 3568–3577.
[171] Y. Yao, X. Li, W. Wang, Z. Liu, J. Chen, M. Ding, X. Huang, MRT, functioning with NURF complex, regulates lipid droplet size, Cell Rep. 24 (2018) 2972–2984.
[172] L. Teixeira, C. Rabouille, P. Rørth, A. Ephrussi, N.F. Vanzo, Drosophila Perilipin/ADRP homologue Lsd2 regulates lipid metabolism, Mech. Dev. 120 (2003) 1071–1081.
[173] J.D. Fauny, J. Silber, A. Zider, Drosophila lipid storage droplet 2 gene (Lsd-2) is expressed and controls lipid storage in wing imaginal discs, Dev. Dyn. 232 (2005) 725–732.
[174] N. Krahmer, Y. Guo, F. Wilfling, M. Hilger, S. Lingrell, K. Heger, H.W. Newman, M. Schmidt-Supprian, D.E. Vance, M. Mann, R.V. Farese, T.C. Walther, Phosphatidylcholine synthesis for lipid droplet expansion is mediated by localized activation of CTP:phosphocholine cytidylyltransferase, Cell Metab. 14 (2011) 504–515.
[175] C. Moessinger, K. Klizaite, A. Steinhagen, J. Philippou-Massier, A. Shevchenko, M. Hoch, C.S. Ejsing, C. Thiele, Two different pathways of phosphatidylcholine synthesis, the Kennedy Pathway and the Lands Cycle, differentially regulate cellular triacylglycerol storage, BMC Cell Biol. 15 (2014), 43.
[176] A.R. Thiam, R.V. Farese, T.C. Walther, The biophysics and cell biology of lipid droplets, Nat. Rev. Mol. Cell Biol. 14 (2013) 775–786.
[177] X. Xu, P. Gopalacharyulu, T. Seppänen-Laakso, A.L. Ruskeepää, C.C. Aye, B. P. Carson, S. Mora, M. Orešič, A.A. Teleman, Insulin signaling regulates fatty acid catabolism at the level of CoA activation, PLoS Genet. 8 (2012), e1002478.
[178] J. Sellin, C. Wingen, D. Gosejacob, D. Senyilmaz, L. Hänschke, S. Büttner, K. Meyer, D. Bano, P. Nicotera, A.A. Teleman, M.H. Bülow, Dietary rescue of lipotoxicity-induced mitochondrial damage in Peroxin19 mutants, PLoS Biol. 16 (2018), e2004893.
[179] A. Lass, R. Zimmermann, M. Oberer, R. Zechner, Lipolysis - a highly regulated multi-enzyme complex mediates the catabolism of cellular fat stores, Prog. Lipid Res. 50 (2011) 14–27.
[180] E.L. Arrese, R.T. Patel, J.L. Soulages, The main triglyceride-lipase from the insect fat body is an active phospholipase A1: identification and characterization, J. Lipid Res. 47 (2006) 2656–2667.
[181] M. Gáliková, P. Klepsatel, J. Münch, R.P. Kühnlein, Spastic paraplegia-linked phospholipase PAPLA1 is necessary for development, reproduction, and energy metabolism in Drosophila, Sci. Rep. 7 (2017), 46516.
[182] C. Heier, O. Knittelfelder, H.F. Hofbauer, W. Mende, I. Pörnbacher, L. Schiller, G. Schoiswohl, H. Xie, S. Grönke, A. Shevchenko, R.P. Kühnlein, Hormone-sensitive lipase couples intergenerational sterol metabolism to reproductive success, Elife 10 (2021), e63252.
[183] J. Zhang, Y. Liu, K. Jiang, J. Jia, Hedgehog signaling promotes lipolysis in adipose tissue through directly regulating Bmm/ATGL lipase, Dev. Biol. 457 (2020) 128–139.
[184] P. Kang, K. Chang, Y. Liu, M. Bouska, A. Birnbaum, G. Karashchuk, R. Thakore, W. Zheng, S. Post, C.S. Brent, S. Li, M. Tatar, H. Bai, Drosophila Kruppel homolog 1 represses lipolysis through interaction with dFOXO, Sci. Rep. 7 (2017), 16369.
[185] M. Molaei, C. Vandehoef, J. Karpac, NF-κB shapes metabolic adaptation by attenuating Foxo-mediated lipolysis in Drosophila, Dev. Cell 49 (2019) 802–810 (e6).
[186] R.T. Patel, J.L. Soulages, B. Hariharasundaram, E.L. Arrese, Activation of the lipid droplet controls the rate of lipolysis of triglycerides in the insect fat body, J. Biol. Chem. 280 (2005) 22624–22631.
[187] S. Grönke, M. Beller, S. Fellert, H. Ramakrishnan, H. Jäckle, R.P. Kühnlein, Control of fat storage by a Drosophila PAT domain protein, Curr. Biol. 13 (2003) 603–606.
[188] N.K. Nirala, M. Rahman, S.M. Walls, A. Singh, L.J. Zhu, T. Bamba, E. Fukusaki, S. M. Srideshikan, G.L. Harris, Y.T. Ip, R. Bodmer, U.R. Acharya, Survival response to increased ceramide involves metabolic adaptation through novel regulators of glycolysis and lipolysis, PLoS Genet. 9 (2013), e1003556.
[189] M.H. Bülow, C. Wingen, D. Senyilmaz, D. Gosejacob, M. Sociale, R. Bauer, H. Schulze, K. Sandhoff, A.A. Teleman, M. Hoch, J. Sellina, Unbalanced lipolysis results in lipotoxicity and mitochondrial damage in peroxisome-deficient Pex19 mutants, Mol. Biol. Cell 29 (2018) 396–407.
[190] W. Jung, C. Liu, Y. Yu, Y. Chang, W. Lien, H. Chao, S. Huang, C. Kuo, H. Ho, C. Chan, Lipophagy prevents activity-dependent neurodegeneration due to dihydroceramide accumulation in vivo, EMBO Rep. 18 (2017) 1150–1165.
[191] D. Pho, M. Pennanec'h, J.-M. Jallon, Lipophorin and its role in hydrocarbon transport, Arch. Insect Biochem. Physiol. 31 (1996) 289–303.
[192] M. Rodríguez-Vázquez, D. Vaquero, E. Parra-Peralbo, J.E. Mejía-Morales, J. Culi, Drosophila lipophorin receptors recruit the lipoprotein LTP to the plasma membrane to mediate lipid uptake, PLoS Genet. 11 (2015), e1005356.
[193] B.J. Blacklock, M. Smillie, R.O. Ryan, Insect lipid transfer particle can facilitate net vectorial lipid transfer via a carrier-mediated mechanism, J. Biol. Chem. 267 (1992) 14033–14037.
[194] L.E. Canavoso, M.A. Wells, Role of lipid transfer particle in delivery of diacylglycerol from midgut to lipophorin in larval Manduca sexta, Insect Biochem. Mol. Biol. 31 (2001) 783–790.

[195] N.P. Dantuma, M. Potters, M.P.J. De Winther, C.P. Tensen, F.P. Kooiman, J. Bogerd, D.J. Van Der Horst, An insect homolog of the vertebrate very low density lipoprotein receptor mediates endocytosis of lipophorins, J. Lipid Res. 40 (1999) 973–978.
[196] N. Matsuo, K. Nagao, T. Suito, N. Juni, U. Kato, Y. Hara, M. Umeda, Different mechanisms for selective transport of fatty acids using a single class of lipoprotein in Drosophila, J. Lipid Res. 60 (2019) 1199–1211.
[197] J. Verdu, M.A. Buratovicht, E.L. Wilder, M.J. Birnbaum, Cell-autonomous regulation of cell and organ growth in Drosophila by Akt/PKB, Nat. Cell Biol. 1 (1999) 500–506.
[198] F. Rintelen, H. Stocker, G. Thomas, E. Hafen, PDK1 regulates growth through Akt and S6K in Drosophila, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 15020–15025.
[199] O. Puig, M.T. Marr, M.L. Ruhf, R. Tjian, Control of cell number by Drosophila FOXO: downstream and feedback regulation of the insulin receptor pathway, Genes Dev. 17 (2003) 2006–2020.
[200] T. Vihervaara, O. Puig, dFOXO regulates transcription of a Drosophila acid lipase, J. Mol. Biol. 376 (2008) 1215–1223.
[201] S. Choi, D.S. Lim, J. Chung, Feeding and fasting signals converge on the LKB1-SIK3 pathway to regulate lipid metabolism in Drosophila, PLoS Genet. 11 (2015), e1005263.
[202] N. Vereshchagina, C. Wilson, Cytoplasmic activated protein kinase Akt regulates lipid-droplet accumulation in Drosophila nurse cells, Development 133 (2006) 4731–4735.
[203] A. Haselton, E. Sharmin, J. Schrader, M. Sah, P. Poon, Y.W.C. Fridell, Partial ablation of adult Drosophila insulin-producing neurons modulates glucose homeostasis and extends life span without insulin resistance, Cell Cycle 9 (2010) 3135–3143.
[204] S. Grönke, D.F. Clarke, S. Broughton, T.D. Andrews, L. Partridge, Molecular evolution and functional characterization of Drosophila insulin-like peptides, PLoS Genet. 6 (2010), e1000857.
[205] J.M. Murillo-Maldonado, G. Sánchez-Chávez, L.M. Salgado, R. Salceda, J. R. Riesgo-Escovar, Drosophila insulin pathway mutants affect visual physiology and brain function besides growth, lipid, and carbohydrate metabolism, Diabetes 60 (2011) 1632–1636.
[206] Y. Liu, W. Wang, G. Shui, X. Huang, CDP-diacylglycerol synthetase coordinates cell growth and fat storage through phosphatidylinositol metabolism and the insulin pathway, PLoS Genet. 10 (2014), e1004172.
[207] S. Oldham, J. Montagne, T. Radimerski, G. Thomas, E. Hafen, Genetic and biochemical characterization of dTOR, the Drosophila homolog of the target of rapamycin, Genes Dev. 14 (2000) 2689–2694.
[208] H. Zhang, J.P. Stallock, J.C. Ng, C. Reinhard, T.P. Neufeld, Regulation of cellular growth by the dTOR, Genes Dev. 14 (2000) 2712–2724.
[209] Y.-Y. Chang, T.P. Neufeld, An Atg1/Atg13 complex with multiple roles in TOR-mediated autophagy regulation, Mol. Biol. Cell 20 (2009) 2004–2014.
[210] A.A. Teleman, V. Hietakangas, A.C. Sayadian, S.M. Cohen, Nutritional control of protein biosynthetic capacity by insulin via Myc in Drosophila, Cell Metab. 7 (2008) 21–32.
[211] S. Schleich, A.A. Teleman, Akt phosphorylates both Tsc1 and Tsc2 in Drosophila, but neither phosphorylation is required for normal animal growth, PLoS One 4 (2009), e6305.
[212] Q. Yang, K. Inoki, E. Kim, K.L. Guan, TSC1/TSC2 and Rheb have different effects on TORC1 and TORC2 activity, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 6811–6816.
[213] C. Géminard, E.J. Rulifson, P. Léopold, Remote control of insulin secretion by fat cells in Drosophila, Cell Metab. 10 (2009) 199–207.
[214] J.H. Lee, A.V. Budanov, E.J. Park, R. Birse, T.E. Kim, G.A. Perkins, K. Ocorr, M. H. Ellisman, R. Bodmer, E. Bier, M. Karin, Sestrin as a feedback inhibitor of TOR that prevents age-related pathologies, Science 327 (2010) 1223–1228.
[215] A.A. Teleman, Y.-W. Chen, S.M. Cohen, 4E-BP functions as a metabolic brake used under stress conditions but not during normal growth, Genes Dev. 19 (2005) 1844–1848.
[216] L.B. Mensah, D.C.I. Goberdhan, C. Wilson, mTORC1 signalling mediates PI3K-dependent large lipid droplet accumulation in Drosophila ovarian nurse cells, Biol. Open 6 (2017) 563–570.
[217] I. Bjedov, J.M. Toivonen, F. Kerr, C. Slack, J. Jacobson, A. Foley, L. Partridge, Mechanisms of life span extension by rapamycin in the fruit Fly Drosophila melanogaster, Cell Metab. 11 (2010) 35–46.
[218] N. Luong, C.R. Davies, R.J. Wessells, S.M. Graham, M.T. King, R. Veech, R. Bodmer, S.M. Oldham, Activated FOXO-mediated insulin resistance is blocked by reduction of TOR activity, Cell Metab. 4 (2006) 133–142.
[219] T. Porstmann, C.R. Santos, B. Griffiths, M. Cully, M. Wu, S. Leevers, J.R. Griffiths, Y.L. Chung, A. Schulze, SREBP activity is regulated by mTORC1 and contributes to Akt-dependent cell growth, Cell Metab. 8 (2008) 224–236.
[220] M. Tiebe, M. Lutz, A. De La Garza, T. Buechling, M. Boutros, A.A. Teleman, REPTOR and REPTOR-BP regulate organismal metabolism and transcription downstream of TORC1, Dev. Cell 33 (2015) 272–284.
[221] F. Staubli, T.J.D. Jørgensen, G. Cazzamali, M. Williamson, C. Lenz, L. Søndergaard, P. Roepstorff, C.J.P. Grimmelikhuijzen, Molecular identification of the insect adipokinetic hormone receptors, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 3446–3451.
[222] Y. Park, Y.J. Kim, M.E. Adams, Identification of G protein-coupled receptors for Drosophila PRXamide peptides, CCAP, corazonin, and AKH supports a theory of ligand-receptor coevolution, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 11423–11428.
[223] Y. Yu, R. Huang, J. Ye, V. Zhang, C. Wu, G. Cheng, J. Jia, L. Wang, Regulation of starvation-induced hyperactivity by insulin and glucagon signaling in adult Drosophila, Elife 5 (2016), e15693.
[224] K.N. Bharucha, P. Tarr, S.L. Zipursky, A glucagon-like endocrine pathway in Drosophila modulates both lipid and carbohydrate homeostasis, J. Exp. Biol. 211 (2008) 3103–3110.
[225] M. Gáliková, P. Klepsatel, Y. Xu, R.P. Kühnlein, The obesity-related Adipokinetic hormone controls feeding and expression of neuropeptide regulators of Drosophila metabolism, Eur. J. Lipid Sci. Technol. 119 (2017) 1–14.
[226] E. Ibrahim, P. Dobeš, M. Kunc, P. Hyršl, D. Kodrík, Adipokinetic hormone and adenosine interfere with nematobacterial infection and locomotion in Drosophila melanogaster, J. Insect Physiol. 107 (2018) 167–174.
[227] S. Lebreton, S. Mansourian, J. Bigarreau, T. Dekker, The adipokinetic hormone receptor modulates sexual behavior, pheromone perception and pheromone production in a sex-specific and starvation-dependent manner in Drosophila melanogaster, Front. Ecol. Evol. 3 (2016), 504.
[228] G. Gäde, L. Auerswald, Mode of action of neuropeptides from the adipokinetic hormone family, Gen. Comp. Endocrinol. 132 (2003) 10–20.
[229] E.L. Arrese, J.L. Soulages, Insect fat body: energy, metabolism, and regulation, Annu. Rev. Entomol. 55 (2010) 207–225.
[230] E.L. Arrese, M.T. Flowers, J.L. Gazard, M.A. Wells, Calcium and cAMP are second messengers in the adipokinetic hormone- induced lipolysis of triacylglycerols in Manduca sexta fat body, J. Lipid Res. 40 (1999) 556–564.
[231] E.L. Arrese, L. Rivera, M. Hamada, S. Mirza, S.D. Hartson, S. Weintraub, J. L. Soulages, Function and structure of lipid storage droplet protein 1 studied in lipoprotein complexes, Arch. Biochem. Biophys. 473 (2008) 42–47.
[232] J. Baumbach, Y. Xu, P. Hehlert, R.P. Kühnlein, Gαq, Gγ1 and Plc21C control Drosophila body fat storage, J. Genet. Genomics 41 (2014) 283–292.
[233] Y. Xu, A.F. Borcherding, C. Heier, G. Tian, T. Roeder, R.P. Kühnlein, Chronic dysfunction of Stromal interaction molecule by pulsed RNAi induction in fat tissue impairs organismal energy homeostasis in Drosophila, Sci. Rep. 9 (2019), 6989.
[234] M. Subramanian, S.K. Metya, S. Sadaf, S. Kumar, D. Schwudke, G. Hasan, Altered lipid homeostasis in Drosophila InsP3 receptor mutants leads to obesity and hyperphagia, DMM Dis. Model. Mech. 6 (2013) 734–744.
[235] M. Blüher, Obesity: global epidemiology and pathogenesis, Nat. Rev. Endocrinol. 15 (2019) 288–298.
[236] Adela Hsruby, Frank B. Hu, The epidemiology of obesity: a big picture, Pharmacoeconomics. 33 (2015) 673–689.
[237] T. Reis, M.R. van Gilst, I.K. Hariharan, A buoyancy-based screen of drosophila larvae for fat- storage mutants reveals a role for Sir2 in coupling fat storage to nutrient availability, PLoS Genet. 6 (2010), e1001206.
[238] M.Y. Pasco, P. Léopold, High sugar-induced insulin resistance in Drosophila relies on the Lipocalin Neural Lazarillo, PLoS One 7 (2012), e36583.
[239] J. Na, M.T. Sweetwyne, A.S.D. Park, K. Susztak, R.L. Cagan, Diet-induced podocyte dysfunction in drosophila and mammals, Cell Rep. 12 (2015) 636–647.
[240] J. Na, L.P. Musselman, J. Pendse, T.J. Baranski, R. Bodmer, K. Ocorr, R. Cagan, A Drosophila model of high sugar diet-induced cardiomyopathy, PLoS Genet. 9 (2013), e1003175.
[241] E. van Dam, L.A.G. van Leeuwen, E. dos Santos, J. James, L. Best, C. Lennicke, A. J. Vincent, G. Marinos, A. Foley, M. Buricova, J.B. Mokochinski, H.B. Kramer, W. Lieb, M. Laudes, A. Franke, C. Kaleta, H.M. Cochemé, Sugar-induced obesity and insulin resistance are uncoupled from shortened survival in Drosophila, Cell Metab. 31 (2020) 710–725 (e7).
[242] K.J. Woodcock, K. Kierdorf, C.A. Pouchelon, V. Vivancos, M.S. Dionne, F. Geissmann, Macrophage-derived upd3 cytokine causes impaired glucose homeostasis and reduced lifespan in Drosophila fed a lipid-rich diet, Immunity 42 (2015) 133–144.
[243] S.H. Hong, M. Kang, K.S. Lee, K. Yu, High fat diet-induced TGF-β/Gbb signaling provokes insulin resistance through the tribbles expression, Sci. Rep. 6 (2016), 30265.
[244] R.T. Brookheart, C.I. Michel, J.E. Schaffer, As a matter of fat, Cell Metab. 10 (2009) 9–12.
[245] R.P. Kühnlein, Drosophila as a lipotoxicity model organism - more than a promise? Biochim. Biophys. Acta - Mol. Cell Biol. Lipids 1801 (2010) 215–221.
[246] M.K. Montgomery, W. De Nardo, M.J. Watt, Impact of lipotoxicity on tissue "cross talk" and metabolic regulation, Physiology 34 (2019) 134–149.
[247] M.C. Guida, R.T. Birse, A. Dall'Agnese, P.C. Toto, S.B. Diop, A. Mai, P.D. Adams, P.L. Puri, R. Bodmer, Intergenerational inheritance of high fat diet-induced cardiac lipotoxicity in Drosophila, Nat. Commun. 10 (2019), 193.
[248] A. Öst, A. Lempradl, E. Casas, M. Weigert, T. Tiko, M. Deniz, L. Pantano, U. Boenisch, P.M. Itskov, M. Stoeckius, M. Ruf, N. Rajewsky, G. Reuter, N. Iovino, C. Ribeiro, M. Alenius, S. Heyne, T. Vavouri, J.A. Pospisilik, Paternal diet defines offspring chromatin state and intergenerational obesity, Cell 159 (2014) 1352–1364.
[249] J.L. Buescher, L.P. Musselman, C.A. Wilson, T. Lang, M. Keleher, T.J. Baranski, J. G. Duncan, Evidence for transgenerational metabolic programming in Drosophila, DMM Dis. Model. Mech. 6 (2013) 1123–1132.