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From worms to humans: Understanding intestinal lipid metabolism via model organisms☆

Darby W. Kozan, Joshua T. Derrick, William B. Ludington, Steven A. Farber *

Department of Biology, Johns Hopkins University, Baltimore, MD, United States
Department of Embryology, Carnegie Institute for Science, Baltimore, MD, United States

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ABSTRACT

The intestine is responsible for efficient absorption and packaging of dietary lipids before they enter the circulatory system. This review provides a comprehensive overview of how intestinal enterocytes from diverse model organisms absorb dietary lipid and subsequently secrete the largest class of lipoproteins (chylomicrons) to meet the unique needs of each animal. We discuss the putative relationship between diet and metabolic disease progression, specifically Type 2 Diabetes Mellitus. Understanding the molecular response of intestinal cells to dietary lipid has the potential to undercover novel therapies to combat metabolic syndrome.

1. Introduction

In 2020, over 600 million people were considered obese [1]. Similarly, the incidence of Diabetes Mellitus affects 1 in 10 Americans with 90–95 % of cases being Type 2 Diabetes Mellitus [2]. Elevated plasma triglyceride levels are a risk factor patients with Type 2 Diabetes Mellitus [3]. The prevalence of Type 2 Diabetes Mellitus patients with dyslipidemia continues to increase, yet, many of the mechanistic links between insulin signaling and lipid homeostasis remain to be elucidated—especially with regard to the contribution of the intestine. In the vertebrate intestinal lumen, dietary lipids are broken down into free fatty acids, free cholesterol, and monoglycerides [4]. These lipids are absorbed by intestinal enterocytes, transported to the endoplasmic reticulum (ER), and then packaged into specialized triglyceride-rich lipoproteins called chylomicrons [5]. Assembled chylomicron particles are excreted by enterocytes into the lymphatics which drain into the circulation [5]. In circulation, chylomicron-lipids are lipolyzed by lipases, releasing free fatty acids that are delivered to peripheral tissues. This process ultimately produces chylomicron remnants in the circulation [5] that are rapidly cleared by the liver where their contents can be repackaged and secreted as components of very-low-density-lipoproteins (VLDL) [6]. VLDL particles carry significantly less triglyceride than chylomicrons [7] and are primarily responsible for the transport of complex lipids synthesized by the liver [4]. Thus, plasma triglyceride levels are influenced by lipoproteins from both the intestine and the liver [4] and yet, many studies of plasma lipid focus on liver VLDL production, despite a rich body of work from many labs specifically focusing on chylomicron biology [8]. This may be partly due to difficulty in isolating the larger, triglyceride-rich chylomicrons. This review will discuss the utility of the unique tools and tractability of nonmammalian models to more broadly explore the influence of the intestine on plasma lipid metabolism.

Most of our current understanding about nutrient processing has been predicated on studies that elucidated the mechanisms by which the mammalian intestine absorbs and intracellularly reprocesses dietary lipids into more complex lipids that can be stored, catabolized or secreted (Fig. 1). The basic anatomy, physiology and molecular mechanisms of lipid absorption and secretion appear to be well conserved among bilaterians [9]: animals with bilateral embryonic symmetry that have an internal digestive cavity with two openings. The clade includes many common laboratory organisms: *Caenorhabditis elegans*, *Drosophila melanogaster*, *Danio rerio*, and *Mus musculus*. Also included are less common models, such as *Mesocricetus auratus* (Syrian hamster), *Gallus domesticus* (chicken), and *Sus domesticus* (domestic pig). In these

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* Corresponding author at: Carnegie Institute for Science, Department of Embryology, 3520 San Martin Drive, Baltimore, MD 21218, United States.
E-mail address: farber@carnegiescience.edu (S.A. Farber).

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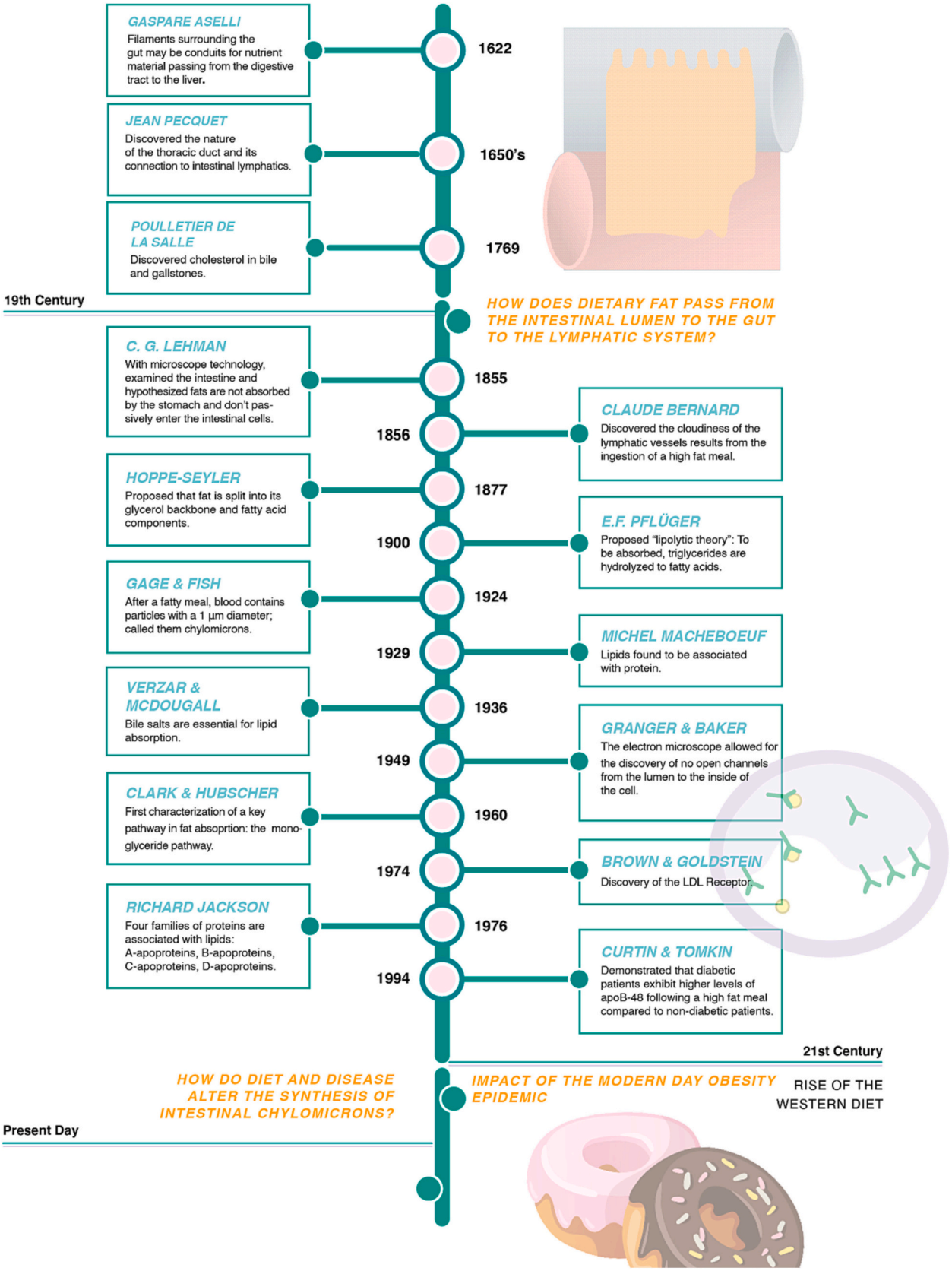

Fig. 1. Timeline on the discoveries of intestinal lipid absorption. Questions surrounding how dietary fat is absorbed by intestinal cells have been at the forefront of lipid research for hundreds of years. The way dietary fat passes from the intestinal lumen to the lymphatic system is still not completely known. With the rise in metabolic-based diseases, the way in which lipid is released from the intestinal cell has become increasingly relevant.

organisms, the absorption and digestion of dietary nutrients is a highly coordinated orchestration of biochemical, microbial, and physical processes. In this review, we discuss the historical discoveries in intestinal lipid biology, the current usage of model organisms, and how these models can be leveraged to answer continuing knowledge gaps in the field. Additionally, this review will discuss how lipids are thought to be absorbed from the diet, non-exchangeable (ApoB) and exchangeable (ApoA4) intestinal lipoproteins, the influence of diet on lipoproteins, and control of intestinal lipid metabolism via hormones. For each of these topics, what is known in humans is initially described, followed by a discussion of other model systems with particularly relevant biology. The purpose of this review is to provide a comprehensive overview of nutrient and molecular factors that regulate intestinal lipid processing—from luminal absorption to chylomicron secretion—in bilaterian model organisms. The known factors that influence chylomicron biogenesis and secretion with a focus on knowledge gaps in the field and suggestions of model organisms that can address these gaps are described in Table 1.

2. Model organisms for study of intestinal lipid metabolism

Research into the structure and function of the human digestive system began in Ancient Greece more than two millennia ago with the theories of Hippocrates and Galen, who accurately described the digestive function of the human gut, although erroneously describing the liver as the organ involved in extracting nutrients from food [38]. Galen's theories were dominant for nearly 1500 years, but with the advent of the Enlightenment in Europe in the 17th century, Italian anatomist Gaspare Aselli [39], and French Scientist Jean Pecquet [40] established that nutrients were likely directly absorbed through the intestine into the thoracic duct. However, it took until the 19th century for the question of absorption of dietary fat in particular to be addressed. C. G Lehman [41] used high-resolution microscopy to establish that fat was not absorbed in the stomach, but the intestine. This was followed up in work by Claude Bernard identifying cloudy lymphatic fluid after a high-fat meal [42]. Further work followed in the 20th century: Gage and Fish identified and named the chylomicron particle [35], Macheboeuf discovered lipid-associated proteins [43], Clark and Hubscher described suggested pathways for triglyceride synthesis in intestinal mucosa [44], Brown and Goldstein characterized the cellular receptor for these "lipoproteins" (the LDL receptor for which they received the Nobel prize) [37], and Richard Jackson separated these putative apolipoproteins into four classes [45] (Fig. 1). While clinical work is still being done in humans, it is held back by the inability to perform genetic manipulations, and difficulty of tissue sampling. Cell-culture models solve some of these issues, but the intestine is a complex organ and is not well recapitulated in human cell lines. Thus, we argue the best option for studying intestinal lipid metabolism has shifted to model organisms.

Four rodent models: the mouse (*Mus musculus*), rat (*Rattus norvegicus domesticus*), Syrian golden hamster (*Mesocricetus auratus*), and the guinea pig (*Cavia porcellus*) have been historically used in lipoprotein and lipid metabolism research. The advantages and disadvantages of each system from a perspective of understanding atherosclerosis is reviewed in [46]. While there are a number of differences between human and rodent intestinal lipid biology, such as the expression profile of the ApoB-48 isoform [47], research in rodents has proven links between diet and atherosclerosis [32], a prominent role for the intestinal microbiome [33], and the function of ApoE in chylomicron clearance [34]. CRISPR-Cas9, which has enabled precise genome editing, will make these models even more attractive (especially guinea pigs and hamsters, which have closer lipid metabolism to humans).

The common chicken (Gallus domesticus), has a rich history in developmental biology and immunology research, and was used to develop the first vaccines by Louis Pasteur in the 1860s [48]. Although less often used as a laboratory model organism, chickens are still an important agricultural species. Lipid and lipoprotein metabolism are of special importance to chicken producers because excess adipose tissue is often lost during processing and cooking, leading to lower meat yields.

Table 1
Comparison of lipoproteins in model organisms.[a]

Model organism	*C. elegans*	*D. melanogaster*	*D. rerio*	*G. domesticus*	*M. musculus*	*H. sapiens*
Lipoprotein origin	Intestine [10]	Fat body [11], heart [12]	Intestine and liver (ApoB) [13]	Intestine (portomicrons [14,15]) and liver (ApoB-100) [16]	Intestine and liver (ApoB-100 and ApoB-48) [17]	Intestine (ApoB-48) and liver (ApoB-100) [18]
Intestinal non-exchangeable lipoprotein	Vitellogenins[10]	ApoLpp [11]	ApoB [13]	ApoB-100 [16]	ApoB-48 and ApoB-100 [17]	ApoB-48 [18]
Primary intestinal lipid transported by lipoproteins	Triglyceride [10]	Diglyceride (medium-chain) [11]	Triglyceride [13]	Triglyceride [15]	Triglyceride [17]	Triglyceride (long-chain) [19]
Exchangeable intestinal lipoproteins	Unknown	NPLP2 [20]	ApoA4 (3 copies), ApoCIII?, ApoA1? [21]	ApoA4 [22], ApoCIII?, ApoA1?	ApoA4 [23], ApoCIII?, ApoA1?	ApoA4 [24], AoCIII?, ApoA1?
Examples of lipid physiology discovered	Conservation of insulin signaling pathway from worms to humans [25]	Dual function of mammalian MTP [26,27], role of dNL in sugar detoxification [28]	Lipoprotein regulation of angiogenesis [29,30], PLA2G12B [31] function in chylomicron loading	Portomicrons [14,15]	Atherosclerosis from diet [32], influence of intestinal microbiome [33], ApoE knockout [34]	Discovery of chylomicrons [35], lipid droplets [36] diabetes associations, LDL receptor [37]
Major advantages	Short lifespan; gut is only source of lipoproteins; attune to genetic manipulation	Short lifespan, genetic tools, tractable microbiome, conserved pathways with humans, separate transport and storage lipids	Vertebrate homology with humans; ApoA4 duplication; good genetic tools	Agricultural animal; portomicron system is a spatially specific location to study chylomicrons	Mammalian system; good genetic tools; closest model system to humans	Target organism; high-plasma volume
Major disadvantages	Only identified lipoproteins are vitellogenins	Unclear if intestinal lipoproteins are produced; low plasma volume	Adult studies labor intensive; experiments can be difficult; low plasma volume	Long lifespan; not used in laboratory; chylomicrons must go through liver	Cost; ApoB-48 and ApoB-100 both produced by liver; HDL dominant	Inability to do genetic manipulations outside of cell culture; cost

[a] Question marks in the table denote hypothetical roles of these proteins that are currently being investigated.

The chicken has a unique "portomicron" system, in which intestinal lipoproteins travel only through the portal vein to the liver, and do not circulate to the rest of the body [14]. This makes the chicken an especially easy model to study chylomicrons, as lymph sampled from the portal vein will only contain chylomicron particles.

Zebrafish (*Danio rerio*) has historically been a model system used to elucidate developmental processes owing to its small size, transparency, and the speed to which it goes from a single cell to a free-swimming larva. Recent work has pioneered the use of the larval zebrafish as a high-throughput system for interrogating vertebrate lipid biology [49]. The zebrafish gut is a simplified, yet highly homologous system to that of mammals [50], and shares conserved lipid absorption [51], lipoprotein [13] and hormonal pathways [52] to humans. Recent work in larval zebrafish has uncovered a negative association between ApoB-lipoproteins and angiogenesis [30], and a putative function of PLA2G12B in lipoprotein loading [31].

Since Thomas Hunt Morgan began his experiments with genetic inheritance in flies in 1910 [53], the fruit fly (*Drosophila melanogaster*) has proved to be an important model organism for genetics, development, neurobiology and biotechnology since flies allow genome-wide whole animal screens and follow up mechanistic studies to delineate cell-specific function of individual genes [54]. Although separated from humans by 750 million years of evolution [55], the conservation of the bilaterian digestive system makes the fruit fly a tractable model for

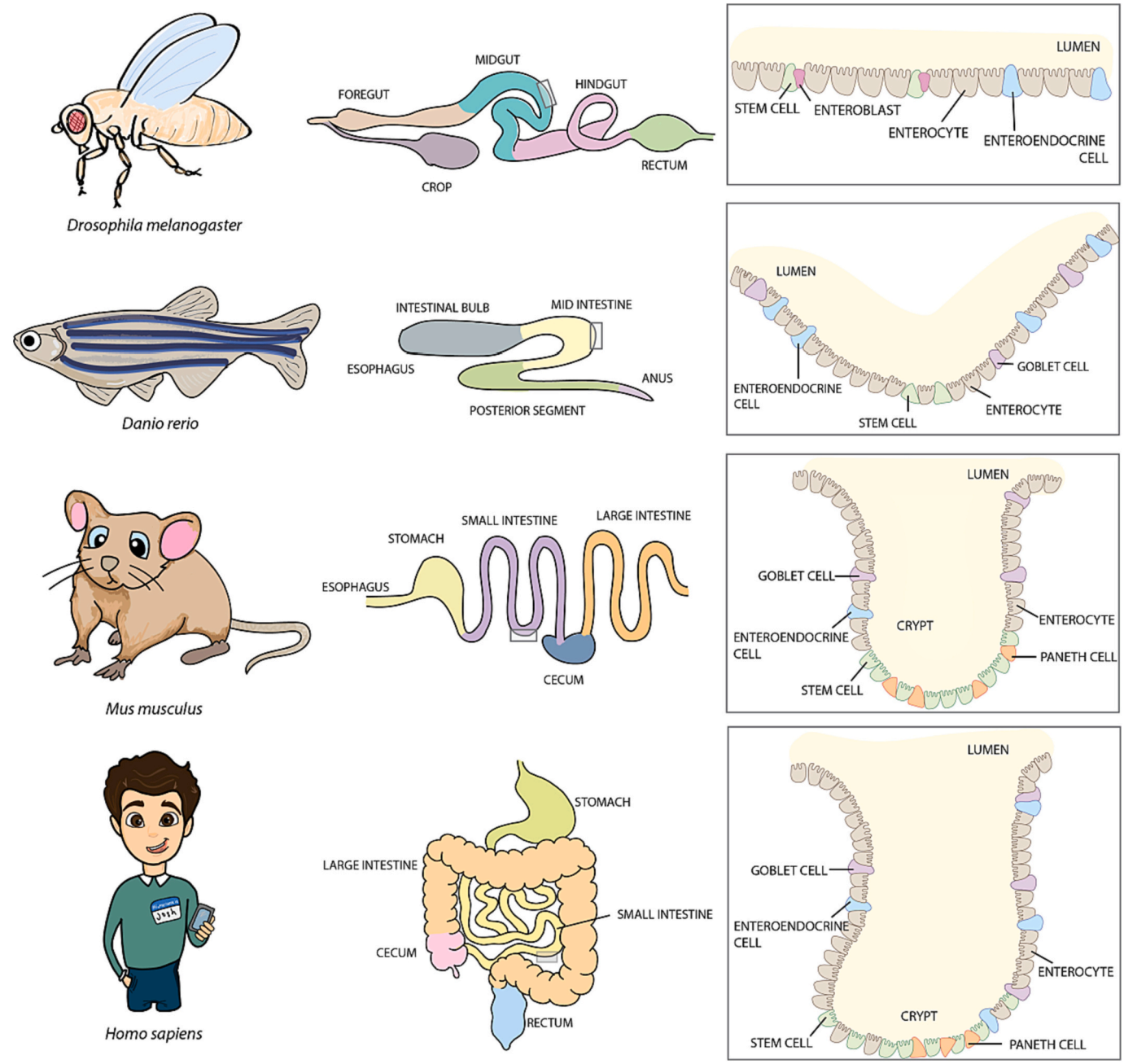

Fig. 2. Comparison of intestinal anatomy between model organisms. Illustrated model organisms (left) include *Drosophila melanogaster* (top), *Danio rerio* (middle), *Mus musculus* (third), and *Homo sapiens* (bottom). Between model organisms, there are variations in the gross anatomy of the intestine (middle panel). *D. melanogaster* contains a crop region not present in other models where the mouse mammalian system and humans have a defined stomach region. At the cellular level (right), depictions of variations of cell types along the intestinal epithelium between organisms with mice and humans sharing the most similarity. Enteroendocrine cells are present in each system, however only mice and humans have Paneth cells.

understanding human lipid absorption, secretion, and disease [56].

Pioneered by Sydney Brenner in the 1960s [57], the roundworm *C. elegans* has become an attractive model system because of its small genome, short lifespan and conserved biosynthetic pathways with mammalian systems. Insulin signaling, and its metabolic effects have been extensively studied in *C. elegans* [58]. The recent identification of a vitellogenin protein with potentially similar to function to ApoB [59] and a homolog of the microsomal triglyceride transfer (MTP) protein [60], make the worm an exciting organism for intestinal lipid metabolism research, especially as the gut is the only organ thought to be able to perform lipid synthesis [61].

3. Luminal absorption of dietary lipid

In all animals, the primary dietary lipids are triglycerides, phospholipids, and sterols (e.g. cholesterol) [62]. Although mammals and flies share a conserved lipoprotein transport system, the main transport lipid in insects is diglyceride rather than triglyceride [11]. In mammals, intestinal digestion of dietary lipids begins with their emulsification in the intestine by liver-derived bile salts [63]. The intestine is responsible for the breakdown of triglyceride into free fatty acids, and monoglycerols, and cholesteryl esters into free cholesterol by the pancreatic secretion of lipases into the intestinal lumen. Triglyceride hydrolysis typically releases long-chain fatty acids and monoglycerides that are then efficiently absorbed primarily in enterocytes located on the upper two-thirds of villi of the jejunum, the medial segment of the small intestine [64] (Fig. 2). A low pH in the apical environment of the enterocyte surrounding the microvilli facilitates the dissociation of the mixed micelles and protonation of long-chain fatty acids [65]. Enterocytes uptake free fatty acids and monoglycerides by both diffusion and protein-mediated transport [64]. The precise mechanism by which proteins facilitate lipid transport is unclear. Long-chain fatty acid protonation promotes the passive diffusion of free fatty acids into the cytoplasm of enterocytes [66]. Diffusion of free fatty acids can occur when the concentration in the intestinal lumen exceeds the concentration of free fatty acids in the enterocyte. Enterocytes can also utilize protein-mediated fatty acid uptake processes although their overall contribution during the postprandial period remains a current area of investigation [67]. After uptake, it is hypothesized that cytoplasmic lipids are transported through the aqueous intracellular environment by fatty acid-binding proteins to different organelles for processing and utilization. However, recent studies of mice deficient in the most abundant fatty acid-binding proteins do not support this model [68].

Two important protein families that can mediate fatty acid transport in vertebrates are cluster of differentiation 36 (CD36), and members of the fatty-acid transport (FATP) family (more thoroughly reviewed here [69]). CD36 is a scavenger receptor with high affinity for long-chain fatty acids located on the apical surface of epithelial cells in the small intestine [70]. The loss of CD36 in mice results in a reduction of fatty acid uptake [71], showing CD36 is partially involved in mediating the transfer of fatty acids across the plasma membrane [72–74]. The mechanistic actions of CD36 are not entirely elucidated, although CD36 has been implicated in many other roles of fatty acid metabolism. CD36 is responsible for taste perception of dietary fat in zebrafish, rodents, and humans, and this lipid sensing via CD36 has been shown to influence eating behavior and energy regulation [75,76]. Intestinal CD36 is required for lipid activation of the extracellular signal-regulated kinase ERK1/2 mitogen-activated protein (MAP) kinase pathway [77]. Through this pathway, CD36 is thought to adapt enterocyte metabolism during the postprandial period to promote the production of lipoproteins since activation of ERK1/2 is associated with an increase in chylomicron synthesis proteins. Furthermore, when diet contains lipids, CD36 protein disappears from the luminal side of the villi during the postprandial period [77].

Lipids are absorbed in the posterior midgut of *Drosophila* (Fig. 2), an organ similar to the mammalian small intestine, as well as the gastric caeca in larvae, which has microvilli-like projections to enhance food absorption [11]. In *Drosophila*, breakdown of lipids also occurs in the intestinal lumen similarly to fish, rodents, and humans. The lipase Magro is secreted by the proventricuclus [78], a bulb-shaped muscular organ at the junction of the drosophila foregut and midgut with diverse functions ranging from peritrophic matrix secretion [79] to regulation of microbial colonization [80]. Magro has both triglyceride lipase and cholesteryl esterase function [78]. There is no equivalent to bile salts in *Drosophila*, but lipids instead are emulsified by forming complexes with amino acid and glycolipids after lipase digestion [81]. The mechanism for crossing from the lumen into enterocytes in *Drosophila* is poorly understood, but homologs of the lipid scavenger CD36, and fatty acid transport proteins have been found to be expressed in enterocytes and linked with lipid transport, suggesting an evolutionarily conserved lipid sensing mechanism [82].

4. Reesterification of dietary lipid and de novo lipogenesis

In vertebrates, once inside the epithelial cell, free fatty acids, free cholesterol, and long-chain fatty acids are reconverted into triglyceride, cholesteryl esters, and phospholipids. The first step in this process involves the activation of fatty acids to fatty acyl-CoAs by fatty-acyl-CoA synthases [83]. Re-esterification of these lipids to diglycerides can occur via one of two pathways: the acylation of monoglyceride with a fatty acyl-CoA by monoacylglycerol transferase (MGAT) [84] or via the Kennedy pathway, which successively esterifies a glycerol-3-phophate backbone with two fatty-acyl CoAs [85]. Diglycerides and additional fatty acyl-CoAs are then converted into triglycerides by diglyceride acyl transferase (DGAT) [84]. Both reactions are thought to occur within the smooth ER [86], although the beginning steps of the Kennedy pathway can also occur in mitochondria [87]. In the intestine, 80 % of triglycerides are thought to come through the MGAT/DGAT pathway, and only 20 % from the Kennedy pathway [88].

A potential alternate source for both the glycerol backbone and fatty acids is the de novo lipogenesis derived from glycolysis (glycerol) and the TCA cycle (fatty acids) of dietary glucose and fructose [89,90]. While it is known that the liver performs large amounts of de novo lipogenesis [89], the existence of intestinal de novo lipogenesis is controversial [91]. There is evidence from both human [92] and hamster [93] models that dietary fructose activates de novo lipogenesis machinery. De novo lipogenesis and glucose uptake also occurs in mammalian adipocytes [90] and liver [94] and is driven by insulin signaling [95].

In *Drosophila*, whose diet often does not contain large sources of fat, free fatty acids are often synthesized from glucose and fructose-derived acetyl-CoA via the TCA cycle [28] by de novo lipogenesis in the larval fly midgut [11]. This, as well as de novo lipogenesis in the fat body [96], generates approximately 30 % of total fat stores [56]. Flies deficient in de novo lipogenesis, by knockout of acetyl CoA carboxylase or fatty acid synthase have defects in sugar catabolism and are unable to maintain healthy levels of circulating sugar [97]. Flies reesterify these fatty acids through both the MGAT and Kennedy pathways (reviewed in [98]), and usually have fewer redundant enzymes in these pathways, suggesting an evolutionary expansion of this pathway in mammals.

Drosophila have a homologous system to insulin signaling that will be discussed later in the review, but levels of de novo lipogenesis in the drosophila gut are instead controlled by the target of rapamycin (TOR) and sterol regulatory element binding proteins (SREBP) pathways [56,98].

C. elegans also performs de novo lipogenesis, which is vital for production of fatty-acids not found in their bacterial diet [99,100]. Interestingly, this process is also driven by insulin signaling [99]. Intestinal de novo lipogenesis represents an exciting area of research in model systems and could be used to explain why diabetic human patients exhibit increased postprandial triglycerides from excess chylomicrons [95].

5. Dietary lipid is packaged into chylomicrons

A single apolipoprotein B (ApoB) molecule provides structure to chylomicrons and other lipoproteins in all metazoans [101]. In a clinical setting, high levels of ApoB-containing lipoproteins are an indicator for metabolic dysfunction [102]. Patients with Type 2 Diabetes Mellitus or insulin resistance typically display higher levels of ApoB-containing lipoproteins. In mammals, the chylomicron is coated by non-exchangeable ApoB-48 protein (a truncated form of ApoB described in more detail below). Synthesis of the chylomicron requires expression of ApoB and MTP [103].

ApoB is co-translationally loaded onto nascent, lipid-rich particles by MTP. A resident ER protein, MTP transfers lipids from the ER membrane to the nascent ApoB polypeptide [104] [105], expanding the core of the primordial lipoprotein. The chylomicron has a lipid-rich core primarily composed of cholesteryl esters and triglycerides (about 90 % combined) [105]. The remaining lipid content is free and esterified cholesterol, phospholipids, retinylesters, and few fatty acids (~10 %) [106]. The molecular mechanisms that control the rate of lipid added from the ER leaflet to the particle are still unknown.

Like mammals, chickens have chylomicrons that are approximately the same size as mammalian chylomicrons [15]. However, unlike mammals, all chicken chylomicrons travel directly to the liver via the portal vein, and are thus more commonly known as portomicrons [14]. This is an advantage when studying chylomicrons in chickens, as to isolate the particle, the portal vein can merely be dissected. Chicken chylomicrons are relatively rare, making up less than 5 % of circulating lipids [107]. This is due to the relatively low lipid content of the typical avian diet, as well as the inability of non-hepatic chicken cells to perform de novo lipogenesis. Most circulating lipid is from VLDL particles from the liver [108]. This is a downside of using chickens as a model species for chylomicron metabolism. VLDL and de novo lipogenesis in the liver are much more important for determining adiposity and other markers of metabolic disease than portomicrons.

VLDL and chylomicrons are defined by post-transcriptional editing of the *apoB* transcript. In humans, post-transcriptional editing by ApoB mRNA-editing enzyme, APOBEC, results in two mRNA isoforms of *apoB*: a full-length form, *apoB-100*, and a truncated form, *apoB-48* that contains 48 % of the full *apoB* transcript. Expression of ApoB-48 occurs in the intestine and the expression of ApoB-100 occurs in the liver because APOBEC is only expressed in the intestine [109]. Thus, truncated ApoB (ApoB-48) serves as a convenient marker of intestine-derived particles in humans. This specific form of post-transcriptional editing of *apoB* is not conserved between vertebrate models. In rats and mice, the liver produces both ApoB-48 and ApoB-100 making it difficult to differentiate between liver- and intestine-derived particles in rodent models [109]. By contrast, the zebrafish does not express an APOBEC paralog in digestive organs. The *apoBb.1* transcript does not appear to undergo post-transcriptional editing in the zebrafish, so full-length ApoB-100 is present on both VLDL and chylomicron particles [109]. Like fish, chickens also do not have APOBEC function: both liver VLDL and portomicrons contain ApoB-100 [16].

Drosophila contains orthologs of ApoB: apolipophorin (Apo-Lpp) and MTP, as well as an additional ApoB-like protein known as lipophorin transport particle (LTP). LTP is unique to insects and has known homologs in locust, honey-bee, beetle, and silkworm [110]. Both Apo-Lpp and LTP are primarily produced by the fat body [11,111], an organ similar to mammalian adipocytes that shares some of the functionality of the liver [112]. However, other tissues may also play an important role in Apo-Lpp generation: the heart has been shown to upregulate lipophorin in response to a high-fat diet [12]. In contrast to vertebrate systems, the fly gut is not thought to produce any lipoprotein [11], although most work has been done in larval stages. However, *Drosophila* lipoproteins are still discussed in this review as they are thought to have a major role in transporting lipids from the intestine to the rest of the body.

In the heart and fat body, ApoLpp proteins requiring MTP are loaded onto nascent lipoproteins in a mechanism that is currently unknown [11]. The mechanism is thought to be conserved with mammalian lipoprotein formation, as *Drosophila* MTP (dMTP) can correctly assemble ApoB in a mammalian system [26]. However, dMTP only loads phospholipids to nascent particles and not neutral lipids [113], suggesting that insects have an independent mechanism for neutral lipid addition to nascent lipoprotein particles. The main neutral lipid component of insect Apo-Lpp is diglyceride [11] as compared to mammalian triglyceride. Although the reason for this difference is unclear, some work suggests that different tissues preferentially utilize triglycerides and diglycerides of different chain lengths [114]. As different mammalian tissues preferentially absorb different fatty acid chain lengths [115], studying how differential lipid loading is accomplished in insects could provide mechanisms that target long chain triglyceride accumulation in adipocytes without disrupting fatty acid metabolism in other organs.

In *Drosophila*, it is known that both ApoLpp and LTP are each composed of two peptide chains [116] that are derived are from cleavage by furin after lipidation [116]. The reason for this cleavage is unclear, but it may allow greater flexibility in particle conformation and size, which are important characteristics addressed later in this review. The nascent particles, which have a density similar to that of vertebrate HDL, are then transported to the midgut from the main site of their production in fat body, where LTP shuttles lipids [111] from enterocytes to Lpp (Fig. 3A). LTP is thought to stabilize interactions between the Apo-Lpp and lipophorin receptors (Lpr2 E/F) on the plasma membrane of enterocytes [111]. A similar interaction is thought to occur during lipid unloading from ApoLpp to tissues (Fig. 3A), which has been shown in the ovaries and larval wing imaginal discs [111]. LTP has also been localized to the enterocyte cytoplasm [11], which suggests that lipid transfer to LTP occurs by endocytosis. However, blocking of endocytosis did not prevent lipid transfer [117], and ApoLpp recycling in insects suggests that lipid transfer is largely accomplished through an endocytosis-independent mechanism. One potential protein candidate for investigation is the plasma membrane-ER associated protein Snazarus (Snz), whose overexpression was associated with increased triglyceride storage in lipoprotein-fed lipid droplets in *Drosophila* [118].

6. ApoA4: a determinant of chylomicron size?

Enterocytes produce the ApoA4 protein in response to lipid absorption. ApoA4 is added to the chylomicron before the nascent chylomicron is passed off from the ER and the protein can also be secreted along with the chylomicron [119]. ApoA4 is a small (46kD), exchangeable, lipid-associated protein that transiently binds to chylomicrons with variable copy number [120]. ApoA4 may serve as a master regulator of the postprandial lipid response as it is involved in chylomicron synthesis and degradation [121]. ApoA4 is a satiety signal in fish and humans and has roles in cholesterol and glucose homeostasis [21,122]. The synthesis of ApoA4 is upregulated in response to a high-lipid meal and enhances triglyceride secretion in swine enterocytes [123]. Polymorphisms in ApoA4 can also drastically affect lipoprotein and triglyceride levels in humans [124]. However, in some mouse models where ApoA4 is stably knocked out or overexpressed, no effect was observed on total body triglycerides, adiposity, or body weight [122,125]. These results are in contrast to animal models where ApoA4 is transiently overexpressed [126].

Expressed primarily in intestinal enterocytes and also in hepatocytes of rodents, ApoA4 is transcriptionally responsive to dietary lipid influx and associated with a higher plasma triglyceride level [125]. A suggested mechanism for the influence of ApoA4 on plasma triglycerides is its effect on chylomicron size. The amphipathic helices of ApoA4 provide a stabilizing hydrophilic coat for the chylomicron in the polar blood plasma [23,24], allowing the particle to transport more lipid. Loss of ApoA4 in mice has been shown to increase levels of chylomicrons by delaying their clearance [127]. The chylomicron exits the enterocyte

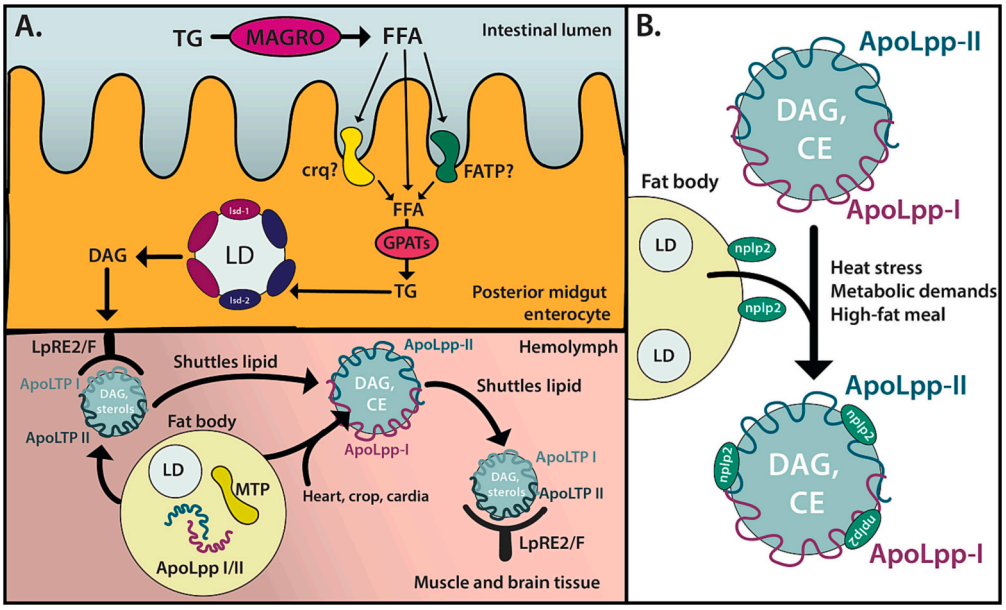

Fig. 3. *Drosophila* lipoprotein formation and transport. (A) In *Drosophila*, dietary lipids are digested by the lipase magro in the midgut lumen into glycerol and free fatty acids. These fatty acids are then absorbed into enterocytes by passive diffusion or through fatty acid transporter (FATP) and crq through an unknown mechanism. Once inside the enterocyte, the fatty acids are reconverted back into triglyceride (TAG) by GPAT enzymes and stored in lipid droplets that are stabilized by lsd1/2, homologs of plin2/3 in humans. Triglyceride in these lipid droplets can either be broken apart for fuel through beta oxidation (not shown) or converted into diglyceride (DAG) for transport to other tissues. Diglyceride is shuttled to transport lipophorins by the small lipophorin transport particle (LTP), itself a lipoprotein, in a mechanism involving the lipoprotein receptor LpRE2/F. Lipids are unloaded at tissues in a similar manner. Both Apo-Lpp and LTP are primarily produced by the fat body, but may also be produced by other organs, such as the heart or foregut, under stress. (B) Under heat stress, and conditions of high energy use, a small, exchangeable lipoprotein, NPLP2, is produced by the fat body and binds transiently to the Apo-Lpp particle, allowing it to increase in size and transport more lipid.

from the basolateral side to enter the lymphatic system. Circulating triglyceride levels are thought to increase in the postprandial state due to increased "rate of entry" of the newly synthesized chylomicron particles into the lymph lacteal [64]. It is unknown how, or if, ApoA4 participates in the absorption of dietary fat from the gut. In chicken, ApoA4 is primarily expressed in the gut: hepatic ApoA4 expression is one-fifth of that seen in the intestine [22]. This suggests a predominant postprandial role of ApoA4 in avian systems.

The role of ApoA4 as a facilitator of increased chylomicron size is controversial. Both over and under expression of ApoA4 have the same observed increase on lipoprotein size [23,123]. Part of this effect may be explained by the off-target effects on neighboring ApoC-III [23] in ApoA4 knockouts, which has been shown to influence chylomicron size [128]. ApoA4 may also act in a tissue specific-manner: hepatocyte-derived lipoproteins contain ApoB-100 and form smaller VLDL rather than the larger ApoB-48 intestinal chylomicrons. Since the longer form of ApoB-100 has extra amphipathic domains to stabilize the lipoprotein particle, ApoA4 may serve other functions in the liver, such as regulating MTP [129,130]. However, as ApoA4 deficiency or overexpression did not change *mttp* mRNA or protein levels [126], regulation is likely to be on the post-translational level.

ApoA4 may also be regulated within tissues by differential phosphorylation. Evidence from mice suggests that ApoA4 is a target of the serine-threonine kinase PRKD2 [131]. Modulation of this kinase did not affect *apoA4* mRNA levels, but did affect protein levels and increased chylomicron size. Other work found that the region containing serine and threonine residues was required for the ApoA4-associated increase in chylomicron size [123]. Taken together, this suggests that ApoA4 phosphorylation may be required for association with chylomicrons, without which ApoA4 may play an inhibitory role. However, future studies are required for the mechanism of PRKD2 acting upon ApoA4, and where this occurrs in the cell. Tissue specific PRKD2 expression thus may mediate the differential function of ApoA4 in the liver and the intestine. Humans with the Thr347Ser mutation in ApoA4 on a diet rich in mono-unsaturated fatty acids also displayed an increased ApoB and triglyceride response after a meal, providing further evidence of a role for phosphorylation in the activity of ApoA4 [124].

In fish, *apoA4* has undergone multiple duplication events suggesting multiple potential roles for the lipoprotein and that the locus is under selective pressure, although these genes are only distantly related to humans [21]. Fish with two copies of *apoA4* include Goldfish, Northern Pike, Spotted Gar, Tetradon, and Coelacanth; the zebrafish has three copies [132]. There appears to be no clear link between the environment of each of these fish and their *apoA4* copy number, but the authors note that all these fish consume high-fat content insects and other fish [133].

In *Drosophila*, no proteins identified share significant sequence similarity to ApoA4. However, migratory insects such *Locusta migratoria* contain a transiently associated apolipophorin known as Apolipophorin-III (Apolpp-III) that may share the same role in lipoprotein expansion putatively assigned to mammalian ApoA4 [134]. This protein transiently associates with lipoprotein particles during times of high energy demands such as long-distance flights [116]. The cleavage of Apo-Lpp during lipophorin particle formation gives the nascent particle the flexibility to absorb varying amounts of neutral lipid. Large amounts of neutral lipid in the particle leads to diglyceride accumulation in the phospholipid monolayer of the lipoprotein particle [135]. Apolpp-III has high affinity for diglyceride and binds to the lipoprotein particle, stabilizing the membrane. As diglyceride is transferred to tissues from the enlarged particle, this affinity wanes and Apolpp-III dissociates. In *Drosophila*, a protein previously identified as a neuropeptide, NPLP2, may play a similar role to ApoA4 in expanding lipoprotein particle size to accommodate additional lipids in the context of heat stress [20] (Fig. 3B). NPLP2 was shown to reduce lipid accumulation in the gut, suggesting a role for the importance of particle expansion in transporting lipids out of the gut after a meal [20]. However, it was not directly shown that NPLP2 was upregulated postprandially. ApoA4 and similar exchangeable lipoproteins in insects, may instead allow the body to better respond to short term energy demands such as exercise, heat stress, or large influxes of dietary nutrients in *Drosophila* and higher-level organisms.

7. The effect of dietary lipid on circulating chylomicrons

In vertebrate organisms, assembled chylomicrons are secreted by

enterocytes into the lymphatics which drain into blood circulation. In circulation, chylomicrons are rapidly lipolyzed generating chylomicron remnants. Due to their large size, chylomicrons themselves are unable to cross the endothelial border and their remnants are quickly cleared by liver uptake. Dietary fat is transported via chylomicrons in the post-prandial state. Postprandial lipemia is measured as blood plasma concentration of triglyceride at different time intervals after a meal [136]. Clinicians often only measure fasting plasma lipids, excluding chylomicron and thus the full lipid profile. Plasma triglyceride levels can increase within minutes after a meal with an "early" peak of increasing triglyceride concentration defined at 10–30 min after a meal [137]. This curious phenomenon is known as the second meal effect, and this early plasma lipid peak originates from stored intestinal lipid from the previous meal [138]. The postprandial peak in humans occurs 3–4 h after a meal, but can persist for at least 8 h [137]. The typical Western diet can result in an 18-hour duration of postprandial lipemia [139]. Using rat intestine, it was shown that the presence of fat in the diet also increases the size of synthesized chylomicron to 140–200 nm postprandially versus 20–80 nm during the fasting state [140].

There is evidence to suggest that the exact composition of lipids in a meal is important in determining the magnitude and duration of the post-prandial triglyceride response. Dietary triglycerides are composed of a glycerol and three fatty acids chains that range in length from 4 to 22 carbons with anywhere from 0 to 6 carbon-carbon double bonds that make the fats unsaturated [141]. In the gut, short chain fatty acids (less than 6 carbons) are rarely formed by the lysis of dietary triglycerides but rather are the products of bacterial fermentation of dietary fiber, sugar and starch [142]. Short chain fatty acids may make up to 10 % of human caloric intake [143] and have documented effects on alleviating hyperinsulinemia, heart disease, and obesity [144]. Similar effects have been documented in *Drosophila* [145]. In mammals, these fatty acids diffuse directly from enterocytes into the portal vein to the liver without entering chylomicrons [146].

Medium-chain fatty acids (chain length 6–12), such as those found in coconut oil and mammalian milk, are processed in a similar way, although their effect on obesity and atherosclerosis in general is more controversial. Medium-chain fatty acids have been shown to be rapidly oxidized by the body and increase basal metabolic rate. The consumption of medium-chain fatty acids may have an anti-obesogenic effect [147,148]. Changes in insulin sensitivity on a diet rich in medium-chain fatty acids have also been reported in mice, but these require a knockout of CD36 [149]. However, whole-body LDL and hormonal changes are likely due to changes in liver lipoprotein metabolism, as medium-chain fatty acids are not incorporated into chylomicrons. Indeed, dietary supplementation of caprenin, which is an artificial fat composed of C8:0, C10:0, and C22:0, was shown to have little effect on the content, or number of chylomicrons as compared to supplementation with palm oil [19]. Most studies of the effects of chain length on lipoproteins and whole organism triglycerides have taken place in humans. However, in zebrafish, it has been shown that different chain lengths of dietary lipids are incorporated into different tissues [150]. In *Drosophila*, study of medium-chain triglycerides is complicated by the fact that *Drosophila* lipoproteins and lipid droplets generally contain shorter chain length fats than their mammalian counterparts. However, further study of the effects of fatty-acid chain length on lipoproteins in model organisms is needed, especially in developing high-fat diet formulations in these animals to develop better models of human obesity and heart disease. The molecular biology of medium-chain and short-chain fatty acid metabolism in mammals is more thoroughly reviewed in [141].

Unsaturated fats, which incorporate carbon-carbon double bonds, have long been associated with positive health outcomes [151]. In mammals, unsaturated fats are associated with larger, more rapidly clearing chylomicrons [152–154] which may have a protective effect against atherosclerosis, as larger, faster clearing particles are less likely to get stuck in the endothelial walls of arteries [155]. However, this is controversial, and may differ between mono- and polyunsaturated fats [155,156]. The presence of unsaturated fats in chylomicrons may also trigger changes in hepatic expression of genes involved in fatty-acid anabolism. A meal of unsaturated fatty acids in mice was shown to reduce the amount of hepatic de novo lipogenesis as compared to a meal high in saturated fat [157]. There is evidence that the composition of a meal influences chylomicron composition, binding to the liver, and, in turn, affects the levels of hepatic VLDL secretion [158–160].

The persistence of plasma chylomicrons carrying triglyceride following a period of fasting is defined as chylomicronemia [161]. Hyperchylomicronemia is the overabundance of chylomicrons in the plasma resulting in hypertriglyceridemia and can clinically present in two separate forms that occur at different rates in the human population [162]. The first form is familial hyperchylomicronemia which is a rare genetic disorder that presents during childhood as a result primarily from single gene mutations in lipoprotein lipase, ApoC2, or ApoA5 [163]. ApoA5 stabilizes the lipoprotein lipase-ApoC2 complex by promoting the binding of the lipoprotein to endothelial surfaces [164]. Therefore, functional breaks in either of these three proteins, results in an inability of the triglyceride-rich lipoproteins to be cleared and a persistence of chylomicrons in circulation. However, this monogenic form of hyperchylomicronemia is extremely rare making up less than 5 % of total cases. The second form is polygenic in nature and is more commonly observed. Polygenic hyperchylomicronemia is caused by simultaneous genetic variants and is exacerbated, or can result from high caloric intake, sedentary lifestyle, obesity, alcohol intake, and/or uncontrolled diabetes [165]. Currently, the primary management for patients with hyperchylomicronemia is improved diet and exercise [163]. Hypochylomicronemia is the absence of post-prandial chylomicrons resulting from genetic causes. An example is a mutation in secretion associated Ras related GTPase 1B (SAR1B) that is a subunit of the coat protein complex II (COPII) complex responsible for secretory transportation of primordial chylomicrons (or pre-chylomicron).

Cytoplasmic lipid droplets are responsible for storage of large amounts of triglyceride in the enterocyte [166]. Although the fly, fish and mammals have secondary organs to process and store fat, more primitive animals, such as *C. elegans* [10] perform all three functions in the gut. Rather than a mere holding station for lipids destined for storage in adipocytes, or processing in the liver, this suggests an evolutionarily conserved role for the gut as a key hub of lipid metabolism. It remains unclear whether postprandial circulating triglycerides are released from storage pools within the enterocyte or directly from lipids provided in the meal (Fig. 4). Absorbed lipid can be packaged immediately into lipoproteins in the enterocyte [103]. Currently, there is no evidence that dietary lipid passes through lipid droplets before being incorporated into the chylomicron. Recent efforts are attempting to resolve the pathways by which lipid droplets release their storage pool of lipids to the ER to build nascent lipoproteins [167].

8. Enteroendocrine response to dietary lipid

Enteroendocrine cells reside along the intestinal epithelium interspersed between enterocytes. Found in *Drosophila*, zebrafish, rodents, and humans, enteroendocrine cells have been shown to sense and absorb available nutrients from the intestinal tract and transduce this information by hormone secretion. Enteroendocrine cells traditionally have "open" apical extensions and microvilli that face the intestinal lumen and have been shown to morphologically respond to a high-fat diet [168]. Studies in zebrafish have found that upon a high fat feed, these cells lose their "open" configuration by retracting the cellular extension [169]. Researchers found that calcium signaling in the cell diminishes when the apical extensions are lost, suggesting a quiescent state of these cells and that this quiescence is a reversible response to dietary lipid. The physiological significance of changes in enteroendocrine cell morphology remains to be defined, yet could point to unappreciated ways that these cells regulate dietary lipid absorption.

It is well established that enteroendocrine cells play an important

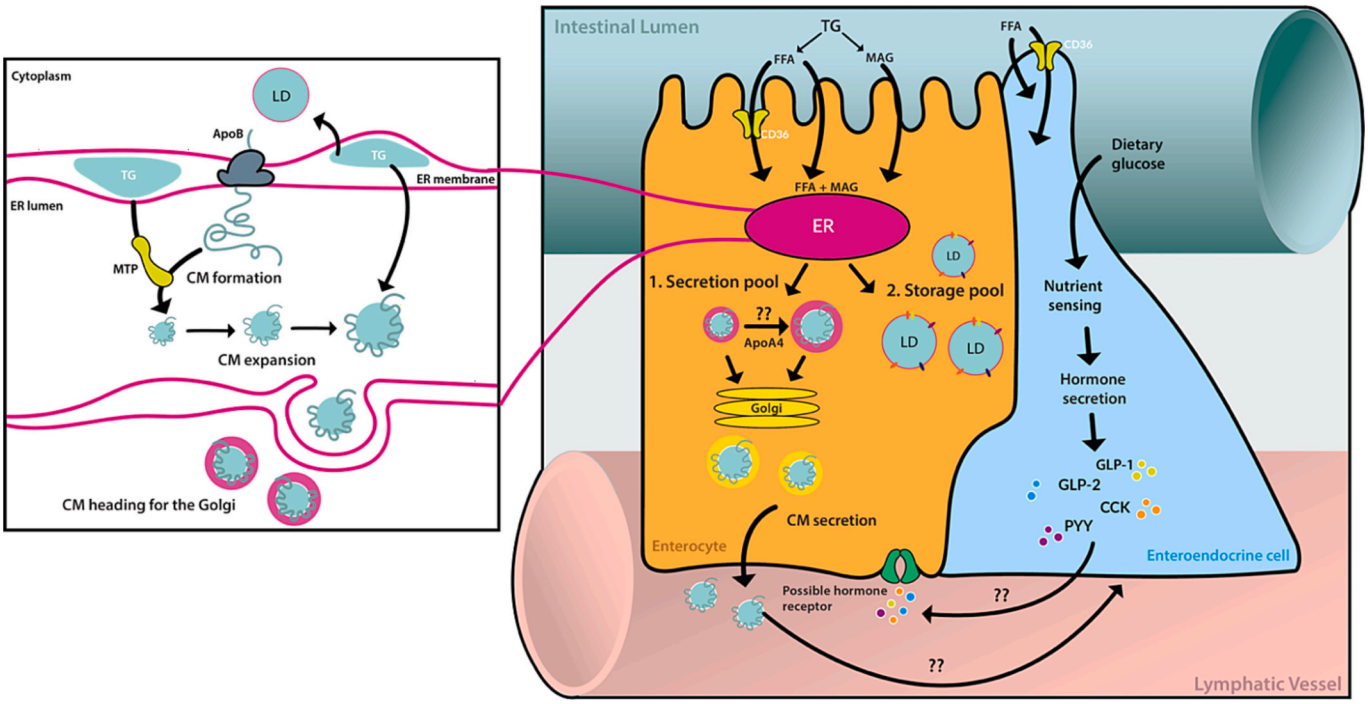

Fig. 4. Chylomicron formation within the enterocyte in response to dietary nutrients. Triglyceride is broken down in the intestinal lumen into free fatty acids and monoglycerols. In addition to diffusion, CD36 can facilitate uptake of free fatty acids. Fatty acids pool in the ER and are packaged into chylomicrons for secretion from the enterocyte. Lipids in the enterocyte may be secreted or stored into lipid droplets (LD). MTP facilitates the formation of the chylomicron within the ER (left) as it co-translationally loads the ApoB-48 particle with lipid to form a chylomicron (CM) that buds off the ER membrane in pre-chylomicron transport vesicles (pink) to the Golgi and are secreted as mature chylomicrons (yellow). ApoA4 potentially plays a role in increasing the amount of lipid loaded onto the chylomicron. Free fatty acids are also taken up by the enteroendocrine cell (enteroendocrine cell) by CD36. The enteroendocrine cell also secretes hormones as a response to the uptake of dietary glucose. It is unknown (denoted by question marks), perhaps possible, that the enterocyte responds to the hormones released by the enteroendocrine cell and controls its release of chylomicron into the lymphatic vessel, or if the enteroendocrine cell has a response to chylomicron secretion.

role in response to nutrient sensing; however, it remains unknown the mechanism by which enteroendocrine cells physically respond and communicate changes in intestinal nutrient levels to the surrounding enterocytes that release triglyceride-rich particles (Fig. 4). As a neuropod, enteroendocrine cells communicate directly along the gut-brain axis to the afferent nerve as the neuropod extends under the base of the lamina propria. Few enterocytes physically contact the enteroendocrine cell. The neuropod of the enteroendocrine cell allows for convenient delivery of peptides to the enterocyte via the mucosa. The ideal positioning of these cells suggests a non-cell autonomous regulation of lipid metabolism, however there is no evidence for how enteroendocrine cells may communicate directly with the enterocyte.

Vital for hormone secretion, enteroendocrine cells are a conserved cell type among bilaterians and present in *Drosophila* [170]. Homologous to the insulin/glucagon signaling pathway in mammals, flies have two antagonistic hormones, adipokinetic hormone (Akh) and *Drosophila* insulin-like peptide (Dilps), which are triggered by fasting (catabolic) and feeding (anabolic) respectively [98]. These master hormones act like insulin and glucagon in mammals and control lipid mobilization by promoting cytoplasmic (Dilps) or nuclear (Akh) retention of the transcription factor foxo [171,172]. Foxo promotes expression of the lipase *brummer* and *lip4*, an acid lipase [171]. Foxo has four homologs in humans which produce around two dozen splice variants with a variety of homeostatic and developmental roles [173]. In addition to Akh and Dilps, *Drosophila* enteroendocrine cells also release a variety of neuropeptides, with homology to mammalian GLP-1, CCK, PYY [174]. These findings suggest chylomicron regulation by intestinally secreted hormones is conserved across bilaterians. The role of some of the most significant of these conserved hormones will be discussed in the next section.

9. Molecular regulators of postprandial chylomicron production

9.1. Gut hormones GLP-1 and GLP-2 affect lipid metabolism

Insulin and its counteracting hormone, glucagon, regulate blood sugar levels and metabolic activity through control of cellular carbohydrate absorption and lipolysis. Insulin resistance occurs when insulin is no longer as able to effectively trigger glucose absorption into somatic cells, leading to higher insulin and glucose levels in the blood plasma [2]. High blood glucose levels (hyperglycemia) occur when insulin is produced by the pancreas and insulin levels rise in the blood stream, however glucose levels do not change, which results in a diabetic state (often referred to as insulin resistance or insulin sensitivity). Increased levels of circulating chylomicrons have been observed in rodent models and humans in insulin resistant states, however the mechanism by which insulin signaling acts upon chylomicron biogenesis or secretion from the enterocyte is yet to be elucidated. *Drosophila* hormonal and peptide response is similar to mammals: Akh and Dilps are homologous to the mammalian glucagon/insulin response [175] and both mammalian and insect enteroendocrine cells secrete similar neuropeptides in response to a meal [98].

As enteroendocrine cells sit along the intestinal epithelium intermixed with enterocytes, intercellular communication is important for nutrient sensing and absorption. In response to external factors, enteroendocrine cells secrete conserved hormones along the intestine, including gut-derived peptides 1 and 2 (GLP-1 and GLP-2). One of the functions of GLP-1 is to increase insulin secretion in response to the presence of glucose [176]. The presence of GLP-1 in the plasma results in an inhibition of glucagon secretion and promotion of satiety. GLP receptors are located on neurons and the pancreas; the exact location of GLP receptors in the gastrointestinal tract has been difficult to

determine. Some studies agree on the presence of GLP receptors in the murine intestinal epithelium [177,178], yet others have not found receptors there [179]. These studies note that these findings may be mouse-specific [179].

Studies have shown that healthy humans given an infusion of GLP-1 do not show an increase in postprandial triglycerides [181]. This is to be expected in a normal insulin signaling state, whereas in Type 2 Diabetes Mellitus patients, GLP-1 normalizes fasting hyperglycemia by lowering plasma glucose levels, inducing insulin secretion and inhibiting glucagon release [182]. GLP-1 is only found in vertebrates [183]. However, recently a homolog to another mammalian incretin, NPY, has been identified in *Drosophila* as neuropeptide-F [184]. Neuropeptide-F is produced by enteroendocrine cells in response to sugar and controls the ratio of Akh and Dilps, which in turn favors organismal anabolism [183].

In a Syrian golden hamster model of diet-induced insulin resistance combined with infusion of GLP-1, secretion of insulin in plasma increased as did expression of insulin mRNA, while ApoB-48 protein levels decreased [185], indicating that the expression of insulin affects ApoB-48 protein expression. The co-infusion of GLP-1 and GLP-2 increased intestinal lipid absorption, triglycerides, and ApoB-48 levels in hamsters after 30 min. After 120 min, the co-infusion reduced postprandial lipemia [185]. These data indicate GLP-2 mediates lipid absorption and chylomicron production in the hamster model.

To further interrogate the role of GLP-1 on intestinal production of chylomicrons, researchers utilized pharmacological inhibition of GLP-1. Dipeptidyl peptidase-4 (DPP-4) is responsible for the breakdown of GLP-1 and rapidly degrades GLP-1 in the plasma with a half-life of <2 min [186]. Postprandial lipemia was observed in mice and hamsters treated with Sitagliptin, a DPP-4 inhibitor [187]. The deletion of the GLP-1 receptor, or the inhibition of the GLP-1 receptor (GLP1R) was shown to enhance the secretion of triglyceride-rich lipoproteins in mice and hamsters [188]. Together, these studies have demonstrated a biological role for the regulation of chylomicron synthesis and/or secretion by GLP1R signaling and have connected lipoprotein regulation to insulin signaling. These studies have shown that infusion of GLP-1 or inhibition of DPP-4 can decrease chylomicron levels, providing a possible use of the GLP-1 pathway as a therapeutic target for controlling postprandial lipid levels. These results suggest that GLP-1 acts preventative towards the assembly of the chylomicron or the secretion of the chylomicron, however, the mechanism has yet to be shown.

GLP-2 has a paradoxical role in relation to GLP-1. Hsieh et al. [188] established a role for GLP-2 in the regulation of intestinal lipid metabolism [95]. The GLP-2 receptor is a G-protein coupled receptor and binding of the ligand was shown to stimulate lipid uptake by the intestine. Upon an oral gavage of triolein and intravenous infusion of GLP-2, measurements of blood plasma from the hamster showed an increase in circulating ApoB-48 and triglyceride. These data show that GLP-2 signaling may promote increased chylomicron assembly, however the mechanism is still unknown [188].

GLP-2 studies showed similar results in human patients who underwent constant intraduodenal feeding. Volunteers treated with GLP-2 showed a transient increase in ApoB-48 particles compared to placebo [188]. In another experiment, volunteers were fed a meal labelled with retinyl palmitate in the morning and then fasted. In the afternoon, GLP-2 was administered by infusion, and after 2 h blood sampling of the volunteers was performed and analyzed for retinyl palmitate signal [189]. Throughout, a pancreatic clamp was utilized to normalize metabolic regulators between volunteers. Researchers found that the GLP-2 treatment increased plasma retinyl palmitate signal 7 h after ingestion of the meal suggesting that the gut released previously stored chylomicrons [189]. The study did not further elucidate the mechanism in the release of stored lipids from the intestine, however, it greatly contributed to the understanding of chylomicron secretion in humans by demonstrating that the administration of GLP-2 releases chylomicrons that were previously synthesized and stored in the intestine, providing further evidence for the aforementioned second meal effect [138].

Similar studies were replicated in the mouse model where mice were challenged with an oral fat load after during GLP-2 treatment. Again, researchers found that GLP-2 treatment increased plasma triglyceride compared to untreated controls. Researchers administered olive oil to the Syrian Golden Hamster and measured lipid absorption in *cd36−/−* hamsters compared to wild-type siblings [188]. CD36 KO mice showed CD36 is not necessary for long-chain fatty acids uptake during postprandial period because CD36 deletion did not change long-chain fatty acids uptake [77]. Overall, the studies found that fat absorption that is promoted by GLP-2 activity requires CD36 [67]. The mechanism by which GLP-2 promotes fatty acid absorption has not been shown. Some hypothesize that GLP-2 helps to promote glycosylation of CD36, which increases recruitment of the protein to the plasma membrane [76].

9.2. PYY and CCK release in response to dietary nutrients

In addition to GLP-1 and GLP-2, enteroendocrine cells release many other peptide hormones into circulation that prime secondary digestive organs, such as the pancreas and gallbladder, to secrete enzymes into the digestive tract and prepare other tissues for nutrient absorption [190,191]. Additional peptides secreted by the enteroendocrine cell include gastric inhibitory polypeptide (GIP) (also known as glucose-dependent insulinotropic) have been shown to mediate lipoprotein lipase activity in response to high fat meals [192]. Other peptides include cholecystokinin (CCK) and peptide tyrosine-tyrosine (PYY).

CCK was discovered in 1928 as a gallbladder contraction factor secreted by the jejunum [193]. More recent research has established it as peptide hormone secreted by enteroendocrine cells in the proximal intestine: the region responsible for absorbing dietary nutrients [51,168]. Like many gastrointestinal peptides, CCK regulates both local and neurological responses to a meal: it stimulates the release of bile and pancreatic enzymes into the digestive tract and the release of leptin into circulation, a signal for satiety [194]. A high-fat diet causes an initial postprandial increase in CCK transcripts in enteroendocrine cells, triggered most strongly by medium and long-chain fatty acids compared to a control salt-solution [195], that levels out after 6 h [168]. It is proposed that enteroendocrine cells sense circulating lipid [196] resulting in CCK secretion, but the mechanism of this is unclear and needs to be deconvolved from the positive correlation between CCK secretion and increased levels of dietary fat, which is also a trigger for chylomicron secretion.

Drosophila contain a CCK-like peptide known as *Drosophila* cholecystokinin-like peptide (DSK) which is also important for satiety [197]. DSK is also activated via the octopamine pathway: neurons producing the neurohormone octopamine activate DSK production in insulin producing cells, which controls satiety and aggression [198]. There is no current link between DSK and lipoprotein metabolism in *Drosophila*.

Peptide tyrosine-tyrosine (PYY) is another peptide hormone secreted from enteroendocrine cells in the small and large intestine in mammals, with highest levels in the rectum [168,199,200]. The role of PYY is primarily a neuropeptide: it prevents gastric emptying and is a satiety factor [201]. However, PYY may also have a direct effect on the intestinal dietary response: it has been shown to stimulate ApoA4 translation in rats and in humans after gastric-bypass surgery [202,203]. With the previously described role of ApoA4 to increase chylomicron size to facilitate movement of lipid from the gut to the rest of the body, PYY may serve as a signal to enhance lipid clearance from the intestine in mammals. There is no direct PYY homolog in flies, but human PYY and NPY, a homolog to the main *Drosophila* incretin NPF [183], are structurally similar. A link between NPF and *Drosophila* putative lipoprotein particle expander NPLP2, has not yet been investigated.

9.3. SREBP: an alternate source of intestinal lipids in animals

The transcription factor family of sterol regulatory element binding

proteins (SREBP) is essential for coordinating the response of digestive and somatic cells to a meal and the regulation of gut de novo lipogenesis in many models [204]. Mammals have two copies of SREBP: SREBP1, which has two splice variants SREBP1a and SREBP1c, and SREBP2 [205,206]. The three proteins are thought to have different tissue localizations and functions: SREBP2 is thought to regulate sterol synthesis, while the two SREBP1 variants are thought to regulate fatty-acid synthesis in the liver (SREBP1c) and other tissues (SREBP1a) [207]. However, these roles are controversial. Work in hamsters has shown that SREBP1c and SREBP2 are the main SREBPs expressed in the gut [208], which is contrast to data from mouse showing the opposite [207]. An SREBP1c knockout in ApoA5 deficient animals, who alone were deficient in lipoprotein clearing, prevented the secretion of large VLDL particles, but had no effect on chylomicron clearance [209]. Fatty acid supplementation also decreased the amount of SREBP expression and fatty acid synthesis in cultured colon cells, but had no effect on lipoprotein secretion [210]. The role of dietary SREBP response in vertebrate intestine remains unclear and needs specific study to be deconvolved from the larger observed hepatic response.

In *Drosophila*, the role of SREBPs is more clearly linked to regulation of de novo lipogenesis, as SREBP mutants are fatty acid auxotrophs [211], and show decreased expression of Acetyl CoA carboxylase and fatty acid synthase, which are required for generation of lipids from sugar-derived acetyl-CoA. Phospholipids inhibit the activation of SREBP in flies in a mechanism that appears to be conserved in mammals [212,213]. Approximately 30 % of total circulating diglyceride is created by de novo lipogenesis in the midgut in flies [11], meaning gut de novo lipogenesis is an important source of fat for the fly, as well as an important way to prevent sugar toxicity [97]. In the fat body, an organ with functions of both mammalian adipocytes and hepatocytes, SREBP also controls de novo lipogenesis, but favors the formation of triglyceride for storage rather than diglyceride for transport [11]. This suggests a potential mechanism by which the SREBP response of the enterocyte and fat body are differentiated, although complicated by the fact that diglyceride lipid transport is not conserved between mammals and insects. Finally, SREBP has recently been implicated to be involved in the NF-κB immune response in *Drosophila*, suggesting a potential link between diet and regulation of the intestinal microbiome [214].

10. Conclusions and future directions

Animal models present a powerful approach for understanding how diet and genetics regulate intestinal lipoprotein metabolism. The different organisms discussed in this review (from *C. elegans* to mice) all contribute to our understanding of human chylomicron biology. *C. elegans* lipid processing and lipoprotein production largely occurs in the gut, making it an excellent system to study intestinal lipoproteins [10]. *C. elegans* also has many hormones that are conserved in the mammalian insulin signaling pathway [172]. Although the current data suggests that *D. melanogaster* produces very little, if any, intestinal lipoprotein, the flexibility of its lipoproteins to change size in response to stress, as well as many conserved intestinal hormonal pathways, give the fly relevance to lipoprotein biology. The tractability of the *Drosophila* microbiome, as well as the ease of high-throughput dietary and genetic studies make *Drosophila* an exciting candidate for studying lipoproteins. Zebrafish are the vertebrate system best suited to high-throughput studies of vertebrate lipoprotein metabolism: zebrafish have separate pools of intestinal and liver-derived lipoproteins. Zebrafish chylomicron assembly, and hormonal control,- are highly conserved and can easily be studied through forward genetics, CRISPR, and small molecule screens in cells and whole animals. Study of chicken portomicrons may help us to understand human chylomicrons from an evolutionary perspective, as well as to make sense of the direct trafficking of medium-chain triglycerides that occurs in the mammalian portal vein.

Unlike fish and humans, mice are HDL-dominant animals that lack the cholesteryl ester transfer protein gene. While mice provide a moderate amount of tissue per animal for physiological studies, and are more closely related to humans, it is more difficult to perform large-scale studies. Forward genetic approaches are cost prohibitive in mice (per diem ~$1/day in mice vs ~$3/year in fish), and due to small litter sizes, experiments involving mice are extremely time consuming. Different model organisms may be better suited than others to address specific questions surrounding intestinal lipid biology. We have described that zebrafish, flies, and worms well recapitulate different aspects of human lipid biology, and do not raise as many ethical issues as compared to potentially more sentient avian and mammalian models [215]. Researchers may wish to consider the use of non-mammalian models for the study of intestinal lipid biology.

Digestion in the intestinal lumen is well understood. In mammals, lipids are emulsified by secretions from the pancreas and gallbladder, or the foregut in insects, and then broken down into free-fatty acids and monoglycerides. While short and medium-chain fatty acids are trafficked directly across the cell membrane of the enterocyte by diffusion, it is an open question in all model systems exactly how longer chain fatty acids are transported from the lumen. There also remains an incomplete understanding of lipid sensing. It is known that enteroendocrine cells and taste-buds also express specific proteins on the their apical, lumen-facing surface: how might these proteins help to coordinate whole-body postprandial hormonal responses? Dietary fat is made up of triglyceride, however the lingual lipase digests triglyceride into fatty acid and the released fatty acids are sensed on the tongue by taste buds. Fatty acids are one substrate that interact with CD36 on taste bud cells suggesting that CD36 may be important for tasting fat. *Drosophila* and *C. elegans* both contain homologs to CD36 and may be strong systems to resolve these questions.

Once inside the enterocyte, free fatty acids are re-esterified into triglyceride, cholesteryl esters, or converted into phospholipids through the Kennedy pathway. These lipids are packed in the ER into either lipid droplets for storage or chylomicrons for export. However, many open questions remain: are these pools mutually exclusive, or is there ready scavenging of chylomicron lipids from lipid droplets? How do diet and genetics determine the specific lipid species content of chylomicrons? Do these different lipid species affect the kinetics of chylomicron utilization? *Drosophila* may be an excellent model species to study these questions as it has a separate pool of circulating lipids in the form of diglyceride. Chickens may also be a useful model system because of the ease of accessing their chylomicrons: all can be found in the portal vein.

All chylomicrons contain one copy of a non-exchangeable lipoprotein. This single lipoprotein is not flexible enough to deal with the different chylomicron sizes and lipid compositions. Exchangeable lipoproteins, such as ApoA4 in vertebrates, NPLP2 in dipterians, and Apolpp-III in other insects, may have independently evolved to help deal with this problem. These proteins transiently associate with chylomicrons and other large lipoproteins and help to stabilize its phospholipid membrane. However, the roles of these particles are not entirely clear: nplp2 may also act as a neuropeptide; ApoA4 has opposing effects in the liver. These proteins may not be the only determinants of chylomicron size: the lipid species present in the nascent particle, especially the ratio of unsaturated to saturated fatty acids, may also be an important determinant. Particle size may be determined more by proteins that facilitate lipid loading, rather than stabilizing, exchangeable lipoproteins. How is the size of the chylomicron by lipid content determined? Is it solely the role of ApoA4? Zebrafish is a particularly intriguing model organism in which to study the function of ApoA4 because of its recent gene duplication, which may have allowed the multiple roles seen in mammals to be assigned to the newly duplicated proteins.

Finally, chylomicron-associated gut hormones represent a promising mechanism through which lipid clearance of the intestine is coordinated with the lipid metabolism of the rest of the organism. Supporting this hypothesis is the association between insulin resistance and increased levels of ApoB-48-containing-lipoproteins [95,216,217]. Gut hormones have been associated with altering chylomicron dynamics and lipid

clearance from the intestine [67,185,188,189]. Thus, the regulation of chylomicron secretion is dependent on the coordination of many processes.

In *Drosophila*, the control of de novo lipogenesis by the SREBP class of proteins is of particular interest, as *Drosophila* consume relatively small amounts of dietary fat. Mouse models also suggest an important role of chylomicrons in regulating SREBP metabolism in the liver. However, many methodological problems remain: the most important of which is to develop tools to separately measure intestinal chylomicrons as compared to liver lipoproteins in model organisms without ApoB-48, such as the zebrafish. Overall, hormonal regulation of chylomicrons is a promising, and evolutionarily conserved, area of research for drug development in model organisms.

CRediT authorship contribution statement

Darby Kozan: Conceptualization, figure generation, writing - original draft preparation, writing - review and editing.

Joshua Derrick: writing - original draft preparation, writing - review and editing.

William Ludington: writing - review and editing.

Steven Farber: Supervision, writing - review and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] R. Elías Zambrano, Children, media and food. a new paradigm in food advertising, social marketing and happiness management, Int. J. Environ. Res. Public Health 18 (7) (2021) 3588.
[2] U.S.D.o.H.H Services, Diabetes - Type 2 Diabetes, December 16, 2021 [cited 2022 May 25].
[3] A. Tirosh, et al., Changes in triglyceride levels over time and risk of type 2 diabetes in young men, Diabetes Care 31 (10) (2008) 2032–2037.
[4] M. Alves-Bezerra, D.E. Cohen, Triglyceride metabolism in the liver, Compr. Physiol. 8 (1) (2017) 1–8.
[5] H.N. Ginsberg, Lipoprotein physiology, Endocrinol. Metab. Clin. N. Am. 27 (3) (1998) 503–519.
[6] H.N. Ginsberg, Effects of statins on triglyceride metabolism, Am. J. Cardiol. 81 (4A) (1998) 32B–35B.
[7] V.P. Skipski, et al., Lipid composition of human serum lipoproteins, Biochem. J. 104 (2) (1967) 340–352.
[8] A. Adam, et al., Abstracts from hydrocephalus 2016, Fluids Barriers CNS 14 (Suppl. 1) (2017) 15.
[9] V. Hartenstein, P. Martinez, Structure, development and evolution of the digestive system, Cell Tissue Res. 377 (3) (2019) 289–292.
[10] B.C. Mullaney, K. Ashrafi, C. elegans fat storage and metabolic regulation, Biochim. Biophys. Acta 1791 (6) (2009) 474–478.
[11] W. Palm, et al., Lipoproteins in Drosophila melanogaster—assembly, function, and influence on tissue lipid composition, PLoS Genet. 8 (7) (2012), e1002828.
[12] S. Lee, et al., Cardiomyocyte regulation of systemic lipid metabolism by the apolipoprotein B-containing lipoproteins in drosophila, PLoS Genet. 13 (1) (2017), e1006555.
[13] P.J. Babin, J.M. Vernier, Plasma lipoproteins in fish, J. Lipid Res. 30 (4) (1989) 467–489.
[14] A. Bensadoun, A. Rothfeld, The form of absorption of lipids in the chicken, Gallus domesticus, Proc. Soc. Exp. Biol. Med. 141 (3) (1972) 814–817.
[15] H. Griffin, G. Grant, M. Perry, Hydrolysis of plasma triacylglycerol-rich lipoproteins from immature and laying hens (Gallus domesticus) by lipoprotein lipase in vitro, Biochem. J. 206 (3) (1982) 647–654.
[16] P. Tarugi, Absence of apolipoprotein B-48 in the chick, Gallus domesticus, J. Lipid Res. 31 (3) (1990) 417–427.
[17] V. Blanc, et al., Intestine-specific expression of Apobec-1 rescues apolipoprotein B RNA editing and alters chylomicron production in Apobec1 -/- mice, J. Lipid Res. 53 (12) (2012) 2643–2655.
[18] N.O. Davidson, G.S. Shelness, APOLIPOPROTEIN B: mRNA editing, lipoprotein assembly, and presecretory degradation, Annu. Rev. Nutr. 20 (2000) 169–193.
[19] J.T. Snook, et al., Chylomicron fatty acid composition and serum lipid concentrations in subjects fed carpenin or palm oil/palm kernel oil as the major dietary fat, Nutr. Res. 16 (6) (1996) 925–936.
[20] S. Rommelaere, et al., The exchangeable apolipoprotein Nplp2 sustains lipid flow and heat acclimation in Drosophila, Cell Rep. 27 (3) (2019) 886–899.e6.
[21] J.P. Otis, et al., Zebrafish as a model for apolipoprotein biology: comprehensive expression analysis and a role for ApoA-IV in regulating food intake, Dis. Model. Mech. 8 (3) (2015) 295–309.
[22] A. Steinmetz, et al., Expression and conservation of apolipoprotein AIV in an avian species, J. Biol. Chem. 273 (17) (1998) 10543–10549.
[23] A.B. Kohan, et al., Apolipoprotein A-IV regulates chylomicron metabolism-mechanism and function, Am. J. Physiol. Gastrointest. Liver Physiol. 302 (6) (2012) G628–G636.
[24] C.L. Bisgaier, et al., Distribution of apolipoprotein A-IV in human plasma, J. Lipid Res. 26 (1) (1985) 11–25.
[25] C.T. Murphy, P.J. Hu, Insulin/insulin-like growth factor signaling in C. Elegans, WormBook (2013) 1–43.
[26] J.A. Sellers, et al., A drosophila microsomal triglyceride transfer protein homolog promotes the assembly and secretion of human apolipoprotein B. Implications for human and insect transport and metabolism, J. Biol. Chem. 278 (22) (2003) 20367–20373.
[27] M.H. Wilson, et al., A point mutation decouples the lipid transfer activities of microsomal triglyceride transfer protein, PLoS Genet. 16 (8) (2020), e1008941.
[28] L.P. Musselman, et al., Role of fat body lipogenesis in protection against the effects of caloric overload in drosophila, J. Biol. Chem. 288 (12) (2013) 8028–8042.
[29] L. Fang, C. Liu, Y.I. Miller, Zebrafish models of dyslipidemia: relevance to atherosclerosis and angiogenesis, Transl. Res. 163 (2) (2014) 99–108.
[30] I. Avraham-Davidi, et al., ApoB-containing lipoproteins regulate angiogenesis by modulating expression of VEGF receptor 1, Nat. Med. 18 (6) (2012) 967–973.
[31] J.H. Thierer, Pla2g12b is Essential for Expansion of Nascent Lipoprotein Particles, bioRxiv, 2022, p. 2022.08.02.502564.
[32] P.M. Nishina, J. Verstuyft, B. Paigen, Synthetic low and high fat diets for the study of atherosclerosis in the mouse, J. Lipid Res. 31 (5) (1990) 859–869.
[33] Y.K. Chan, et al., High fat diet induced atherosclerosis is accompanied with low colonic bacterial diversity and altered abundances that correlates with plaque size, plasma A-FABP and cholesterol: a pilot study of high fat diet and its intervention with lactobacillus rhamnosus GG (LGG) or telmisartan in ApoE(-/-) mice, BMC Microbiol. 16 (1) (2016) 264.
[34] M.M. Véniant, S. Withycombe, S.G. Young, Lipoprotein size and atherosclerosis susceptibility in Apoe(-/-) and Ldlr(-/-) mice, Arterioscler. Thromb. Vasc. Biol. 21 (10) (2001) 1567–1570.
[35] S.H. Gage, P.A. Fish, Fat digestion, absorption, and assimilation in man and animals as determined by the dark-field microscope, and a fat-soluble dye, Am. J. Anat. 34 (1) (1924) 1–85.
[36] J. Hanstein, Ueber die gestaltungsvorgange in den zellkerne bei der theilung der zellen, Botan Abhandl. Morphol. Physiol. Bonn 4 (2) (1880).
[37] M.S. Brown, J.L. Goldstein, Receptor-mediated endocytosis: insights from the lipoprotein receptor system, Proc. Natl. Acad. Sci. U. S. A. 76 (7) (1979) 3330–3337.
[38] A.G.C.G. Galen, On the Natural Faculties, Library of Alexandria, 2020.
[39] G. Asellius, Dissertatio, Etc, in: A. Tadinus, S. Septalius (Eds.), De Lactibus Siue Lacteis Uenis Quarto Uasorum Mesaraicorum Genere Nouo Inuento Gasparis Asellii, 1645.
[40] J. Pecquet, De Thoracicis Lacteis, 1653.
[41] H.I. Friedman, B. Nylund, Intestinal fat digestion, absorption, and transport. A review, Am. J. Clin. Nutr. 33 (5) (1980) 1108–1139.
[42] C. Bernard, Leçons Sur Les Phénomènes de la Vie Communs Aux Animaux Et Aux Végétaux, Baillière, 1878.
[43] M. Macheboeuf, Recherches Sur les phosphoaminolipideset les sterids du serum et du plasma sanguins. II. Etudephysiochimique de la fraction proteidique la plus riche enphospholipids et in sterides, Bull. Soc. Chim. Biol. 11 (1929) 485–503.
[44] B. Clark, G. HÜBscher, Biosynthesis of glycerides in the mucosa of the small intestine, Nature 185 (4705) (1960) 35–37.
[45] J.D. Morrisett, R.L. Jackson, A.M. Gotto Jr., Lipid-protein interactions in the plasma lipoproteins, Biochim. Biophys. Acta 472 (2) (1977) 93–133.
[46] Y. Zhao, et al., Small rodent models of atherosclerosis, Biomed. Pharmacother. 129 (2020), 110426.
[47] E. Kim, S.G. Young, Genetically modified mice for the study of apolipoprotein B, J. Lipid Res. 39 (4) (1998) 703–723.
[48] L. Pasteur, Sur les maladies virulentes: et en particulier sur la maladie appelée vulgairement choléra des poules, Gauthier-Villars, 1880.
[49] J.L. Anderson, J.D. Carten, S.A. Farber, Zebrafish lipid metabolism: from mediating early patterning to the metabolism of dietary fat and cholesterol, Methods Cell Biol. 101 (2011) 111–141.
[50] J.D. Carten, S.A. Farber, A new model system swims into focus: using the zebrafish to visualize intestinal metabolism in vivo, Clin. Lipidol. 4 (4) (2009) 501–515.
[51] J.D. Carten, M.K. Bradford, S.A. Farber, Visualizing digestive organ morphology and function using differential fatty acid metabolism in live zebrafish, Dev. Biol. 360 (2) (2011) 276–285.
[52] K. Hoshijima, S. Hirose, Expression of endocrine genes in zebrafish larvae in response to environmental salinity, J. Endocrinol. 193 (3) (2007) 481–491.
[53] T.H. Morgan, Sex limited inheritance in drosophila, Science 32 (812) (1910) 120–122.

[54] H.J. Bellen, C. Tong, H. Tsuda, 100 years of drosophila research and its impact on vertebrate neuroscience: a history lesson for the future, Nat. Rev. Neurosci. 11 (7) (2010) 514–522.
[55] S.B. Hedges, J. Dudley, S. Kumar, TimeTree: a public knowledge-base of divergence times among organisms, Bioinformatics 22 (23) (2006) 2971–2972.
[56] N. Chatterjee, N. Perrimon, What fuels the fly: energy metabolism in drosophila and its application to the study of obesity and diabetes, Sci. Adv. 7 (24) (2021).
[57] S. Brenner, The genetics of behaviour, Br. Med. Bull. 29 (3) (1973) 269–271.
[58] S.G. Biglou, W.G. Bendena, I. Chin-Sang, An overview of the insulin signaling pathway in model organisms Drosophila melanogaster and Caenorhabditis elegans, Peptides 145 (2021), 170640.
[59] J. Zhang, et al., Regulation of lipoprotein assembly, secretion and fatty acid β-oxidation by Krüppel-like transcription factor, klf-3, J. Mol. Biol. 425 (15) (2013) 2641–2655.
[60] Y. Shibata, et al., Redox regulation of germline and vulval development in Caenorhabditis elegans, Science 302 (5651) (2003) 1779–1782.
[61] R. Branicky, et al., Lipid transport and signaling in Caenorhabditis elegans, Dev. Dyn. 239 (5) (2010) 1365–1377.
[62] B. Corvilain, Lipoprotein metabolism, Rev. Med. Brux. 18 (1) (1997) 3–9.
[63] B. Borgstrom, The action of bile salts and other detergents on pancreatic lipase and the interaction with colipase, Biochim. Biophys. Acta 488 (3) (1977) 381–391.
[64] M.M. Hussain, Intestinal lipid absorption and lipoprotein formation, Curr. Opin. Lipidol. 25 (3) (2014) 200–206.
[65] A.B. Thomson, et al., Lipid absorption: passing through the unstirred layers, brush-border membrane, and beyond, Can. J. Physiol. Pharmacol. 71 (8) (1993) 531–555.
[66] T.Y. Wang, et al., New insights into the molecular mechanism of intestinal fatty acid absorption, Eur. J. Clin. Investig. 43 (11) (2013) 1203–1223.
[67] E.P. Newberry, N.O. Davidson, Intestinal lipid absorption, GLP-2, and CD36: still more mysteries to moving fat, Gastroenterology 137 (3) (2009) 775–778.
[68] A.I. Lackey, et al., Mechanisms underlying reduced weight gain in intestinal fatty acid-binding protein (IFABP) null mice, Am. J. Physiol. Gastrointest. Liver Physiol. 318 (3) (2020) G518–g530.
[69] M. Furuhashi, G.S. Hotamisligil, Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets, Nat. Rev. Drug Discov. 7 (6) (2008) 489–503.
[70] M.V. Lobo, et al., Localization of the lipid receptors CD36 and CLA-1/SR-BI in the human gastrointestinal tract: towards the identification of receptors mediating the intestinal absorption of dietary lipids, J. Histochem. Cytochem. 49 (10) (2001) 1253–1260.
[71] N.-H. Son, et al., Endothelial cell CD36 optimizes tissue fatty acid uptake, J. Clin. Invest. 128 (10) (2018) 4329–4342.
[72] F.P. Martin, et al., Metabolic phenotyping of an adoptive transfer mouse model of experimental colitis and impact of dietary fish oil intake, J. Proteome Res. 14 (4) (2015) 1911–1919.
[73] J.-W. Hao, et al., CD36 facilitates fatty acid uptake by dynamic palmitoylation-regulated endocytosis, Nat. Commun. 11 (1) (2020) 4765.
[74] Y. Chen, et al., CD36, a signaling receptor and fatty acid transporter that regulates immune cell metabolism and fate, J. Exp. Med. 219 (6) (2022).
[75] M. Buttet, et al., Deregulated lipid sensing by intestinal CD36 in diet-induced hyperinsulinemic obese mouse model, PloS one 11 (1) (2016) e0145626-e0145626.
[76] M.Y. Pepino, et al., Structure-function of CD36 and importance of fatty acid signal transduction in fat metabolism, Annu. Rev. Nutr. 34 (2014) 281–303.
[77] T.T.T. Tran, et al., Luminal lipid regulates CD36 levels and downstream signaling to stimulate chylomicron synthesis, J. Biol. Chem. 286 (28) (2011) 25201–25210.
[78] M.H. Sieber, C.S. Thummel, Coordination of triacylglycerol and cholesterol homeostasis by DHR96 and the drosophila LipA homolog magro, Cell Metab. 15 (1) (2012) 122–127.
[79] D.G. King, Cellular organization and peritrophic membrane formation in the cardia (proventriculus) of Drosophila melanogaster, J. Morphol. 196 (3) (1988) 253–282.
[80] R. Dodge, A Gut Commensal Niche Regulates Stable Association of a Multispecies Microbiota, bioRxiv, 2021, p. 2021.09.30.462663.
[81] M.H. Sieber, C.S. Thummel, The DHR96 nuclear receptor controls triacylglycerol homeostasis in drosophila, Cell Metab. 10 (6) (2009) 481–490.
[82] L. Herboso, et al., Expression of the scavenger receptor class B type I (SR-BI) family in Drosophila melanogaster, Int. J. Dev. Biol. 55 (6) (2011) 603–611.
[83] R.A. Coleman, et al., Do long-chain acyl-CoA synthetases regulate fatty acid entry into synthetic versus degradative pathways? J. Nutr. 132 (8) (2002) 2123–2126.
[84] J. Iqbal, M.M. Hussain, Intestinal lipid absorption, Am. J. Physiol. Endocrinol. Metab. 296 (6) (2009) E1183–E1194.
[85] K. Takeuchi, K. Reue, Biochemistry, physiology, and genetics of GPAT, AGPAT, and lipin enzymes in triglyceride synthesis, Am. J. Physiol. Endocrinol. Metab. 296 (6) (2009) E1195–E1209.
[86] C.-L.E. Yen, et al., Thematic review series: glycerolipids. DGAT enzymes and triacylglycerol biosynthesis, J. Lipid Res. 49 (11) (2008) 2283–2301.
[87] M.R. Gonzalez-Baró, T.M. Lewin, R.A. Coleman, Regulation of Triglyceride Metabolism. II. Function of mitochondrial GPAT1 in the regulation of triacylglycerol biosynthesis and insulin action, Am. J. Physiol. Gastrointest. Liver Physiol. 292 (5) (2007) G1195–G1199.
[88] J.M. Johnston, et al., The utilization of the alpha-glycerophosphate and monoglyceride pathways for phosphatidyl choline biosynthesis in the intestine, Biochim. Biophys. Acta 218 (1) (1970) 124–133.
[89] F. Ameer, et al., De novo lipogenesis in health and disease, Metabolism 63 (7) (2014) 895–902.
[90] J.C.P. Silva, et al., Determining contributions of exogenous glucose and fructose to de novo fatty acid and glycerol synthesis in liver and adipose tissue, Metab. Eng. 56 (2019) 69–76.
[91] S. Hoffman, D. Alvares, K. Adeli, Intestinal lipogenesis: how carbs turn on triglyceride production in the gut, Curr. Opin. Clin. Nutr. Metab. Care 22 (4) (2019) 284–288.
[92] S. Steenson, et al., The effect of fructose feeding on intestinal triacylglycerol production and De novo fatty acid synthesis in humans, Nutrients 12 (6) (2020).
[93] M. Haidari, et al., Fasting and postprandial overproduction of intestinally derived lipoproteins in an animal model of insulin resistance. Evidence that chronic fructose feeding in the hamster is accompanied by enhanced intestinal de novo lipogenesis and ApoB48-containing lipoprotein overproduction, J. Biol. Chem. 277 (35) (2002) 31646–31655.
[94] F.W. Sanders, J.L. Griffin, De novo lipogenesis in the liver in health and disease: more than just a shunting yard for glucose, Biol. Rev. Camb. Philos. Soc. 91 (2) (2016) 452–468.
[95] J. Hsieh, et al., Postprandial dyslipidemia in insulin resistance: mechanisms and role of intestinal insulin sensitivity, Atheroscler. Suppl. 9 (2) (2008) 7–13.
[96] J.P. Parvy, et al., Drosophila melanogaster acetyl-CoA-carboxylase sustains a fatty acid-dependent remote signal to waterproof the respiratory system, PLoS Genet. 8 (8) (2012), e1002925.
[97] D. Garrido, et al., Fatty acid synthase cooperates with glyoxalase 1 to protect against sugar toxicity, PLoS Genet. 11 (2) (2015), e1004995.
[98] C. Heier, R.P. Kühnlein, Triacylglycerol metabolism in Drosophila melanogaster, Genetics 210 (4) (2018) 1163–1184.
[99] C.L. Perez, M.R. Van Gilst, A 13C isotope labeling strategy reveals the influence of insulin signaling on lipogenesis in C. Elegans, Cell Metab. 8 (3) (2008) 266–274.
[100] J.L. Watts, Fat synthesis and adiposity regulation in Caenorhabditis elegans, Trends Endocrinol. Metab. 20 (2) (2009) 58–65.
[101] M.D. Shapiro, S. Fazio, Apolipoprotein B-containing lipoproteins and atherosclerotic cardiovascular disease, F1000Res. 6 (2017) 134.
[102] J. Behbodikhah, et al., Apolipoprotein B and cardiovascular disease: biomarker and potential therapeutic target, Metabolites 11 (10) (2021).
[103] M.M. Hussain, N. Nijstad, L. Franceschini, Regulation of microsomal triglyceride transfer protein, Clin. Lipidol. 6 (3) (2011) 293–303.
[104] J.R. Wetterau, D.B. Zilversmit, A triglyceride and cholesteryl ester transfer protein associated with liver microsomes, J. Biol. Chem. 259 (17) (1984) 10863–10866.
[105 R.A. Cox, M.R. García-Palmieri, Cholesterol, triglycerides, and associated lipoproteins, in: H.K. Walker, W.D. Hall, J.W. Hurst (Eds.), Clinical Methods: The History, Physical, and Laboratory Examinations, Butterworths Copyright © 1990, Butterworth Publishers, a division of Reed Publishing, Boston, 1990.
[106] Y. Li, N. Wongsiriroj, W.S. Blaner, The multifaceted nature of retinoid transport and metabolism, Hepatobiliary Surg. Nutr. 3 (3) (2014) 126–139.
[107] D. Hermier, Lipoprotein metabolism and fattening in poultry, J. Nutr. 127 (5) (1997) 805S–808S.
[108] F.B. Hillgartner, L.M. Salati, A.G. Goodridge, Physiological and molecular mechanisms involved in nutritional regulation of fatty acid synthesis, Physiol. Rev. 75 (1) (1995) 47–76.
[109] N.O. Davidson, Apolipoprotein B mRNA editing: a key controlling element targeting fats to proper tissue, Ann. Med. 25 (6) (1993) 539–543.
[110] M.C. Van Heusden, J.H. Law, An insect lipid transfer particle promotes lipid loading from fat body to lipoprotein, J. Biol. Chem. 264 (29) (1989) 17287–17292.
[111] M. Rodríguez-Vázquez, et al., Drosophila lipophorin receptors recruit the lipoprotein LTP to the plasma membrane to mediate lipid uptake, PLoS Genet. 11 (6) (2015), e1005356.
[112] E. Gutierrez, et al., Specialized hepatocyte-like cells regulate drosophila lipid metabolism, Nature 445 (7125) (2007) 275–280.
[113] P. Rava, et al., Phospholipid transfer activity of microsomal triacylglycerol transfer protein is sufficient for the assembly and secretion of apolipoprotein B lipoproteins *, J. Biol. Chem. 281 (16) (2006) 11019–11027.
[114] N. Matsuo, et al., Different mechanisms for selective transport of fatty acids using a single class of lipoprotein in drosophila, J. Lipid Res. 60 (7) (2019) 1199–1211.
[115] C. Jang, et al., Metabolite exchange between mammalian organs quantified in pigs, Cell Metab. 30 (3) (2019) 594–606, e3.
[116] D.J. Van der Horst, K.W. Rodenburg, Lipoprotein assembly and function in an evolutionary perspective, Biomol. Concepts 1 (2) (2010) 165–183.
[117] 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 (2) (2011), e1001297.
[118] R. Ugrankar, et al., Drosophila snazarus regulates a lipid droplet population at plasma membrane-droplet contacts in adipocytes, Dev. Cell 50 (5) (2019) 557–572, e5.
[119] F. Wang, et al., Apolipoprotein A-IV: a protein intimately involved in metabolism, J. Lipid Res. 56 (8) (2015) 1403–1418.
[120] J. Qu, et al., Apolipoprotein A-IV: a multifunctional protein involved in protection against atherosclerosis and diabetes, Cells 8 (4) (2019).
[121] C. Xiao, P. Stahel, G.F. Lewis, Regulation of chylomicron secretion: focus on post-assembly mechanisms, Cell. Mol. Gastroenterol. Hepatol. 7 (3) (2019) 487–501.
[122] K. Fujimoto, J.A. Cardelli, P. Tso, Increased apolipoprotein A-IV in rat mesenteric lymph after lipid meal acts as a physiological signal for satiation, Am. J. Phys. 262 (6 Pt 1) (1992) G1002–G1006.

[123] S. Lu, et al., Overexpression of apolipoprotein A-IV enhances lipid secretion in IPEC-1 cells by increasing chylomicron size, J. Biol. Chem. 281 (6) (2006) 3473–3483.
[124] I. Rudkowska, M.-C. Vohl, Interaction between diets, polymorphisms and plasma lipid levels, Clin. Lipidol. 5 (3) (2010) 421–438.
[125] T.F. Apfelbaum, N.O. Davidson, R.M. Glickman, Apolipoprotein A-IV synthesis in rat intestine: regulation by dietary triglyceride, Am. J. Phys. 252 (5 Pt 1) (1987) G662–G666.
[126] M.A. VerHague, et al., Apolipoprotein A-IV expression in mouse liver enhances triglyceride secretion and reduces hepatic lipid content by promoting very low density lipoprotein particle expansion, Arterioscler. Thromb. Vasc. Biol. 33 (11) (2013) 2501–2508.
[127] A.B. Kohan, et al., ApoA-IV: current and emerging roles in intestinal lipid metabolism, glucose homeostasis, and satiety, Am. J. Physiol. Gastrointest. Liver Physiol. 308 (6) (2015) G472–G481.
[128] J. Jattan, et al., Using primary murine intestinal enteroids to study dietary TAG absorption, lipoprotein synthesis, and the role of apoC-III in the intestine, J. Lipid Res. 58 (5) (2017) 853–865.
[129] Y. Yao, Regulation of microsomal triglyceride transfer protein by apolipoprotein A-IV in newborn swine intestinal epithelial cells, Am. J. Physiol. Gastrointest. Liver Physiol. 300 (2) (2011) G357–G363.
[130] X. Pan, et al., Circadian regulation of intestinal lipid absorption by apolipoprotein AIV involves forkhead transcription factors A2 and O1 and microsomal triglyceride transfer protein *, J. Biol. Chem. 288 (28) (2013) 20464–20476.
[131] J. Trujillo-Viera, et al., Protein kinase D2 drives chylomicron-mediated lipid transport in the intestine and promotes obesity, EMBO Mol. Med. 13 (5) (2021) e13548-e13548.
[132] Nga Thi T. Nguyen, Genomicus 2018: karyotype evolutionary trees and on-the-fly synteny computing, Nucleic Acids Res. 46 (D1) (2017) D816–D822.
[133] K. Schwalme, A quantitative comparison between diet and body fatty acid composition in wild northern pike (Esox lucius L.), Fish Physiol. Biochem. 10 (2) (1992) 91–98.
[134] P.M. Weers, R.O. Ryan, Apolipophorin III: a lipid-triggered molecular switch, Insect Biochem. Mol. Biol. 33 (12) (2003) 1249–1260.
[135] D.R. Breiter, et al., Molecular structure of an apolipoprotein determined at 2.5-. ANG. Resolution, Biochemistry 30 (3) (1991) 603–608.
[136] J. Dallongeville, J.C. Fruchart, Postprandial dyslipidemia: a risk factor for coronary heart disease, Ann. Nutr. Metab. 42 (1) (1998) 1–11.
[137] J.E. Lambert, E.J. Parks, Postprandial metabolism of meal triglyceride in humans, Biochim. Biophys. Acta 1821 (5) (2012) 721–726.
[138] M. Jacome-Sosa, Human intestinal lipid storage through sequential meals reveals faster dinner appearance is associated with hyperlipidemia, JCI Insight 6 (15) (2021).
[139] A.R. Sharrett, et al., Metabolic and lifestyle determinants of postprandial lipemia differ from those of fasting triglycerides, Arterioscler. Thromb. Vasc. Biol. 21 (2) (2001) 275–281.
[140] K. Nakajima, et al., Postprandial lipoprotein metabolism: VLDL vs chylomicrons, Clin. Chim. Acta 412 (15–16) (2011) 1306–1318.
[141] P. Schönfeld, L. Wojtczak, Short- and medium-chain fatty acids in energy metabolism: the cellular perspective, J. Lipid Res. 57 (6) (2016) 943–954.
[142] J.H. Cummings, et al., Short chain fatty acids in human large intestine, portal, hepatic and venous blood, Gut 28 (10) (1987) 1221–1227.
[143] E.N. Bergman, Energy contributions of volatile fatty acids from the gastrointestinal tract in various species, Physiol. Rev. 70 (2) (1990) 567–590.
[144] R. Ishizawa, et al., Effects of different fatty acid chain lengths on fatty acid oxidation-related protein expression levels in rat skeletal muscles, J. Oleo Sci. 64 (4) (2015) 415–421.
[145] J.G. McMullen II, et al., How gut microbiome interactions affect nutritional traits of Drosophila melanogaster, J. Exp. Biol. 223 (19) (2020).
[146] A.C. Bach, V.K. Babayan, Medium-chain triglycerides: an update, Am. J. Clin. Nutr. 36 (5) (1982) 950–962.
[147] C.C. Metges, G. Wolfram, Medium- and long-chain triglycerides labeled with 13C: a comparison of oxidation after oral or parenteral administration in humans, J. Nutr. 121 (1) (1991) 31–36.
[148] S.J.G. Knottnerus, et al., Exploring the metabolic fate of medium-chain triglycerides in healthy individuals using a stable isotope tracer, Clin. Nutr. 40 (3) (2021) 1396–1404.
[149] T. Hajri, et al., Defective fatty acid uptake in the spontaneously hypertensive rat is a primary determinant of altered glucose metabolism, hyperinsulinemia, and myocardial hypertrophy, J. Biol. Chem. 276 (26) (2001) 23661–23666.
[150] V.H. Quinlivan, et al., An HPLC-CAD/fluorescence lipidomics platform using fluorescent fatty acids as metabolic tracers, J. Lipid Res. 58 (5) (2017) 1008–1020.
[151] F.M. Sacks, et al., Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association, Circulation 136 (3) (2017) e1–e23.
[152] D.M. Dreon, et al., Change in dietary saturated fat intake is correlated with change in mass of large low-density-lipoprotein particles in men, Am. J. Clin. Nutr. 67 (5) (1998) 828–836.
[153] T. Tholstrup, et al., Effect of 6 dietary fatty acids on the postprandial lipid profile, plasma fatty acids, lipoprotein lipase, and cholesterol ester transfer activities in healthy young men, Am. J. Clin. Nutr. 73 (2) (2001) 198–208.
[154] S.W. Sakr, et al., Fatty acid composition of an oral load affects chylomicron size in human subjects, Br. J. Nutr. 77 (1) (1997) 19–31.
[155] J.J. DiNicolantonio, J.H. O'Keefe, Effects of dietary fats on blood lipids: a review of direct comparison trials, Open Heart 5 (2) (2018), e000871.
[156] M.S. Weintraub, et al., Dietary polyunsaturated fats of the W-6 and W-3 series reduce postprandial lipoprotein levels. Chronic and acute effects of fat saturation on postprandial lipoprotein metabolism, J. Clin. Invest. 82 (6) (1988) 1884–1893.
[157] A.B. Kohan, et al., Chylomicron remnants and nonesterified fatty acids differ in their ability to inhibit genes involved in lipogenesis in rats, J. Nutr. 141 (2) (2011) 171–176.
[158] J.H. Bragdon, A. Karmen, The fatty acid composition of chylomicrons of chyle and serum following the ingestion of different oils, J. Lipid Res. 1 (2) (1960) 167–170.
[159] M.S. Lambert, et al., The fatty acid composition of chylomicron remnants influences their binding and internalization by isolated hepatocytes, Eur. J. Biochem. 268 (14) (2001) 3983–3992.
[160] I. Lopez-Soldado, M. Avella, K.M. Botham, Comparison of the effects of dietary saturated, mono-unsaturated and polyunsaturated fatty acids on very-low-density lipoprotein secretion when delivered to hepatocytes in chylomicron remnant-like particles, Biochem. Soc. Trans. 35 (Pt 3) (2007) 440–441.
[161] G. Yuan, K.Z. Al-Shali, R.A. Hegele, Hypertriglyceridemia: its etiology, effects and treatment, CMAJ 176 (8) (2007) 1113–1120.
[162] J.D. Brunzell, E.L. Bierman, Chylomicronemia syndrome. Interaction of genetic and acquired hypertriglyceridemia, Med. Clin. N. Am. 66 (2) (1982) 455–468.
[163] A.J. Brahm, R.A. Hegele, Chylomicronaemia–current diagnosis and future therapies, Nat. Rev. Endocrinol. 11 (6) (2015) 352–362.
[164] G. Paragh, et al., Causes, clinical findings and therapeutic options in chylomicronemia syndrome, a special form of hypertriglyceridemia, Lipids Health Dis. 21 (1) (2022), 21-21.
[165] A. Hruby, F.B. Hu, The epidemiology of obesity: a big picture, PharmacoEconomics 33 (7) (2015) 673–689.
[166] T. D'Aquila, A.S. Zembroski, K.K. Buhman, Diet induced obesity alters intestinal cytoplasmic lipid droplet morphology and proteome in the postprandial response to dietary fat, Front. Physiol. 10 (2019) 180.
[167] M.J. Olarte, et al., The CYTOLD and ERTOLD pathways for lipid droplet-protein targeting, Trends Biochem. Sci. 47 (1) (2022) 39–51.
[168] L. Ye, et al., High fat diet induces microbiota-dependent silencing of enteroendocrine cells, elife (2019) 8.
[169] P. Richards, et al., High fat diet impairs the function of glucagon-like peptide-1 producing L-cells, Peptides 77 (2016) 21–27.
[170] S. Takashima, D. Gold, V. Hartenstein, Stem cells and lineages of the intestine: a developmental and evolutionary perspective, Dev. Genes Evol. 223 (1–2) (2013) 85–102.
[171] O. Puig, et al., Control of cell number by drosophila FOXO: downstream and feedback regulation of the insulin receptor pathway, Genes Dev. 17 (16) (2003) 2006–2020.
[172] N. Alic, et al., Genome-wide dFOXO targets and topology of the transcriptomic response to stress and insulin signalling, Mol. Syst. Biol. 7 (2011) 502.
[173] G. Tuteja, K.H. Kaestner, Forkhead transcription factors II, Cell 131 (1) (2007) 192.
[174] I. Miguel-Aliaga, H. Jasper, B. Lemaitre, Anatomy and physiology of the digestive tract of Drosophila melanogaster, Genetics 210 (2) (2018) 357–396.
[175] M. Ahmad, L. He, N. Perrimon, Regulation of insulin and adipokinetic hormone/glucagon production in flies, Wiley Interdiscip. Rev. Dev. Biol. 9 (2) (2020), e360.
[176] L.L. Baggio, D.J. Drucker, Biology of incretins: GLP-1 and GIP, Gastroenterology 132 (6) (2007) 2131–2157.
[177] B. Yusta, et al., GLP-1R agonists modulate enteric immune responses through the intestinal intraepithelial lymphocyte GLP-1R, Diabetes 64 (7) (2015) 2537–2549.
[178] D.B. Andersen, et al., Using a reporter mouse to map known and novel sites of GLP-1 receptor expression in peripheral tissues of male mice, Endocrinology 162 (3) (2020).
[179] P. Richards, et al., Identification and characterization of GLP-1 receptor-expressing cells using a new transgenic mouse model, Diabetes 63 (4) (2014) 1224–1233.
[180] K.V. Grunddal, et al., Expression profile of the GLP-1 receptor in the gastrointestinal tract and pancreas in adult female mice, Endocrinology 163 (1) (2021).
[181] J.J. Meier, et al., The glucagon-like peptide-1 metabolite GLP-1-(9–36) amide reduces postprandial glycemia independently of gastric emptying and insulin secretion in humans, Am. J. Physiol. Endocrinol. Metab. 290 (6) (2006) E1118–E1123.
[182] P. Nadkarni, O.G. Chepurny, G.G. Holz, Regulation of glucose homeostasis by GLP-1, Prog. Mol. Biol. Transl. Sci. 121 (2014) 23–65.
[183] Y. Yoshinari, et al., The sugar-responsive enteroendocrine neuropeptide F regulates lipid metabolism through glucagon-like and insulin-like hormones in Drosophila melanogaster, Nat. Commun. 12 (1) (2021) 4818.
[184] T. Ameku, et al., Midgut-derived neuropeptide F controls germline stem cell proliferation in a mating-dependent manner, PLoS Biol. 16 (9) (2018) e2005004-e2005004.
[185] G.J. Hein, et al., GLP-1 and GLP-2 as yin and yang of intestinal lipoprotein production: evidence for predominance of GLP-2-stimulated postprandial lipemia in normal and insulin-resistant states, Diabetes 62 (2) (2013) 373–381.
[186] H. Hui, et al., The short half-life of glucagon-like peptide-1 in plasma does not reflect its long-lasting beneficial effects, Eur. J. Endocrinol. 146 (6) (2002) 863–869.
[187] C. Xiao, et al., Sitagliptin, a DPP-4 inhibitor, acutely inhibits intestinal lipoprotein particle secretion in healthy humans, Diabetes 63 (7) (2014) 2394–2401.
[188] J. Hsieh, et al., Glucagon-like peptide-2 increases intestinal lipid absorption and chylomicron production via CD36, Gastroenterology 137 (3) (2009) 997–1005, 1005 e1–4.

[189] S. Dash, et al., Glucagon-like peptide-2 regulates release of chylomicrons from the intestine, Gastroenterology 147 (6) (2014) 1275–1284, e4.
[190] J.F. Rehfeld, A centenary of gastrointestinal endocrinology, Horm. Metab. Res. 36 (11–12) (2004) 735–741.
[191] J.B. Furness, et al., The gut as a sensory organ, Nat. Rev. Gastroenterol. Hepatol. 10 (12) (2013) 729–740.
[192] M.C. Murphy, et al., Postprandial lipid and hormone responses to meals of varying fat contents: modulatory role of lipoprotein lipase? Eur. J. Clin. Nutr. 49 (8) (1995) 578–588.
[193] J.F. Rehfeld, The measurement of cholecystokinin, J. Clin. Pathol. Suppl. (Assoc. Clin. Pathol.) 8 (1978) 26–30.
[194] J. Gibbs, R.C. Young, G.P. Smith, Cholecystokinin elicits satiety in rats with open gastric fistulas, Nature 245 (5424) (1973) 323–325.
[195] J.T. McLaughlin, et al., Fatty acids stimulate cholecystokinin secretion via an acyl chain length-specific, Ca2+-dependent mechanism in the enteroendocrine cell line STC-1, J. Physiol. 513 (Pt 1) (Pt 1) (1998) 11–18.
[196] J. Glatzle, et al., Chylomicron components activate duodenal vagal afferents via a cholecystokinin a receptor-mediated pathway to inhibit gastric motor function in the rat, J. Physiol. 550 (Pt 2) (2003) 657–664.
[197] J.A.E. Söderberg, M.A. Carlsson, D.R. Nässel, Insulin-producing cells in the drosophila brain also express satiety-inducing cholecystokinin-like peptide, Drosulfakinin, Front. Endocrinol. 3 (2012), p. 109-109.
[198] D.R. Nässel, M.J. Williams, Cholecystokinin-like peptide (DSK) in drosophila, not only for satiety signaling, Front. Endocrinol. (Lausanne) 5 (2014) 219.
[199] T.E. Adrian, et al., Effect of peptide YY on gastric, pancreatic, and biliary function in humans, Gastroenterology 89 (3) (1985) 494–499.
[200] T.E. Adrian, et al., Human distribution and release of a putative new gut hormone, peptide YY, Gastroenterology 89 (5) (1985) 1070–1077.
[201] C. Beglinger, L. Degen, Gastrointestinal satiety signals in humans–physiologic roles for GLP-1 and PYY? Physiol. Behav. 89 (4) (2006) 460–464.
[202] T.J. Kalogeris, M.-D. Rodriguez, P. Tso, Control of synthesis and secretion of intestinal apolipoprotein A-IV by lipid, J. Nutr. 127 (3) (1997) 537S–543S.
[203] L.M. Beckman, et al., Changes in gastrointestinal hormones and leptin after roux-en-Y gastric bypass surgery, JPEN J. Parenter. Enteral Nutr. 35 (2) (2011) 169–180.
[204] A.K. Walker, et al., A conserved SREBP-1/phosphatidylcholine feedback circuit regulates lipogenesis in metazoans, Cell 147 (4) (2011) 840–852.
[205] M.S. Brown, J.L. Goldstein, The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor, Cell 89 (3) (1997) 331–340.
[206] X. Hua, et al., Structure of the human gene encoding sterol regulatory element binding protein-1 (SREBF1) and localization of SREBF1 and SREBF2 to chromosomes 17p11. 2 and 22q13, Genomics 25 (3) (1995) 667–673.
[207] I. Shimomura, et al., Differential expression of exons 1a and 1c in mRNAs for sterol regulatory element binding protein-1 in human and mouse organs and cultured cells, J. Clin. Invest. 99 (5) (1997) 838–845.
[208] F.J. Field, et al., Gene expression of sterol regulatory element-binding proteins in hamster small intestine, J. Lipid Res. 42 (1) (2001) 1–8.
[209] M. Takanashi, et al., Critical role of SREBP-1c large-VLDL pathway in environment-induced hypertriglyceridemia of apo AV deficiency, Arterioscler. Thromb. Vasc. Biol. 39 (3) (2019) 373–386.
[210] F.J. Field, et al., Regulation of sterol regulatory element-binding proteins by cholesterol flux in CaCo-2 cells, J. Lipid Res. 42 (10) (2001) 1687–1698.
[211] A.S. Kunte, K.A. Matthews, R.B. Rawson, Fatty acid auxotrophy in drosophila larvae lacking SREBP, Cell Metab. 3 (6) (2006) 439–448.
[212] I.Y. Dobrosotskaya, et al., Regulation of SREBP processing and membrane lipid production by phospholipids in drosophila, Science 296 (5569) (2002) 879–883.
[213] R. Bertolio, et al., Sterol regulatory element binding protein 1 couples mechanical cues and lipid metabolism, Nat. Commun. 10 (1) (2019) 1326.
[214] B. Charroux, J. Royet, Gut-derived peptidoglycan remotely inhibits bacteria dependent activation of SREBP by drosophila adipocytes, PLoS Genet. 18 (3) (2022), e1010098.
[215] R.L. Walker, M. Eggel, From mice to Monkeys? Beyond orthodox approaches to the ethics of animal model choice, Animals (Basel) 10 (1) (2020).
[216] H.N. Ginsberg, Y.L. Zhang, A. Hernandez-Ono, Regulation of plasma triglycerides in insulin resistance and diabetes, Arch. Med. Res. 36 (3) (2005) 232–240.
[217] T. Hirano, Pathophysiology of diabetic dyslipidemia, J. Atheroscler. Thromb. 25 (9) (2018) 771–782.