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Modeling dietary influences on offspring metabolic programming in *Drosophila melanogaster*

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Abstract

The influence of nutrition on offspring metabolism has become a hot topic in recent years owing to the growing prevalence of maternal and childhood obesity. Studies in mammals have identified several factors correlating with parental and early offspring dietary influences on progeny health; however, molecular mechanisms that underlie these factors remain undiscovered. Mammalian metabolic tissues and pathways are heavily conserved in *Drosophila melanogaster*, making the fly an invaluable genetic model organism for studying metabolism. In this review, we discuss the metabolic similarities between mammals and *Drosophila* and present evidence supporting its use as an emerging model of metabolic programming.

Introduction

The environmental impact during *in utero* and childhood development on adult health has recently emerged as a hot topic due to the increased prevalence of obesity in childhood and adolescence and the fact that 25–30% of pregnant women in the United States are obese, both of which place offspring at an increased risk for developing major health complications (O'Brien *et al.*, 2003; Freedman *et al.*, 2005, 2009; Dokras *et al.*, 2006; Metwally *et al.*, 2008; Catalano *et al.*, 2009; Nohr *et al.*, 2009; Stothard *et al.*, 2009; Vahratian, 2009; Clausen *et al.*, 2009; Biro and Wien, 2010; Lowe *et al.*, 2011; Forno *et al.*, 2014; Diesel *et al.*, 2015). David Barker introduced the concept that maternal malnourishment as well as altered infant nutrition can permanently influence offspring metabolism and pre-dispose progeny to cardiovascular and metabolic diseases (Barker, 1990; Hales and Barker, 1992). Additional studies have also demonstrated strong correlations between the malnourished parent and compromised offspring health (Painter *et al.*; Stanner *et al.*, 1997; Ravelli *et al.*, 1998; Kaati *et al.*, 2002; Pembrey *et al.*, 2006). Substantial evidence from both human and animal models has implicated several factors including altered epigenetic gene regulation, ER stress, and mitochondrial disruption as vehicles through which parental diet impacts offspring development and health (Gemma *et al.*, 2006, 2009; Bruce *et al.*, 2009; Ng *et al.*, 2010; Vucetic *et al.*, 2010; Wu *et al.*, 2010, 2015; Carone *et al.*, 2010; Igosheva *et al.*, 2010;

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Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Borengasser *et al.*, 2011; Luzzo *et al.*, 2012; Soubry *et al.*, 2013; Herbstman *et al.*, 2013; Malti *et al.*, 2014; Melo *et al.*, 2014; Radford *et al.*, 2014; Sharp *et al.*, 2015; Casas-Agustench *et al.*, 2015; Gallardo *et al.*, 2015). However, to date, the molecular mechanisms by which altered nutrition influences these factors to impact offspring health are not entirely clear.

Recently, *Drosophila melanogaster* has emerged as a promising tool to uncover the molecular mechanisms of metabolic programming. In the fly, the impact of parental diet on offspring health can be determined by altering the maternal or paternal diet, or both. Because fly embryogenesis occurs outside of the maternal female, scientists can also investigate the influence of the pre-gestational maternal diet on offspring nutritional programming without the highly invasive procedures of *in vitro* fertilization and intracytoplasmic sperm injection required of mammalian studies (Ceelen *et al.*, 2007, 2008; Giritharan *et al.*, 2007; Scott *et al.*, 2010; Wu *et al.*, 2015). Moreover, understanding the impact of nutrition during early development on adult health within a single generation can be modeled in the holometabolous fly by manipulating the larval diet and assessing changes in adulthood. Use of the fly in nutritional programming is attractive for several additional reasons including the ease by which laboratories can economically design and produce customized diets, the high conservation of metabolic pathways in *Drosophila,* and the already extensive use of the fly in metabolic and developmental research. Also, because one of the main questions regarding metabolic programming is the impact it has on subsequent generations, the rapid fly life cycle, 10 days from embryo to adult, provides a further benefit for using *Drosophila* to understand the molecular mechanisms of the transgenerational impact of the parental diet. This review will focus on the benefits of using *Drosophila* to understand human metabolism and the emergence of the fly as a tool to model the impact of parental and early offspring nutrition on metabolic programming.

Benefits of the *Drosophila* model in metabolic studies

Genetics and dietary manipulation

Mammalian models have been successful in identifying several factors that may contribute to metabolic programming; however, many of these observations remain correlative. Recently, *Drosophila melanogaster* has proven a powerful tool in uncovering the molecular mechanisms involved in several human metabolic diseases – in fact an average of 75% of the known human disease-related genes are conserved in the fly (Reiter *et al.*, 2001; Sanchez-Martinez *et al.*, 2006; Baker and Thummel, 2007; Fernández-Moreno *et al.*, 2007; Birse *et al.*, 2010; Musselman *et al.*, 2011; Na *et al.*, 2013). Methods exist in the fly for the analysis of metabolic profiles including measurement of circulating and stored lipids and carbohydrates and ATP levels as well as tools for metabolomics (Tennessen *et al.*, 2014).

Much of the interest in *Drosophila* is due to the exceptionally well-developed genetic tools allowing for the rapid generation of whole-body, tissue-specific, and/or developmental stage-specific gene manipulated strains as well as the development of sophisticated genetic screens (del Valle Rodríguez *et al.*, 2012). *Drosophila* offer enormous transgenic libraries, some covering up to 91% of the fly protein-coding genome and include over 26,000 RNAi lines and a plethora of overexpression strains, enabling researchers to investigate various mutant

versions of a single gene (Dietzl *et al.*, 2007; Center, 2015). Specific gene mutants that are not commercially available can be quickly and relatively easily generated using either the classic method of transposon-mediated mutagenesis or the new approach of CRISPR genome editing (Bassett *et al.*, 2013). Several groups have taken advantage of the sophistication and ease of fly genetics to identify novel metabolic regulators (Beller *et al.*, 2008; Guo *et al.*, 2008; Jumbo-Lucioni *et al.*, 2010; Pospisilik *et al.*, 2010; Baumbach *et al.*, 2014). One such study used large-scale RNAi to knockdown 49% of protein-coding *Drosophila* genes in the fat body and portions of the midgut and identified 77 genes that altered organismal fat content, 83% of which have a human ortholog (Baumbach *et al.*, 2014). One of the conserved gene, store-operated calcium entry, was identified as a novel regulator of adiposity (Baumbach *et al.*, 2014). Another group performed a *Drosophila* genome-wide obesity screen, targeting 10,489 open reading frames with 11,594 transgenic RNAi fly lines to identify genes involved in fly adiposity (Pospisilik *et al.*, 2010). From their screen Pospisilik *et al.* identified 500 candidate regulators of fly triglyceride levels, including genes involved in feeding behavior and key lipid regulators such as *fatty-acid synthetase* and *Drosophila* homologs to *PI3K* and the insulin receptor. Interestingly, this screen revealed a previously unknown role for hedgehog signaling in fat body adiposity and identified the hedgehog pathway as a determinate of mammalian brown versus white adipocyte cell fate (Pospisilik *et al.*, 2010).

Dietary manipulations in the fly are relatively easy, economical, and the variations in diet are limitless primarily due to the fact that most diets can be produced in the laboratory. Moreover, several methods exist to quantify food ingestion (Deshpande *et al.*, 2014; Tennessen *et al.*, 2014). The concentrations and types of lipids, carbohydrates, amino acids, and other ingredients can be easily and quickly adjusted or omitted from fly diets to test the contribution of specific nutrients to metabolic programming. Specific compounds and pharmaceuticals can also be added to fly diets to either assess their therapeutic potential or as a method of inhibiting or activating a particular signaling pathway (Kang *et al.*, 2002; Agrawal *et al.*, 2005). Taking advantage of these benefits, many studies have used *Drosophila* to investigate the mechanisms involved in dietary restriction and overnutrition (previously reviewed by Tatar *et al.*, 2014).

Overnutrition in the form of excess fat and sucrose in *Drosophila* mimics the pathophysiology of mammalian obesity including insulin resistance, hyperglycemia, non-adipose lipid accumulation, cardiomyopathy, shortened lifespan, and elevated expression of lipogenic and gluconeogenic genes (Birse *et al.*, 2010; Musselman *et al.*, 2011, 2013; Pasco and Leopold, 2012; Na *et al.*, 2013). Using these models of overnutrition, several studies identified new roles for classic metabolic pathways in obesity-related human disease including insulin-TOR pathway, SREBP, PGRC-1, Retinol-Binding Protein 4, and the hexosamine biosynthetic pathway (Birse *et al.*, 2010; Pasco and Leopold, 2012; Na *et al.*, 2013; Diop *et al.*, 2015). Such studies underscore the many benefits of using the fly to uncover new functions for known genes as well as to identify novel genes related to human metabolic disease.

Metabolic tissue and pathway conservation

Midgut – Nutrient absorption—There exist many similarities between the mammalian and fly digestive systems (Apidianakis and Rahme, 2011) (Figure 1). The pharynx, esophagus, and crop (analogous to the stomach) comprise the fly foregut, one of three sections of the *Drosophila* gut. The hindgut follows the midgut and is the site of water absorption. While nutrient absorption and digestion occur in the mammalian stomach and small intestines, in the fly these activities are primarily restricted to the midgut. The gut is also the site of lipid absorption whereby dietary TAG is metabolized most notably by a homolog of mammalian gastric lipase, Magro, into monoacylglycerides and fatty acids which can then be absorbed by enterocytes, converted to diacylglycerides, and transported in the hemolymph as lipoproteins (Sieber and Thummel, 2009). Malpighian tubules are at the junction of the midgut and hindgut and perform functions analogous to mammalian kidneys.

Fat body – Nutrient storage, mobilization, and sensing—Nutrients absorbed by the midgut are circulated through the hemolymph, the *Drosophila* equivalent of mammalian blood, and delivered to the fat body. The fat body is analogous to the liver and white adipose tissue and is the site of lipid and carbohydrate storage and mobilization and *de novo* lipogenesis (Dobrosotskaya *et al.*, 2002; Seegmiller *et al.*, 2002; Liu and Huang, 2013). Lipids reach the fat body in the form of lipoproteins, with lipophorin being the most abundant type (Kutty *et al.*, 1996; Arrese *et al.*, 2001; Palm *et al.*, 2012). Lipophorins are taken up by the fat body via the lipophorin receptor, a member of the LDL receptor family, and converted to TAG and stored in lipid droplets (Arrese and Soulages, 2010). Dietary sugars are metabolized in the midgut and transferred to the fat body for storage in the form of glycogen. A fairly recent discovery identified larval oenocytes as *Drosophila* hepatocyte counterparts, expressing many genes homologous to mammalian lipid metabolic genes, as well as serving a key role in lipid droplet storage and fatty acid utilization (Gutierrez *et al.*, 2007).

In addition to nutrient storage, the fat body is also a site of lipid and carbohydrate mobilization. During times of nutrient deprivation or increased energy expenditure, the fat body synthesizes trehalose from glycogen stores for release into the hemolymph for subsequent use by other tissues. Mobilization of fat body lipid droplets requires the hydrolysis of TAG to DAG by the specialized lipase Brummer, a homolog of human adipose triglyceride lipase (Grönke *et al.*, 2005). As in mammals, specific signaling events regulate nutrient mobilization in *Drosophila* and are discussed in further detail.

The fat body also functions as a nutrient sensor in the control of organismal growth. Studies have shown that modulating components specifically in the fat body of the insulin/insulin-like growth factor and TSC/TOR pathways, both highly conserved in the fly, alter organismal size. Inhibiting activation of the insulin receptor (InR)/PI3K pathway through fat body-specific expression of a dominant negative p60 produces developmentally arrested larvae with proportionately small organs; on the other hand, promotion of insulin signaling either by inducing fat body-specific expression of the insulin-like peptide dILP6 or by targeting the PI3K inhibitor u-shaped (USH) through fat body-expressed microRNA mir-8 increases growth of both fat body cells and the organism (Britton *et al.*, 2002; Hyun *et al.*,

2009; Okamoto *et al.*, 2009; Slaidina *et al.*, 2009). As in mammals, *Drosophila* TOR (dTOR) can be activated by both the InR/PI3K pathway and extracellular nutrient availability to control cellular growth (Oldham *et al.*, 2000; Zhang *et al.*, 2000). Depletion of the amino acid transporter *slimfast* in the fat body produces developmentally delayed and smaller larvae relative to control animals that die during the pupal stage (Colombani *et al.*, 2003). When a milder RNAi knockdown condition was used, *slimfast*-depleted larvae developed beyond the pupal stage, producing adults that were over 50% smaller than control flies (Colombani *et al.*, 2003). Interestingly, the growth defect in the *slimfast* mutant was partially rescued by expression of the dTOR downstream target S6 Kinase and larvae expressing dominant negative dTOR in the fat body phenotypically resembled *slimfast* knockdown animals (Colombani *et al.*, 2003). Depletion of *slimfast* in the fat body also inhibited dILP2 release from IPCs and systemically suppressed the InR/PI3K pathway (Colombani *et al.*, 2003; Géminard *et al.*, 2009). This failure to secrete dILP2 in response to suppressing amino acid import in the fat body was also observed in dietary restricted animals when dTOR signaling was disrupted, indicating that notification of amino acid availability is relayed from the fat body to the brain by dTOR (Géminard *et al.*, 2009).

The nutrient sensing capabilities of the fat body are also modulated by the steroid hormone ecdysone. Suppressing ecdysone signaling in the fat body by targeting the ecdysone receptor (EcR) produced larger larvae and pupae compared to control animals (Colombani *et al.*, 2005). Two distinct mechanisms by which ecdysone may control organismal size have been reported. One study demonstrated that fat body knockdown of EcR increases dMyc expression causing both a decrease in fat cell ribosomal number and overall animal size (Delanoue *et al.*, 2010). Additionally, it was also shown that overexpressing dMyc in the fat body increases larval size (Delanoue *et al.*, 2010; Parisi *et al.*, 2013). Another report showed, using fat body EcR knockdown and a dominant negative EcR, that ecdysone controls organismal size by inhibiting expression miR-8 in the fat body, which leads to increased USH activity and blunted organismal growth (Jin *et al.*, 2012).

Conservation of nutrient pathways—Several signaling pathways that control the sensing and utilization of carbohydrates, lipids, and amino acids are highly conserved in the fly. In the pancreas, α- and β-cells control blood glucose levels through the balanced secretion of glucagon and insulin, respectively, and are secreted at low levels in the basal non-fasting state (Campbell and Drucker, 2015). In the fly, there are three tissues that regulate glucose levels, the corpora cardiaca, the IPCs in the brain, and the fat body. The ring gland houses the neurosecretory cells of the corpora cardiaca, which, like pancreatic α-cells, secrete the glucagon-like protein adipokinetic hormone (AKH) (Kim and Rulifson, 2004). Like glucagon, AKH is derived from the processing of a preprohormone and in its mature form binds to the AKH G-protein-coupled transmembrane receptor located on the plasma membrane of fat body cells (Rayne and O'Shea, 1994; Noyes *et al.*, 1995; Staubli *et al.*, 2002). AKH receptor binding promotes glycogenolysis, the synthesis and subsequent release of trehalose, the major circulating sugar in the fly, and lipolysis (Staubli *et al.*, 2002; Van der Horst, 2003; Rhea *et al.*, 2010).

Another highly conserved gene in the regulation of carbohydrate metabolism is the *Drosophila* ChREBP homologue *Mlx interactor* (*Mio/Mondo*), which is activated in

response to increased glucose and induces expression of genes involved in lipid biosynthesis and glycolysis, and as such, it's promotion of lipogenesis is required for survival on an obesogenic high-sucrose diet (Postic *et al.*, 2007; Musselman *et al.*, 2013). Recently it has been reported that, in the brain, Mio can also regulate nutrient storage and feeding and that control of food consumption occurs in the IPCs likely via the Mio-driven down regulation of *dILP3* mRNA (Docherty *et al.*, 2015).

Insulin in the fly exists as eight (1–8) distinct homologs denoted as *Drosophila* insulin-like-peptides (dILPs). In larvae, 5 of the 8 dILPs (dILPs 1–5) are secreted from specialized neurosecretory cells known as IPCs found in the brain. IPC ablation decreases adult and larval size and increases circulating glucose and trehalose levels, which can be rescued by restoring dILP2 expression (Rulifson *et al.*, 2002). In addition to the brain, several dILPs are expressed in multiple tissues, including the fat body, depending on fly developmental stage (Brogiolo *et al.*, 2001).

Similar to mammalian insulin, dILP secretion is controlled by nutrient availability. Under starvation and amino acid-poor conditions, transcript levels of many IPC originating *dILP*s are altered with some dILP proteins being sequestered to IPCs as well (Ikeya *et al.*, 2002; Géminard *et al.*, 2009). Contrary to IPC produced dILPs, *dILP6*, which originates in the fat body, is increased in response to starvation (Slaidina *et al.*, 2009). The known physiological functions of dILPs are varied and, depending on the developmental stage of the organisms, include regulation of organismal growth, cell size, lifespan, lipid storage, and carbohydrate metabolism (Brogiolo *et al.*, 2001; Broughton *et al.*, 2008; Slaidina *et al.*, 2009; Grönke *et al.*, 2010).

Activation and regulation of the insulin signaling pathway is highly conserved in the fly and is a key component of lipid and carbohydrate mobilization, uptake, and storage. Recent studies have demonstrated that release of dILPs from the IPCs is controlled by changes in amino acid and trehalose levels in a TOR-dependent fashion as well as lipids involving the leptin homolog Unpaired 2 (Géminard *et al.*, 2009; Rajan and Perrimon, 2012; Kim and Neufeld, 2015). dILP secretion is also regulated by the *Drosophila* short neuropeptide F (sNPF), an ortholog of mammalian neuropeptide Y (Lee *et al.*, 2008). Overexpression of either sNPF or its receptor, sNPFR1, results in increased food intake and overall organismal size and, at the molecular level, down regulation of fat body AKT signaling (Lee *et al.*, 2004, 2008). sNPF orchestrates these effects by controlling dILP secretion via ERK signaling in IPCs (Lee *et al.*, 2008). Secreted dILPs circulate and bind to *Drosophila* InR causing the receptor to oligomerize and activating a highly conserved set of molecular events that lead to AKT activation (Garofalo, 2002; Oldham and Hafen, 2003). Active *Drosophila* AKT inhibits many of the same metabolic targets as mammalian AKT including dFOXO, dTSC2, and GSK-3β (Garofalo, 2002).

Additional lipid regulatory components conserved in the fly include the *Drosophila* sterol regulatory element-binding protein (dSREBP) transcription factor. Unlike in mammals where sterols regulate SREBP activation, in the cholesterol auxotrophic fly, dSREBP is controlled by intracellular levels of phosphatidylethanolamine (PE), the most abundant phospholipid in flies, and undergoes proteolytic cleavage in the absence of phospholipids

leading to transcription of genes for fatty acid and phospholipid biosynthesis (Dobrosotskaya *et al.*, 2002; Seegmiller *et al.*, 2002). Inducing dSREBP activity by decreasing PE not only impacts whole body lipid homeostasis, but leads to cardiac hyperlipidemia and dysfunction (Lim *et al.*, 2011). Using a *Drosophila* model of obesity-associated heart dysfunction, Diop *et al.* demonstrated that dSREBP contributed to cardiac lipotoxicity in flies fed a high-fat diet, highlighting a potential role for SREBP in the control of human obesity-associated cardiomyopathies (Diop *et al.*, 2015). Drosophila also controls lipid levels by modulation of lipid storage via the fly perilipin homologue Lsd2 that resides on the surface of lipid droplets (Grönke *et al.*, 2003; Teixeira *et al.*, 2003).

Lipid homeostasis is also regulated by AKH-dependent lipid mobilization, although the precise mechanisms by which AKH promotes lipid release from the fat body is not fully understood (Trinh and Boulianne, 2013). Binding of AKH to its receptor activates glycogen phosphorylase leading to breakdown of glycogen stores and subsequent synthesis of trehalose (Leopold and Perrimon, 2007). Control of lipid stores by AKH is less clear and is thought to involve a mechanism similar to fat mobilization in mammalian adipose tissue. AKH binding to the AKH receptor stimulates Brummer lipase activity, a homolog of human adipose triglyceride lipase, leading to breakdown of TAG lipid droplet stores and release of DAG into hemolymph (Trinh and Boulianne, 2013). Secretion of AKH relies on the activity of AMPK, whose function as an energy sensor is conserved in *Drosophila* (Pan and Hardie, 2002; Braco *et al.*, 2012). In the fly, depleting AMPK activity produces small larvae with depleted TAG stores that die in the pupal stage (Bland *et al.*, 2010). This phenotype was shown to be due to a requirement for AMPK in the visceral musculature to promote normal gut function and subsequent uptake of dietary nutrients (Bland *et al.*, 2010). Several other important studies on AMPK in the fly have described a conserved role for the energy sensor in autophagy and organismal longevity, starvation, and maintenance of cell structure, further highlighting *Drosophila* as a model tool in understanding the physiological impact and molecular mechanisms of nutrient sensing and energy expenditure (Lee *et al.*, 2007; Johnson *et al.*, 2010; Stenesen *et al.*, 2013; Ulgherait *et al.*, 2014). However, with regards to lifespan, treatment of flies with the AMPK agonist metformin failed to increase fly longevity – resulting in a dose-response increase in animal mortality; yet, metformin did activate AMPK and decrease TAG stores (Jafari *et al.*, 2007; Slack *et al.*, 2012). Interestingly, metformin also activates the TOR pathway, independently of AMPK, suggesting that off-target effects of the drug may be a contributing factor and that the function of metformin with regards to lifespan may prove more complex (Kalender *et al.*, 2010).

Metabolic programming in the offspring

Larval influence on the adult

In addition to the influences of parental diet, the contributions of gestational and early childhood nutrition on the progeny are key for understanding the mechanisms of metabolic programming. Many studies have used *Drosophila* to successfully model the effects of caloric restriction during early development (i.e, at the larval stage) on adult lifespan and reproductive capacity (Min *et al.*, 2006; Aguila *et al.*, 2007, 2013; Kolss *et al.*, 2009; Andersen *et al.*, 2010; May *et al.*, 2015). Several reports have also demonstrated the

metabolic influences of larval overnutrition on adulthood. Feeding larvae a high-sucrose diet significantly prolonged pupation time and produced adults with heightened levels of whole-body lipids and protein (Musselman *et al.*, 2011; Rovenko *et al.*, 2015a). High-sucrose fed larvae exhibited increased circulating dILPs in hemolymph, whether this continues into adulthood has not been reported; however, these adults did show increased amounts of brain *dILP* mRNAs (Musselman *et al.*, 2011; Rovenko *et al.*, 2015a). Interestingly, adults raised on high-sucrose diet as larvae also exhibited decreased lipid peroxides and reduced *superoxide dismutase* mRNA and activity levels, but increased *catalase* mRNA and activity compared to controls on a low-sucrose high-protein diet (Rovenko *et al.*, 2015a). When comparing the impact of rearing larvae on glucose versus fructose, while both sugars produced an obese-like phenotype, fructose-fed larvae consumed more food, and as adults had increased stores of carbohydrates and lipids and decreased *dILP* mRNAs compared to glucose-fed larvae (Rovenko *et al.*, 2015b). However, glucose-fed larvae had prolonged pupation rates and increased mortality (Rovenko *et al.*, 2015b). Conversely access to excess dietary protein early in life proved beneficial for survival of physical stress including exposure to extreme temperatures and generated females with increased fecundity (Andersen *et al.*, 2010).

Parental influence

In light of the global obesity epidemic and the increased prevalence of maternal obesity, a greater understanding of how parental diet influences offspring health as well as its impact on subsequent generations is of paramount importance. The benefits afforded by the fly, including ease of genetic and dietary manipulation, a rapid life-cycle, conserved metabolic tissues and signaling pathways, make it an ideal tool for elucidating molecular mechanisms of parental metabolic programming. Several *Drosophila* studies have focused on the contribution of parental diet on offspring health focusing on both under- and overnutrition (Vijendravarma *et al.*, 2010; Valtonen *et al.*, 2012a; Matzkin *et al.*, 2013; Colines *et al.*, 2015; Hardy *et al.*, 2015).

When male and female *Drosophila* were exposed to isocaloric diets that varied in protein and sucrose concentrations, flies fed a high-sucrose, low-protein diet had elevated levels of whole-body glycogen, decreased protein amounts, and females laid fewer eggs than flies raised on a low-sucrose, high-protein diet (Matzkin *et al.*, 2013) (Table 1). Although progeny from both groups were reared on standard diets, offspring of the high-sucrose, low-protein parents underwent a longer metamorphosis than offspring from high-protein, low-sucrose parents (Matzkin *et al.*, 2013). However, while developmental timing was effected, altering the parental diet did not impact offspring survival, but it did alter offspring reproduction (Matzkin *et al.*, 2013). Female offspring of high-sucrose, low-protein parents produced fewer eggs and exhibited increased body weight and overall glycogen content compared to females from low-sucrose, high-protein parents (Matzkin *et al.*, 2013). Decreasing both dietary sucrose and protein to one quarter of the amounts of a general laboratory fly diet resulted in a less profound result than the high-sucrose diet – when both parents were reared on the malnourished diet, females produced heavier eggs than those fed a standard diet (Vijendravarma *et al.*, 2010). When eggs of malnourished parents were laid on nutrient poor food they pupated at a faster rate than eggs from standard diet-fed parents (Vijendravarma *et*

al., 2010). Studies in the fly have also demonstrated that a carbohydrate enriched parental diet can ameliorate the influence of mature parental age on offspring asymmetry relative to old parents reared solely on a protein-rich diet (Colines *et al.*, 2015).

These data demonstrate that altering parental diet in *Drosophila*, as in mammals, not only produces reproductive repercussions in the parents, but also impacts offspring health. However, whether the observed impact of diet on parental and offspring health is a result of excess sugar, decreased protein, or both remains to be understood. One study has specifically focused on the contribution of a low protein parental diet on developmental programming and demonstrated that offspring from low protein-fed parents had longer developmental times relative to progeny from standard diet-fed parents and when only a single parent was malnourished (Valtonen *et al.*, 2012b). It is interesting to note that the offspring developmental time when only a single parent was malnourished was shorter than the standard diet timing, but progeny from two malnourished parents was not faster than the single-parent result, but rather slower than both single malnourished parent progeny and the control standard parent progeny. With regards to severe malnourishment, studies have shown that selecting for starvation resistant flies produces cohorts with altered metabolic features (Schwasinger-Schmidt *et al.*, 2012; Hardy *et al.*, 2015). One particular group demonstrated that selecting for starvation resistant flies for over 65 generations produced organisms with anatomically mislocalized hearts that had decreased contractility and were dilated (Hardy *et al.*, 2015). These cardiac dysfunctions correlated with an accumulation of lipids in the dorsal cuticle, since prolonged fasting of these animals was able to rescue the observed dilation and impaired contractility (Hardy *et al.*, 2015). Interestingly, in another study, selecting for flies exposed to a high-protein diet over 17 generations produced progeny with increased total body mass and lipids and significantly increased mortality rates relative to standard fed controls (Kristensen *et al.*, 2011). Taken together these studies demonstrate that the dietary inclination of each parent has a complex impact on the offspring and that the combined influence of both parent's diets leads to a further complexity in offspring health.

Paternal influence

Teasing out the contribution to metabolic programming of each parent is imperative in order to elucidate the molecular mechanisms at play in controlling offspring health. Work in *Drosophila* has demonstrated a paternal contribution to metabolic programming (Valtonen *et al.*, 2012b; Ost *et al.*, 2014; Aldrich and Maggert, 2015). Exposure of male flies to a low-protein diet from embryo through adulthood resulted in progeny with shortened developmental times and larger male offspring, but no change in female offspring size, relative to paternal males raised on standard food (Valtonen *et al.*, 2012b). When dietary sucrose rather than protein amounts were altered in paternal flies, it caused paternal TAG levels to increase in correlation with sugar concentrations and also resulted in a concentration dependent increase in offspring body weight (Ost *et al.*, 2014). Offspring of high sucrose fed males appeared to be pre-sensitized to an obesogenic diet since, upon exposure to the diet, body weight, TAG and lipid droplet size all increased (Ost *et al.*, 2014). Interestingly, this obese phenotype was evident in progeny whose fathers had only been on a high sucrose diet for two days (Ost *et al.*, 2014). Developmental times and overall offspring size remained unchanged regardless of the paternal diet (Ost *et al.*, 2014). Moreover, there

was no apparent transgenerational impact of the high sucrose paternal diet to generations after F1 (Ost *et al.*, 2014).

Taking full advantage of the benefits of fly genetics and dietary manipulation, two groups have uncovered profound insight into the mechanistic underpinnings of metabolic programming, highlighting a key role for genomic alteration (Ost *et al.*, 2014; Aldrich and Maggert, 2015). Male flies fed a protein-rich diet exhibit decreased rDNA copy numbers resulting in rDNA instability in both somatic and germ cells which was InR-dependent (Aldrich and Maggert, 2015). To investigate the impact on germline transmission, Aldrich *et al.* crossed these male flies with females carrying an rDNA-deficient compound X chromosome to generate female progeny whose only source of rDNA originated from the Y-linked *rDNA* gene. This genetic strategy revealed the rDNA phenotype was transferred to female offspring, resulting in progeny with reduced rDNA copy numbers and persisted for up to two generations even though progeny were fed a standard diet (Aldrich and Maggert, 2015). The observation that the generational impact on rRNA copy number was blocked by inhibition of the TOR pathway coupled with the fact that the impact of protein-rich diet on fathers is InR-dependent implicate the insulin/TOR signaling pathway as a mechanism of germline rDNA instability (Aldrich and Maggert, 2015). How paternal-diet-induced rDNA instability impacts offspring gene expression and subsequent health is not known; however, alterations to rDNA integrity have been linked to changes in the global chromatin state and organismal longevity (Paredes and Maggert, 2009; Kobayashi, 2011; Kwan *et al.*, 2013).

Changes in fly paternal diet have also been associated with an altered offspring chromatin state (Ost *et al.*, 2014). Male *Drosophila* fed a high-sucrose diet produced offspring with desilenced peri-centric heterochromatin on the X chromosome and an increase in gene expression including genes involved in energy metabolism as well as several unknown genes (Ost *et al.*, 2014). Gene desilencing was also observed in the sperm of the high sucrose-fed fathers, suggesting that diet-induced changes to sperm gene expression is a vehicle by which progeny gene expression is influenced (Ost *et al.*, 2014).

Maternal influence

Several studies in *Drosophila* have focused on understanding the contribution of maternal diet to metabolic programming (Buescher et al., 2013; Matzkin et al., 2013; Prasad et al., 2003; Valtonen et al., 2012; Vijendravarma et al., 2010). Most maternal programming studies have focused on the influence of undernourishment on progeny health and have demonstrated that females exposed to a protein- and sucrose- poor diet produce heavier eggs (Vijendravarma *et al.*, 2010). However, decreased nutrition in the form of sucrose and protein also results in decreased egg production and fewer mating events for females (Chapman and Partridge, 1996). When maternal dietary protein levels were decreased, females produced larger progeny with shorter developmental times compared to offspring of protein-rich females (Valtonen *et al.*, 2012b). Additionally, protein-poor females produced progeny with increased survivorship at the larval stage compared to offspring of protein-rich females; however, by the pupal stage, survivorship between both groups was comparable (Prasad et al., 2003). It is interesting to note that, although protein deficient females generated larger offspring, actual maternal egg production and ovary size correlate

negatively with dietary protein concentrations (Drummond-Barbosa and Spradling, 2001). While the molecular mechanisms by which maternal diet controls reproduction and offspring health are not completely understood, there is evidence demonstrating a role for Hedgehog and insulin signaling pathways in regulating the diet-induced proliferation of ovarian stem cells (Drummond-Barbosa and Spradling, 2001; Hsu *et al.*, 2008; Hsu and Drummond-Barbosa, 2009; Hartman *et al.*, 2013).

Most maternal diet studies in *Drosophila* focus on undernourished conditions; however, to understand the molecular mechanisms of maternal overnutrition (i.e., maternal obesity) we developed a fly model that incorporated comparing the effects of a high versus low sucrose diet on offspring health (Buescher *et al.*, 2013). Rearing female flies on a high sucrose diet produced an obese-like phenotype, marked by increased whole-body TAG, glycogen, and trehalose, insulin resistance, and elevated *dILP* expression compared to females on a low sucrose diet (Buescher et al., 2013; J G Duncan, unpublished observations). High sucrose-fed females produced male offspring with increased whole-body glucose and trehalose levels, while female progeny only had decreased levels of whole-body cholesterol (Buescher *et al.*, 2013). Changes in gene expression levels of male offspring were assessed by RNA sequencing, which revealed several differentially expressed genes involved in lipid and carbohydrate metabolism, including lipases Lip3 and CG17191, fatty acid synthase, acetyl-CoA-carboxylase, pyruvate kinase, enolase, and a putative sugar transporter CG4797 (Buescher *et al.*, 2013). Offspring of high sucrose-fed females were pre-sensitized to an obesogenic diet, exhibiting increased whole-body TAG, glycogen, and trehalose levels as well as altered expression of several carbohydrate and lipid metabolic genes (Buescher *et al.*, 2013). A transgenerational effect was also observed whereby F2 male progeny of high sucrose-fed F0 females showed increased glycogen and trehalose levels while F2 females displayed increased trehalose and decreased TAG levels (Buescher *et al.*, 2013). The factors contributing to these transgenerational observations are currently being investigated by the lab and are hypothesized to involve inheritance of altered maternal mitochondria – a phenomena that has been reported in mammalian metabolic programming studies; however, these reports only investigated the F1 generation (Grindler and Moley, 2013). The multigenerational reach of the maternal obesogenic diet as well as the transmission of maternal mitochondria makes the organelle a strong candidate for influencing metabolic programming across generations.

Conclusion

The fly is quickly emerging as an important ally for understanding human metabolic diseases, a trend in part owed to the highly conserved series of metabolic tissues and pathways present within the fly and a multitude of genetic tools available (Liu and Huang, 2013; Rajan and Perrimon, 2013). As the prevalence of maternal and paternal obesity increase the threat to offspring health and to subsequent generations will only worsen, making *Drosophila* an invaluable tool in uncovering the complexity of metabolic programming.

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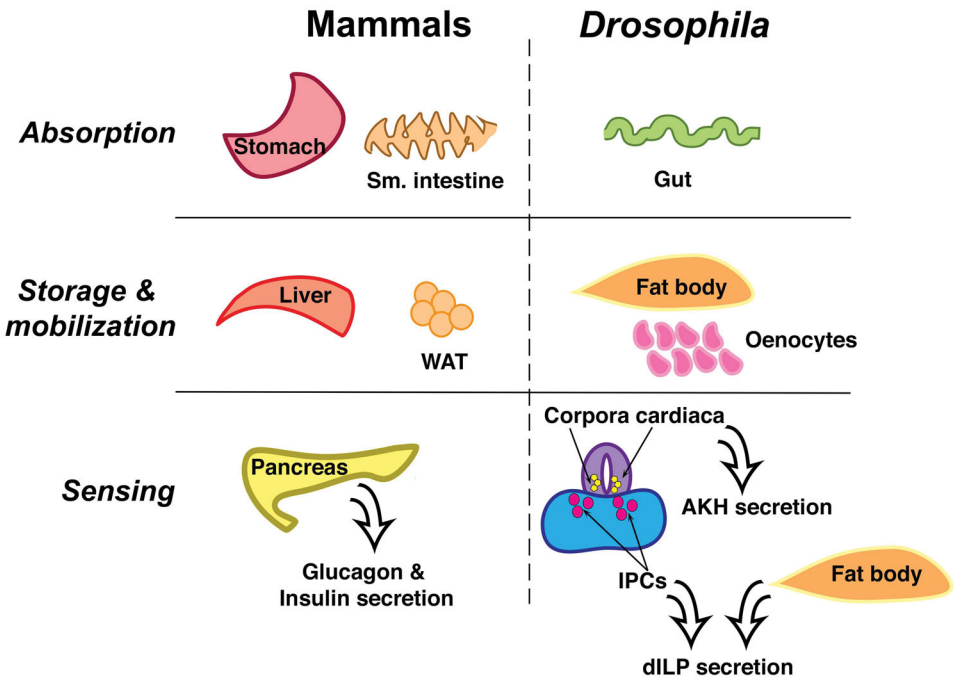

Figure 1. Conservation of metabolic tissues in *Drosophila*

Nutrient absorption and digestion in mammals primarily occurs in the stomach and small intestine. *Drosophila* contain a three-sectioned gut (foregut, midgut, and hindgut) in which the midgut performs the bulk of these functions. The fly malpighian tubules at the junction of the midgut and hindgut perform functions similar to the mammalian kidney. Storage and mobilization of carbohydrates and lipids occurs in the fat body and is analogous to mammalian white adipose tissue (WAT) and the liver. Oenocytes also play a key role in lipid storage and mobilization. The action of glucagon in response to decreased glucose levels mirrors that of the fly adipokinetic hormone (AKH), while, like insulin, *Drosophila* insulin-like peptides (dILPs) respond to increased nutrient availability. AKH is also known to act similarly to mammalian β3 agonist and induce mobilization of TAG from lipid droplets.

Table 1

Effect of high sucrose diet on metabolic programming in *Drosophila*

	Paternal High Sucrose **Ost *et al.* 2014**	**Maternal High Sucrose** **Buescher *et al.* 2013**	**Parental High Sucrose - Low Protein** **Matzkin *et al.* 2013**
F0	↑ TAG *Adult stage*	↑TAG, trehalose, & glycogen ↓ Glucose & body weight *Adult stage*	↑ Glycogen; ↓ Protein Fewer eggs laid *Adult stage*
F1	↑ Body weight (adult males & females) *Obesogenic Challenge (adult males & females):* ↑ Body weight, TAG, & lipid droplet size ↔ Development time & body size Desilenced peri-centric X chromosome (adult females)	*Larval stage (males):* ↑ Glucose & trehalose ↓ Glycogen & cholesterol; ↔ TAG Altered lipid & cholesterol gene expression *Adult stage (males):* ↓ Glucose & body weight* ↑ Trehalose*, TAG*, & glycogen Altered lipid & cholesterol gene expression	↑ Development time (males & females) Fewer eggs laid (adult females)
F2	No effect observed (adult males; females unreported)	*Larval males:* ↑ Glucose & trehalose *Larval females:* ↑ Trehalose; ↓ TAG	Not reported

*Observed impact is exacerbated by obesogenic challenge