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Gaining insights into diabetic cardiomyopathy from *Drosophila*

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Abstract

The high degree of genetic conservation between *Drosophila melanogaster* and mammals has helped to translate many important findings into new knowledge, and has led to better understanding of many biological processes in vertebrates. For over a century, the *Drosophila* model has been used in studies aimed at understanding molecular mechanisms implicated in heredity, development, disease progression, and aging. The current epidemic of obesity and associated diabetic cardiomyopathy and heart failure has led to a shift in *Drosophila* research towards understanding the basic mechanisms leading to metabolic syndrome and associated cardiac risk factors. Here, we discuss recent findings in *Drosophila* that highlight the importance of this organism as an excellent model to study the effects of metabolic imbalance on cardiac function.

Keywords

Metabolism; obesity; cardiomyopathy; TOR; ATGL; PGC-1

Introduction

In 1910, Thomas Hunt Morgan published a first paper demonstrating sex-linked heredity in the fruit fly *Drosophila* melanogaster [1]. Since then, studies in this organism have played pioneering roles in understanding human genetics, development, biology, physiology, and many aspects of disease mechanisms. Early functional genetic investigations led to the discovery of the circadian clock [2], homeotic selector genes [3], and segment polarity genes that govern embryonic developmental patterning [4]. Subsequent studies identified the homeotic selector gene complexes (hox genes) in mice and humans [5–6] and clock genes in humans [7], highlighting the genetic conservation between flies and mammals.

These groundbreaking findings throughout the 20th century were made possible by the unique advantages offered by the *Drosophila* model organism. The fruit fly has a short life cycle and relatively simple genetic structure, characterized by a smaller number of genomic

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duplications than in vertebrates. Sequencing of the fly and human genomes and comparative bioinformatics analysis revealed that approximately 75% of human disease genes had *bona fide* homologs in *Drosophila* [8]. Indeed, numerous studies have improved our understanding of human disease mechanisms by manipulating human disease genes in *Drosophila* and by studying fly orthologues of key genes. These studies have established *Drosophila* as an excellent model in which to investigate fundamental mechanisms implicated in many human diseases, including cancer [9] and developmental and neurological disorders [10].

Among all of the genetically tractable, invertebrate model systems, *Drosophila* is the only organism that has a beating heart with pumping functions and other characteristics remarkably similar to the human heart [11]. Anatomically, the tubular fly heart is much simpler than the complex four-chambered heart of mammals; however, the developmental processes governing heart morphogenesis are evolutionarily conserved. Initial evidence for such conservation came from the homeobox gene *tinman*, which was first identified in flies [12–13] and subsequently shown to also control cardiac specification and morphogenesis in mice and humans [14]. Thus, the combination of genetic and functional conservation of the fly heart together with the availability of sophisticated methods for cardiac analysis [15, 16] have made *Drosophila* an outstanding model organism to investigate mechanisms of human cardiac disease. More recently, *Drosophila* has also become a genetic model of choice to study the effects of metabolic disturbances on heart function in the context of the whole organism [17–18]. In this review, we discuss recent advances in our understanding of the effects of perturbed metabolic processes and genetic pathways resulting from obesity, aging, diet, and exercise on heart function and the development of diabetic cardiomyopathy.

Conservation of fat and sugar metabolism between mammals and *Drosophila*

As is the case for mammals and vertebrates in general, individual organs serve distinct metabolic functions in *Drosophila* (Fig. 1). In both flies and mammals, the gut absorbs nutrients and metabolites for delivery to other organs [19]. In mammals, insulin and glucagon secreted by pancreatic β-cells and α-cells, respectively, maintain tight control over blood glucose levels, and perturbation of this hormonal regulation leads to type 2 diabetes [20]. In the fly, the functions of mammalian β-cells are mediated mostly by insulin-producing neuronal cells (IPCs), which are located in the brain and secrete several insulin-like peptides (Dilps) [21]. The corpora cardiaca located in the ring gland secretes the glucagon-like peptide adipokinetic hormone (AKH) [22]. Analogous to mammals, Dilps and AKH peptides have opposing regulatory effects on glucose and lipid metabolism analogous to the mammalian system, and perturbations in Dilp/AKH functions also affect energy metabolism and lead to metabolic syndrome-like phenotypes in *Drosophila* [23–24]. In mammals, the liver is a vital metabolic organ responsible for gluconeogenesis, glycogenesis, lipogenesis, and lipoprotein synthesis. In *Drosophila*, liver-like functions are mediated by oenocytes located near the body wall surface, and by the fat body, which additionally has adipose tissue-like functions [Fig. 1] [25]. However, unlike mammals, the fly does not synthesize cholesterol [26–27], and lipid metabolism occurring via Sterol Regulatory

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Binding Proteins (SREBPs) is regulated by the major phospholipid phosphatidylethanolamine (PE) [28–29].

Under normal feeding conditions, mammalian adipose tissue secretes leptin to signal to the brain the need to modulate metabolism via insulin action [30]. Analogously, the fat body of *Drosophila* secretes the cytokine Unpaired 2 (Upd2) to regulate insulin action by the neurosecretory IPCs in the brain during the fed state [31]. Interestingly, mammalian leptin can rescue the effects of the *upd2* mutant phenotype in *Drosophila* [31], suggesting that *upd2* is the functional homolog of leptin.

Just as many fundamental aspects of metabolic regulation are conserved between *Drosophila* and mammals, so too are the genes that control these metabolic processes. For example, one of the most important regulators of lipid and glucose metabolism in mammals is the nutrient-sensing Target of Rapamycin (TOR) pathway. This pathway is conserved in *Drosophila* where it controls not only metabolism but also developmental growth [32]. Several other conserved metabolic components are the SREBP pathway and its lipogenesis-controlling target genes [28, 33–35], as well as hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL; *bmm* in flies) both of which control fat breakdown [36–39]. The PPARγ co-activator-1 (PGC-1) family of co-regulators plays important roles in gluconeogenesis, mitochondrial biogenesis, and β-oxidation in mammals; in *Drosophila*, PGC-1 is represented by the *Spargel* (*srl*) gene and, as in mammals, its deregulation is linked to disruption of tissue homeostasis, obesity, diabetes, and cardiomyopathy [40–43]. These findings underscore the utility of *Drosophila* as a model to study the effects of diet, exercise, and aging on the heart, including dysfunction induced by metabolic disturbances.

Nutrient excess in *Drosophila* causes diabetic cardiomyopathy-like symptoms

Consumption of a high caloric diet and reduced energy expenditure dictated by our modern lifestyle are important contributors to cardiomyopathies [44], which are classified by the American Heart Association as a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction. They include dilated and restrictive cardiomyopathies and diastolic and systolic dysfunctions, all of which often lead to lethal heart failure. In mammals, the causes and mechanisms of diabetic cardiomyopathies are often difficult to determine because of additional complications such as coronary heart disease and hypertension. Because *Drosophila* lacks coronary vessels, we are able to study the direct effects of diet on cardiomyocytes.

Effect of high fat diet (HFD) on Drosophila heart function

Wild-type adult flies fed a HFD (30% coconut oil) have increased levels of fat, glucose, and Dilp, and myofibrillar disorganization within the cardiomyocytes [43, 45] Functionally, these hearts have reduced fractional shortening (comparable to reduced left ventricle ejection fraction in diabetic cardiomyopathy patients), increased heart rate, and an increased incidence of non-contractile heart regions, regional arrhythmias and dysfunctional outflow tracks (Ostia) [Fig. 2][43, 45]. Thus, in *Drosophila,* a HFD can provoke not only metabolic

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syndrome-like symptoms but also cardiac dysfunction resembling human diabetic cardiomyopathies.

Several conserved key metabolic regulators such as the TOR pathway, *PGC-1,* and the lipase ATGL have previously been associated with obesity and heart disease [46–50], but the underlying genetic links between them have not been clear. Interestingly, HFD-fed flies exhibit increased activation of the TOR pathway (exemplified by elevated phosphorylation of AKT and S6K) and increased SREBP levels, whereas genetic reduction of TOR signaling blocks the effects of HFD and prevents the increased fat content and cardiac dysfunction [43, 45]. Conversely, expression of *PGC-1/srl* and ATGL/*bmm* is markedly decreased in HFD-fed flies, and ATGL/*bmm* or *PGC-1/srl* heterozygotes display an 'HFD phenotype' that is further exacerbated by HFD feeding. In contrast, augmenting ATGL/*bmm* or *PGC-1/srl* expression, either systemically or specifically in the heart, counteracts HFD-induced obesity and cardiac dysfunction [43]. Since ATGL/*bmm* and *PGC-1/srl* levels are increased in TOR mutant flies, these genes may act downstream of TOR signaling. Indeed, reducing ATGL/*bmm* or *PGC-1/srl* levels in TOR mutant flies, which are normally protected from HFD-induced pathologies, leads to obesity and heart dysfunction [43]. These findings indicate that TOR signaling may also contribute to obesity-induced diabetic cardiomyopathies in higher organisms via regulation of ATGL/*bmm* and PGC-1/*srl* levels (Fig. 3). Similarly, SREBP and its target fatty acid synthase (FAS) also appear to be regulated by TOR signaling, but this is likely in parallel to ATGL/*bmm* and PGC-1/*srl* (Fig. 3) [43].

Experiments investigating genetic epistasis between metabolic regulators have identified a network of interacting genes in *Drosophila* [Fig. 3]. The currently proposed model suggests that HFD feeding causes overactivation of the TOR pathway, leading to downregulation of the ATGL/*bmm*-PGC-1/*srl* axis and upregulation of SREBP-FAS [43]. These two TOR-regulated pathways then mediate the increase in fat accumulation and subsequent development of cardiac lipotoxicity [Fig. 3] [43]. Analysis of the transcriptome combined with mass spectrometry-based analysis of the metabolome has identified possible links between the HFD-induced metabolic imbalance and cardiomyopathy. Flies fed a HFD had elevated levels of fatty acids, including myristate, palmitate, oleate, and stearate. These flies also had decreased amino acid concentrations and increased urea and uric acid levels, indicative of an imbalance in protein metabolism. Glucose metabolism was also altered, resulting in elevated pyruvate and lactic acid levels, pointing to a possible HFD-induced glycolytic shift. Detailed transcriptomic profiling and further genetic characterization of candidate regulators identified CG9510 identified the *Drosophila* homologue of human argininosuccinate lyase (ASL), an enzyme that controls amino acid metabolism, as playing a role in HFD-induced obesity and associated cardiac dysfunction [Fig. 3] [51]. HFD feeding was shown to reduce CG9510 expression, and mutation or RNAi knockdown of CG9510 caused increased fat accumulation under normal feeding conditions. Conversely, CG9510 overexpression under HFD conditions decreased fat levels. In regard to heart function, down-regulation of CG9510 under normal feeding conditions caused deterioration of heart function, similar to the effects of HFD [51]. Future studies will determine whether

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interactions between the TOR/ATGL-PGC-SREBP axis and amino acid metabolism occur in heart disease.

Effects of high sugar diet (HSD) on Drosophila heart function

Excess consumption of sugar leads to obesity and heart disease in *Drosophila* just as it does in mammals. A high sugar diet (HSD) was shown to augment fat content and insulin resistance [52–53], and analysis of heart function in HSD-fed flies revealed an increase in cardiac arrhythmia that became more pronounced with age. Hearts from aged flies also exhibited a significant decrease in contractile function, characterized by reduced fractional shortening [53]. These functional defects were associated with increased cardiac expression of pericardin, a *Drosophila* collagen IV-like peptide indicative of increased fibrosis. Similar to the effects of a HSD, glucosamine feeding also causes deterioration of heart function with muscle fiber disorganization and further reduced fractional shortening [53]. Heart-specific knockdown of GFAT (glutamine fructose-6-phosphate amidotransferase) and OGT (O-linked N-acetylglucosamine transferase), two enzymes that drive hexosamine biosynthesis, ameliorated the effect of a HSD on heart function, as manifested by a reduced incidence of arrhythmias [53]. These data suggest that increased glucose flux via the hexosamine pathway may be a contributing mechanism of HSD-associated heart dysfunction [Fig. 3]. Although it remains to be determined, the similarity between obesity and heart dysfunction phenotypes induced by defects in the hexosamine biosynthetic pathway and the TOR-ATGL-PGC-SREBP suggests potential regulatory links between HSD- and HFD-induced diabetic cardiomyopathy.

Effects of time-restricted feeding on heart function

There has been recent interest in the influence of a new concept, time-restricted feeding (TRF), on metabolic disease. TRF entails confining food consumption to a 9–12 h period during an animal's active phase. Compared with mice fed a HFD *ad libitum,* mice subjected to HFD with TRF showed decreased body weight even though the total daily energy intake under the two conditions was similar. The TRF mice also exhibited improved circadian rhythms, increased glucose tolerance, and decreased fatty acid levels, and they were protected from hepatic steatosis [54–55]. These findings suggested that perturbation of metabolic cycles might be a contributing factor in HFD-induced metabolic syndrome. Recent studies in *Drosophila* have further clarified the functional implications of TRF for cardiac homeostasis. TRF with normal food slowed or even reversed age-associated cardiac pathologies, such as bradycardia, arrhythmia, and reduced fractional shortening (compromised contractile function [56], whereas TRF with a HFD decreased arrhythmia index and heart period [56]. These data suggest that TRF ameliorates age- and diet-associated heart dysfunction in *Drosophila* [56]. Temporal gne expression profiling in *Drosophila* in combination with genetic validation has demonstrated that the TCP-1 (T-complex protein-1) ring complex, mitochondrial electron transport chain complex genes, and circadian clock genes mediate the beneficial effects of TRF [Fig. 3] [56], reinforcing the ability of fly studies to identify genetic control mechanisms.

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Metabolic regulation of *Drosophila* heart function during aging

Aging is a complex multifactorial process, modulated in part by genetics and the environment and characterized by declining physical and mental function and increased susceptibility to disease, including cardiomyopathies. Many structural proteins in the mammalian heart are conserved in *Drosophila* and have been found to modulate cardiac aging; these include dystrophin, myosin, integrin linked-kinase (ilk), and ion channels [57–61]. In this section, we focus on the metabolic control of heart function in aging *Drosophila*.

The aging fly heart exhibits features similar to hearts of aging mammals, including myofibrillar derangements, increased arrhythmia index, decreased contractile function, and increased heart failure rates under pacing stress [60, 62]. Genetic studies of cardiac aging thus play an important role in the development of therapeutics to improve or prevent age-associated cardiac decline and health in humans. In *Drosophila*, the conserved insulin and TOR pathways have emerged as important modulators of aging heart function [Fig. 3]. Reduction of insulin-IGF signaling, either by mutation of genes encoding the insulin receptor or its substrate chico or by ablation of IPCs expressing Dilp, have been shown to improve cardiac performance with age [62]. Similarly, age-associated declines in cardiac function are ameliorated by reducing TOR function, or overexpressing the TOR negative effector d4E-BP or dFoxO [62–63]. An important TOR negative feedback regulator is dSestrin (dSesn) [64], which has known antioxidant effects but was recently also implicated in the control of heart function during *Drosophila* aging [65]. Not surprisingly, dSesn mutants exhibit increased TOR activity and phenotypes of age-associated cardiac pathologies. Moreover, dSesn flies also have increased levels of lipogenic genes, including SREBP, FAS, and ACC, which correlates well with the increase in triglyceride content [65]. Similar to flies fed a HFD, the dSesn mutants exhibited abnormal heart rhythms and a decreased heart period, suggestive of deteriorating cardiac function, which was prevented by pharmacological inhibition of TOR or AMPK [65].

Feedback inhibition of TOR via dSesn involved elevation of ROS levels [64]. While the involvement of ROS and oxidative stress in mammalian aging is controversial, studies performed in *Drosophila* model have shown that elevating ROS levels by catalase knockdown or reducing ROS by catalase overexpression leads to an increase in arrhythmias and a constrictive heart. These data indicate that the heart requires a basal level of ROS signaling to function properly, and that perturbation of normal ROS levels has a detrimental effect on cardiac function [66]. Collectively, these studies suggest that manipulating insulin/TOR or downstream effectors dramatically alters cardiac health with age.

Metabolic control of *Drosophila* heart function during exercise

In humans, regular aerobic exercise has beneficial effects on cardiac aging and the overall health span [67–68]. PGC-1α has been implicated as a key factor in controlling exercise's positive effects on muscle metabolism and function in mammals [69]. Similarly, exercised flies display increased PGC-1/srl levels that correlate with increased locomotor activity and resistance to heart failure from electrical pacing [70]. Overexpression of PGC-1/srl in muscle and heart protects against pacing-induced heart failure, increases locomotor activity,

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and prolongs exercise endurance [70]. Thus, exercise-associated increases in PGC-1/srl expression appear to have conserved protective effects on *Drosophila* and mammalian heart function [Fig. 3]. More studies are needed to fully understand the contribution of co-regulators and targets of PGC-1 to heart health during exercise.

The *Drosophila* heart functions as a metabolic organ

Communication between organs is vital for maintaining metabolic homeostasis. Recent studies in mice have shown that the heart not only receives and functionally adapts to input from other organs but may itself function as an important regulator of systemic glucose and lipid metabolism [71–72]. In the mouse, cardiac-specific overexpression of MED13, an inhibitor of the general transcriptional activator mediator complex, was shown to autonomously alter cardiac metabolism through decreased mitochondrial function, and to increase metabolic flexibility in the face of changing substrate availability [72]. Interestingly, cardiac-specific MED13 expression also had long-ranging, non-autonomous effects on the liver and adipose tissue, causing increased lipid uptake, mitochondrial biogenesis, and fatty acid oxidation [71–72]. Importantly, the cardiac-specific MED13 transgenic mice were protected against HFD-induced obesity and insulin resistance, and pharmacological inhibition of miR-208, a negative regulator of MED13, phenocopied MED13 overexpression [71].

Similar studies in *Drosophila* showed that heart- or muscle-specific knockdown of MED13 (skd) caused systemic disruption of metabolism, resulting in increased fat content on a normal diet and increased susceptibility to obesity on HFD feeding [73]. Microarray analysis combined with genetic validation experiments has shown that the conserved secreted protein wg (wingless) mediates the effects of heart-specific skd manipulation on fat body metabolism [73]. These findings suggest that the heart functions as a metabolic organ in both *Drosophila* and mice and that its genetic control of metabolism is also highly conserved [Fig. 4]. As mentioned above, cardiac-specific overexpression of ATGL/*bmm* or PGC-1/*srl* autonomously protected the heart from obesity-induced cardiac lipotoxicity and also decreased triglyceride content in the fat body under both normal diet and HFD conditions [43]. Since genetic manipulation of either ATGL/*bmm*-PGC-1/*srl* or MED13/MED12 in the heart causes metabolic imbalance and is associated cardiac dysfunction, we speculate that the two pathways may be connected, perhaps via regulation of TOR activity. It will also be of interest to investigate possible functional interactions between ATGL/*bmm*-PGC-1/srl and MED13/MED12 in the regulation of systemic metabolism by the heart [Fig. 4].

Concluding remarks and future directions

Despite fundamental anatomical differences between *Drosophila* and mammals, many key metabolic processes and regulatory mechanisms, including those functioning in the heart, are highly conserved in these species. The strong conservation of lipid and glucose metabolism extends to the hormonal regulation and overall genetic control of obesity in response to HSD and HFD, and their effects on cardiac function. Age-related changes in metabolism leading to heart dysfunction and the beneficial effects of exercise on heart

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performance also seem to be remarkably conserved. However, more studies are needed to identify new regulators and downstream effectors of the pathways established thus far to play critical roles in cardiomyopathies due to metabolic imbalance. For example, it will be important to find the points at which the effects of HFD and HSD intersect by investigating possible interactions between the ATGL/*bmm*-PGC-1/*srl* axis and the regulation of hexosamine biosynthesis. Given that ROS levels in the heart are increased by high caloric diets, it will also be important to investigate the functional relevance of oxidative stress and related ER stress during diet-induced obesity and associated heart dysfunction. From a therapeutic point of view, studies in *Drosophila* should also focus on screening for small molecules targeting new and previously identified pathways involved in the development of cardiomyopathies, which ultimately may lead to new treatments for heart disease.

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Trends Box

Metabolic imbalance induced by a high caloric diet leads to obesity and lipotoxic cardiomyopathy in the Drosophila model.

Because of its fundamentally conserved genetic and metabolic control pathways, the fruit fly constitutes a unique tool to elucidate mechanisms implicated in diabetic cardiomyopathy.

Insulin/TOR signaling plays a central role in the development of lipotoxic cardiomyopathy.

Conserved functions of AGTL/bmm, PGC-1/srl, SREBP and FAS participate in mediating diet-induced cardiomyopathy downstream of TOR.

As observed in mammals, the Drosophila heart can function as a metabolic regulatory organ to control systemic lipid metabolism.

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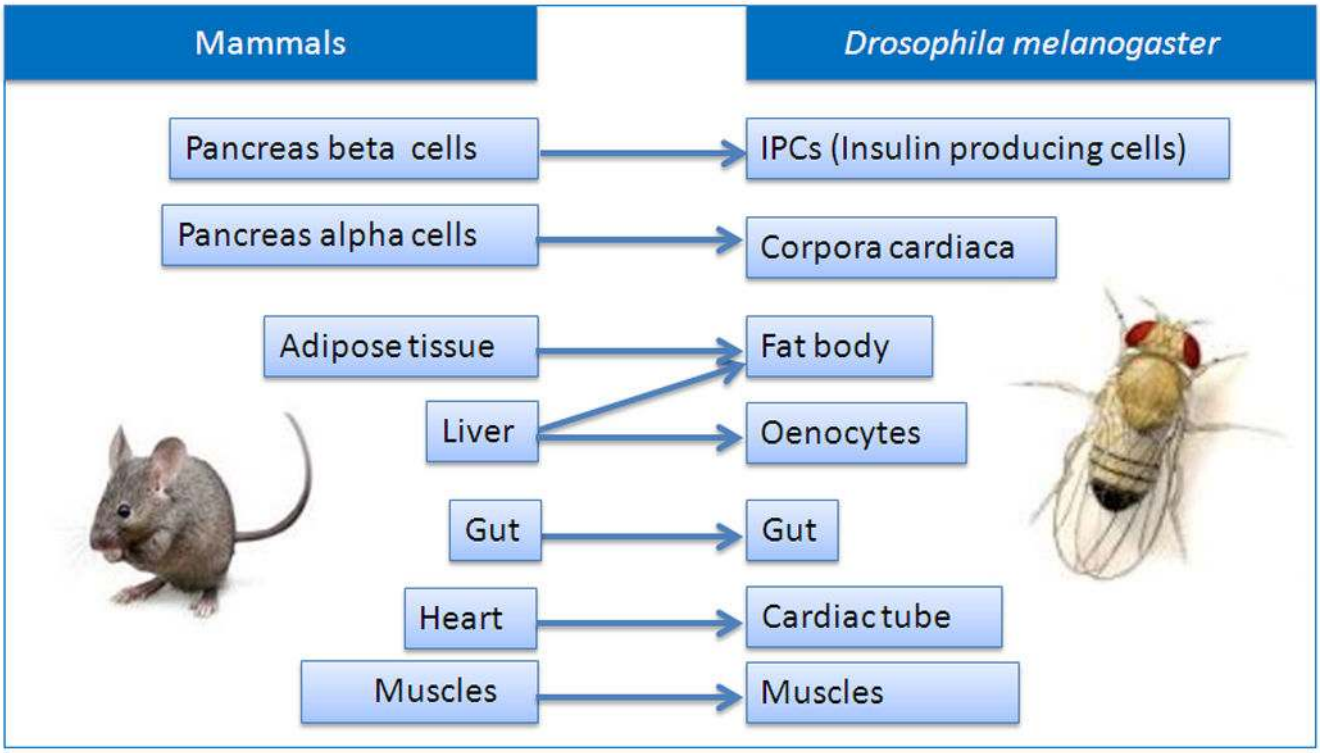

Figure 1. Comparison of metabolic organs in mammals and *Drosophila melanogaster*

In *Drosophila*, the function of the mammalian pancreas is carried out by IPCs and the corpora cardiaca. The fat body plays the role of mammalian adipose tissue, while both the fat body and oenocytes carry out the functions of the mammalian liver. The gut, heart, and somatic muscles of *Drosophila* function similarly to their mammalian counterparts.

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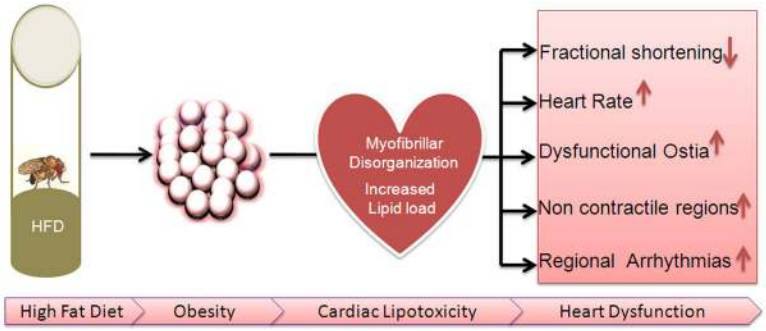

Figure 2. Diabetic cardiomyopathy in the *Drosophila* high-fat diet (HFD) model

HFD causes obesity as well as muscle derangement and lipid droplet accumulation in the heart. This leads to reduced fractional shortening, increased heart rate, ostia closure defects, non-contractile cardiomyocytes, and asynchronous heart beat along the heart tube (regional arrhythmias).

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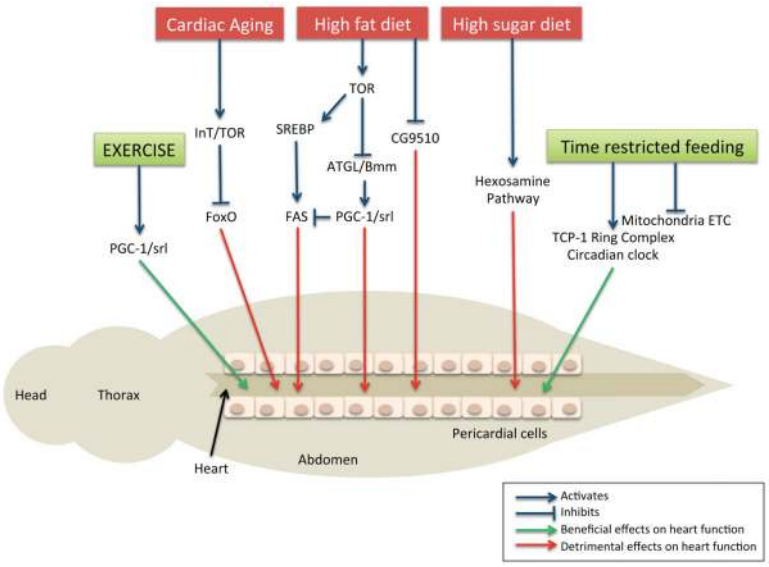

Figure 3. Impact of nutrient excess on cardiac function in *Drosophila*

Consumption of a high-fat diet (HFD) increases TOR signaling, leading to decreased ATGL/Bmm-PGC-1/srl and increased SREBP-FAS functions. ATGL-PGC-1 also regulates FAS independently of SREBP. HFD decreases the expression of CG9510 which itself can negatively affects heart function. High-sugar diet (HSD) controls obesity-induced heart dysfunction via the hexosamine biosynthetic pathway. Time-restricted feeding protects against cardiac dysfunction by regulating genes controlling the circadian clock, mitochondrial electron transport chain, and the TCP-1 Ring chaperone complex. Age-associated deterioration of heart function occurs via insulin/TOR signaling pathway and dFoxO. Exercise has a protective effect on heart function through upregulation of PGC-1/srl.

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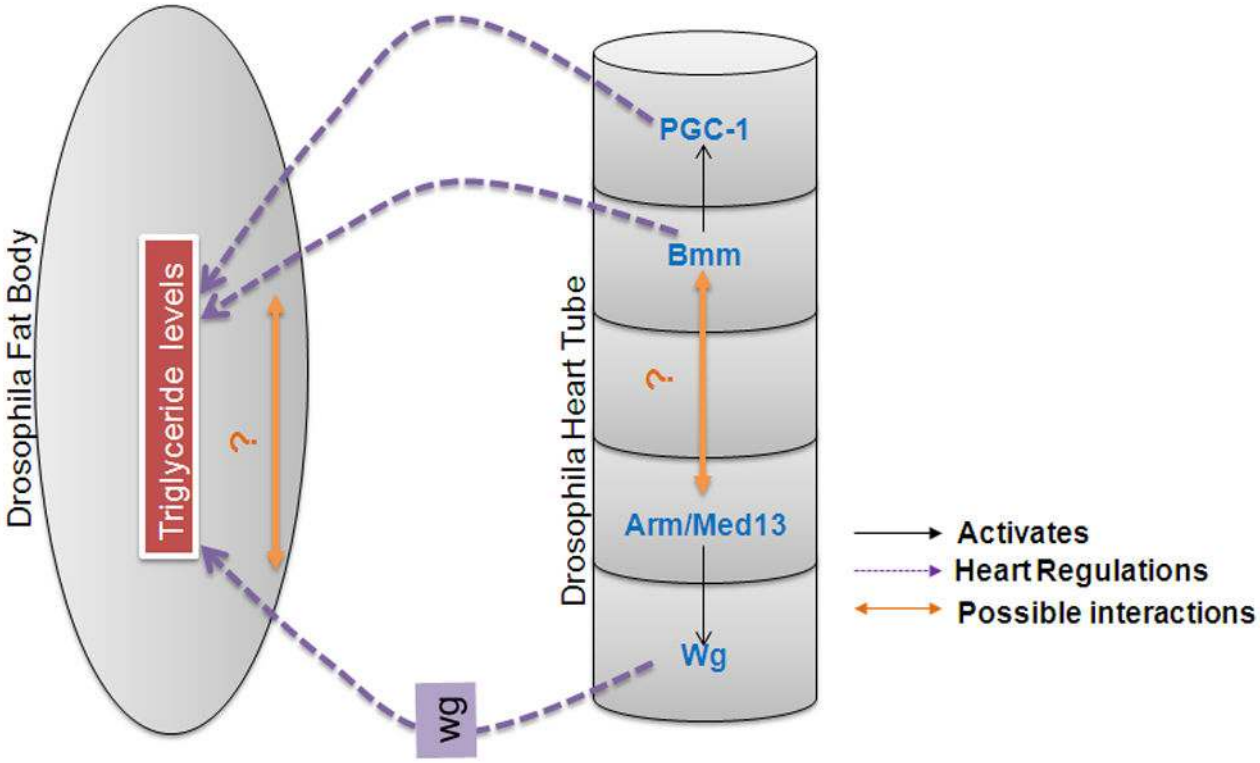

Figure 4. The *Drosophila* heart regulates fat content

In mice and *Drosophila*, heart-specific overexpression of MED13 has long-range effects on adipose tissue and decreases the fat content. These effects are mediated by wg (wingless) in *Drosophila melanogaster*. Heart-specific overexpression of ATGL/Bmm and PGC-1/srl reduces similarly to MED13 fat content in the *Drosophila* fat body. These two different modes of regulation might be functionally interconnected in the heart and/or the fat body.