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High Fat Diet Induced Obesity and Nutrient Sensing TOR Signaling

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Abstract

Obesity has grown to epidemic proportions globally, with 400 million considered obese. Evidence indicates that excessive dietary accumulation of lipids (obesity) is a risk factor in causing deleterious effects on metabolism and has been strongly linked to the progression of heart disease and Type 2 diabetes. Investigating the origin and effects of high fat diet (HFD)-induced obesity and its genetic mediators is an important step in understanding the mechanisms that contribute to obesity. However, the mechanisms that underlie HFD pathophysiology have yet to be fully elucidated. Here, we describe recent work in the *Drosophila* model to investigate the origin and genetic mechanisms that may underlie HFD-induced obesity, Type 2 diabetes, and cardiac dysfunction.

HFD-Induced Obesity

The occurrence of obesity worldwide has dramatically increased in a relatively short time period. Poor diets including those high in fat, in combination with sedentary lifestyles are the predominant causes of obesity in the Western world. Clearly, investigating the effects of high fat dietary intake is an important step in understanding the factors that contribute to the increase in obesity and in turn the secondary diseases caused by it.

Drosophila has recently emerged as a simplified model for lipid metabolism and homeostatic regulation, which demonstrates that the basic metabolic functions are evolutionarily and functionally conserved [3-7]. Disorders of energy homeostasis like obesity have reached epidemic proportions world-wide. High Fat Diet (HFD)-induced obesity is a multi-factorial disease with genetic/physiological, behavioral, and environmental components. Critically, HFD-induced obesity is a major contributor to chronic diseases, such as cancer, diabetes and cardiovascular disease (CVD). Ideas to explain the surge in obesity include the thrifty gene theory, which posits that genetic variants selected recently in evolution by sparse environments (famines) predispose to HFD obesity [8]. Another theory is that the HFD effects are due to the commandeering of an ancient conserved response to manage energy/lipids. In this case, disease ensues if the capacity to manage excess energy crosses a critical threshold level [9]. To determine whether responses of caloric/lipid excess are a universal, conserved feature across metazoa, we created a simple *Drosophila* model to determine the effects of HFD-induced obesity and the conserved genetic pathways that may mediate its effects [9].

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A HFD regimen results in increases in triglyceride (TG) levels, signs of insulin and glucose dysregulation and deterioration of heart function in *Drosophila*, which are the hallmarks of HFD effects in mammals. A HFD also causes cardiac lipid accumulation, reduced cardiac contractility, conduction block and severe structural pathologies, perhaps similar to diabetic cardiomyopathies [9]. These results suggest that *Drosophila* may be a useful model of metabolic diseases including HFD-induced obesity, diabetes and heart disease.

Diabetes: Role of Insulin Pathway

Insulin signaling is known for its function in regulating metabolism and its involvement in type 2 diabetes. Although the molecular basis of regulating and coordinating these processes are far from being understood, they can dramatically influence metabolic responses as suggested by manipulation of components of these signal transduction pathways in species ranging from flies to humans [10].

The classical components of the insulin receptor (InR) pathway like insulin, the InR itself, insulin receptor substrate (IRS), phosphoinositide 3-kinase (PI3K), protein kinase B (PKB, a.k.a. Akt) and the forkhead box transcription factor (FOXO) are involved in metabolic homeostasis (Figure 1). The *Drosophila* insulin/IGF-1 signaling pathway is dedicated to growth control and metabolism. The *Drosophila* insulin receptor (InR) and IRS1-4 ortholog, chico, have equivalent amino acid sequence identity to the Insulin/IGF-1 receptors and IRS1-4 proteins, respectively, in vertebrates. Both have properties of the vertebrate Insulin and Insulin-like Growth Factor (IGF-1) receptors and IRS1-4 proteins – growth control as well as metabolic regulation, which highlights the functional conservation [11-13]. Because of these considerations, InR can be considered the evolutionary precursor to both the Insulin/IGF-1 receptors in vertebrates. The homology between InR and Insulin/IGF-1 receptors suggests that insulin/IGF-1 signaling may control metabolism in a manner similar to mammalian IR. Indeed, mutations in the genes coding for the *Drosophila* orthologs of the insulin/IGF-1 receptor and IRS1-4 proteins affect lipid and glucose metabolism [11-13].

Insulin activation of the PI3K branch results in increased PIP3 levels that lead to recruitment and activation of Akt/PKB that is counteracted by the lipid phosphatase PTEN. One important downstream target of Akt/PKB is the transcription factor FOXO, which is a member of the winged helix family of DNA binding proteins [14-16]. FOXO was first identified in *C. elegans* as Daf-16, which when mutated, suppresses the increased longevity caused by loss of Daf-2, the worm InR ortholog [17]. There is a unique evolutionarily conserved FOXO ortholog present in the *Drosophila* genome [18-20]. There are three mammalian FOXO genes (FOXO1, FOXO3a, and FOXO4). Akt/PKB mediates signaling from PI3K to FOXO by inhibiting FOXO function by phosphorylation. Upon insulin/IGF stimulation, Akt/PKB phosphorylates multiple sites on FOXO, which results in the blocking of DNA binding, exclusion from the nucleus, and inactivation of FOXO function [14-16]. Thus, FOXO functions as a negative regulator of the insulin/IGF pathway.

Typically, insulin resistance from obesity begins in peripheral tissues, which leads to an increase in blood glucose levels. However, this effect is kept in check by compensation from the pancreatic β cells that respond to hyperglycemia by increased insulin secretion that counteracts this rise. As long as the increased insulin secretion can match, diabetes does not develop. If the pancreatic β cells cannot compensate, then overt diabetes happens. So, two critical steps in the pathogenesis of diabetes are insulin resistance in the periphery and the ability of the pancreatic β cells to compensate.

Insulin Producing Cells and Insulin-like Peptides in *Drosophila*

HFD-induced obesity is also linked to the eventual loss of insulin production and type 2 diabetes. Acute loss of insulin production and signaling activity in adult *Drosophila* results in hyperglycemia, indicating that insulin regulates blood glucose homeostasis in this system as well [21-23]. *Drosophila* contains seven insulin-like peptides (ILPs). The DILPs display a spatial tissue expression pattern, which predominantly includes a specialized set of seven bilateral neuroendocrine cells (neurosecretory cells, NSC) within the CNS [24]. The DILP precursor proteins contain the signal peptide and the three conserved disulphide bonds, the proteolytic processing sites between the A and B chains [24].

The DILPs and mature mammalian insulin can activate the *Drosophila* InR, which suggests evolutionary conserved functions like insulin and IGF [24]. The bilateral set of seven median neurosecretory cells in the fly brain hemispheres co-express DILP2, 3, and 5 [21,25]. To show that the IPCs regulate changes in metabolism, the pro-apoptotic protein Reaper was specifically expressed in these neurons and resulted in the ablation of these neurons with concomitant loss of DILP2, DILP3, and DILP5 [21,25]. Ablation of the IPCs causes hyperglycemia, and DILP2 overexpression can reverse this effect [21,25]. Thus, the IPCs and DILPs are required for maintaining glucose metabolism in *Drosophila* in a functionally analogous role to the pancreatic β cells.

Blocking insulin signaling in the IPCs leads to lower DILP2 levels and hyperglycemia [23]. This effect may be functionally similar to the role of insulin signaling in mammalian pancreatic β cells, i.e. to regulate growth, survival, and insulin secretion [26,27]. For example, disruption of the IGFR gene in the whole animal reduces islet size and insulin secretion [28,29]. Despite IRS1 knock-out mice being smaller, their pancreatic β cells hypertrophy to compensate for increased peripheral insulin resistance [27]. In contrast, IRS2 knock-out mice are not smaller but their pancreatic β cells are absent due to increased cell death mediated by increased FOXO activation [27]. From the pancreatic β cell-specific insulin receptor and IGF receptor knock-out (β IRKO and β IGFRKO) mice, it is clear that insulin and IGF signaling play an important autonomous role in regulating pancreatic β cell functions [30,31]. One possible signal is insulin itself as the β IRKO mice lack a pancreatic β cell compensatory response caused by peripheral insulin resistance [32].

Nutrient Sensing TOR Pathway: Role in Obesity and Diabetes

We and others have hypothesized that the underlying cause of HFD-induced obesity is a dysregulated nutrient sensing network. One idea is that increased cellular lipid levels is mediated by the activation of the nutrient sensing TOR pathway, as the TOR pathway is a major and highly conserved regulator in the control of metabolism. A major component of the InR pathway is protein kinase B (PKB, a.k.a. Akt), which inhibits FOXO activity by phosphorylation, but is also thought to be a crucial link between InR and the nutrient-sensitive TOR pathway (Box 1). PKB/AKT does this by interfering with the tuberous sclerosis complex proteins (TSC1-2) and by FOXO-dependent upregulation of 4E-BP, which are negative regulators of TOR signaling [33]. In the past years, evidence has accumulated that these pathways are highly interrelated, involving extensive cross talk and coordination (Figure 1) [3,34]. TOR is a PI3K-related ser/thr kinase that regulates translation factors such as ribosomal protein S6 kinase (S6K) and eIF-4E binding protein (4E-BP). TOR can also be regulated by changes in the cellular levels of amino acids through Rag and Rheb GTPases, growth factors like insulin/IGF, and intracellular changes in the AMP:ATP ratio through AMP-activated protein kinase (AMPK) [33,35,36].

To determine which genetic pathways may be mediating these HFD-induced obesity responses, we assessed the role of the nutrient sensing TOR pathway in mediating HFD

responses on TG levels and heart function. Inhibition of the TOR pathway systemically prevents the increased triglyceride levels and decreased insulin signaling in flies fed a HFD and suggests that systemic reduction of TOR function protects against HFD-induced obesity despite the polygenic and multi-tissue complexity of obesity [9]. Recent work has delineated TOR-dependent tissue crosstalk that can non-autonomously alter the levels of the DILPs [9,23,37-39]. Importantly, TOR signaling is also required in the IPCs to control the levels of the DILPs. Furthermore, the insulin-TOR signaling pathway dramatically influences the functional aging characteristics of the *Drosophila* heart, including non-autonomously by reducing insulin production in the IPCs [40,41]. These results show not only that TOR signaling has important roles in both the periphery and within the IPCs but also the functional conservation to mammalian TOR signaling.

The TOR pathway has been implicated in mediating the effects of HFD-induced obesity in mammals. Loss of the TOR effector, S6K1, prevents lipid accumulation after HFD treatment, and ablation of the TORC1 component, raptor, in adipose tissue also prevents HFD-induced obesity, which suggests that adipose is a critical site for TOR to mediate its effect [42,43]. Furthermore, TOR signaling mediates nutrient (insulin and glucose) responses of pancreatic β cell growth and function [44-46]. Nutrients are important factors for pancreatic β cell growth and insulin production in normal states and have been proposed to mediate nutrient toxicity upon chronic exposure to the pancreatic β cell, leading to loss of pancreatic β cell survival and function [47,48]. Thus, the contribution of the nutrient sensing TOR pathway to pancreatic β cell growth and function is significant and likely complex. Furthermore, loss of TSC2 function in the pancreatic β cells results in increased TOR signaling, pancreatic β cell mass and insulin secretion, despite downregulation of insulin signaling (i.e., insulin resistance) and elevated ER stress [49-51]. Emerging evidence for a role of TOR effectors in pancreatic β cell growth and function is supported by the S6K1 knock-out mice in which insulin levels are decreased due to reduced pancreatic β cell mass [52,53]. Furthermore, m4E-BP1 knock-out mice display hypoglycemia, which shows that these TOR effectors may have differential regulation of glucose homeostasis [54]. It is also unknown where TOR pathway function is required in the body for glucose homeostasis as S6K1 knock-out mice have enhanced cell uptake of glucose in peripheral tissues, yet these mice are hyperglycemic, possibly due to blocked pancreatic β cell growth and insulin production [42].

Thus, there may be many levels where TOR signaling may positively and negatively regulate both pancreatic β cell function and peripheral insulin sensitivity, yet how TOR signaling regulates glucose homeostasis and pancreatic β cell function remains unclear, given the complexity of the possible interactions with the insulin pathway. It will be important to determine how TOR signaling regulates pancreatic β cell function and genetically interacts with insulin signaling to control metabolic homeostasis. Although TOR has been suggested as the cell autonomous nutrient sensor and insulin as the systemic sensor, the insulin and TOR pathways both have functions in the periphery and the pancreatic β cells, which suggests they can both act autonomously and non-autonomously in these capacities. The differences may relate to dosage/levels and whether the stimuli are chronic versus acute, cellular and physiological feedback, tissue specific environment, insulin-TOR effectors utilized, and disease context, all of which are critically important to interpret the results in the context of the physiological maintenance of metabolic homeostasis & pancreatic β cell function and the pathological progression of obesity and diabetes.

Obesity and Heart Disease

Importantly, diet-induced obesity is frequently attributed to many secondary diseases, including heart disease [55,56]. *Drosophila* is also the simplest genetic model with a heart [57], thus making it ideal for studying the basic principles of lipid metabolism and its effects on heart function. Moreover, we and others have established a variety of metabolic and heart-specific assays and manipulations in the *Drosophila* model that are relatively easy and efficient [23,40,41,58-62]. The relevance of current studies in *Drosophila* to mammals is further supported by recent evidence suggesting the control of cardiac physiology in mammals and flies requires regulators and effectors that are already known for their conserved role in cardiac development [63,64]. However, the genetics of the fat phenotypes are largely unknown and thus in need of investigation.

The mechanisms whereby obesity leads to metabolic syndrome remain to be fully elucidated. As epidemiological studies have linked high fat diets with heart disease [65], it is critical to determine the genetic basis underlying the cardiac defects. Chronic caloric excess leads to increased delivery of adipose-derived fatty acids (FA) and cytokines to insulin responsive tissues such as skeletal muscle and heart, which can result in toxic effects (termed cellular “lipotoxicity”) [66-71]. Lipotoxicity of muscle and other peripheral tissues is associated with insulin resistance, glucose impairment, lipid accumulation, and mitochondrial alterations, yet causal relationships have not been established. Moreover, the molecular mechanisms that can prevent or promote the cellular lipotoxic responses have not been defined. Even though obesity and/or diabetes are often associated with coronary artery disease, lipid overload has also a direct toxic effect on the heart causing cardiomyocyte and eventually organ dysfunction [66-71]. For example, transgenically mediated increases in lipid transport and synthesis or altering mitochondrial regulators in the myocardium leads to severe cardiac dysfunction and ensuing death [72-74]. These studies suggest that elevated adiposity and circulating lipids directly alter cardiac performance. However, the causal mechanism by which elevated lipid levels and mitochondrial dysregulation in cardiomyocytes cause cardiac functional defects is still a mystery.

Effects of HFD Treatment on Heart Function in *Drosophila*

Flies fed a HFD exhibit a decrease in heart beat length as well as decreases in diastolic diameter and fractional shortening [9]. Other cardiac defects include partial conduction blocks, non-contractile myocardial cells and dysfunctional inflow tracts. Reduction of TOR function can block the HFD-induced obesity phenotypes [9]. Tissue-specific inhibition of TOR signaling also indicates a prominent role for TOR signaling in both the adipose and heart to mediate HFD responses. These findings establish the conserved nature of the HFD effect on TG levels and heart function, and indicate that inhibition of the TOR pathway effectively prevents the detrimental effects of HFD on lipid accumulation and heart function. Thus, *Drosophila* is a useful model to study the genetic components that mediate HFD effects on fat metabolism and cardiac performance [9]. We anticipate that this *Drosophila* model will help us understand the basic mechanisms involved in lipid-heart interactions and further elucidate the role of the TOR pathway cascade in mediating obesity’s influence on the heart. Our model suggests that functionally conserved genetic cascades that control energy balance can modify the HFD response in *Drosophila*.

Role of Lipid and Mitochondrial Regulators

The regulation of lipid levels is mediated by a balance between lipid synthesis and lipid breakdown. For lipid biosynthesis, levels of phosphatidylethanolamine (PE), a major membrane lipid in insects [75,76], regulate sterol response element binding protein (SREBP) which responds to decreased levels of PE and thereby increases fatty acid synthase (FAS)

expression [77]. This result is in keeping with previous studies which found that loss of SREBP and FAS function leads to low TG levels [78]. Thus, findings from genetic *in vivo* analyses suggest that aberrant stimulation of SREBP signaling leads to defective lipid metabolism. For lipid utilization, lipid lipases like Brummer (Bmm)/Adipose triglyceride lipase (ATGL) are required for the breakdown of lipid droplets. The *Drosophila* Bmm encodes a triacylglycerol lipase, which is conserved from nematodes to mammals and has been shown to genetically interact with TOR signaling [9,23,79]. Bmm mutants have increased TGs, while ectopic Bmm expression results in decreased TG levels [79]. A recent study identified a key regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor- γ coactivator (PGC-1), in *Drosophila* [80]. PGC-1 controls mitochondrial biogenesis and functions in a necessary and sufficient fashion that is essential for cardiac physiology [74]. Furthermore, genetic screens have identified novel candidate factors involved in lipid utilization that will add interesting new areas to study [81,82].

We and others have identified insulin-TOR as a key regulator of these lipid metabolic processes and of PGC-1, a key regulator of mitochondrial biogenesis [23,74,80,83,84]. Altered insulin-TOR signaling leads to lipid metabolic changes through lipogenic regulators, like SREBP-FAS, and mitochondrial biogenesis, via changes in PGC-1 levels [85,86]. Likely, increased insulin-TOR signaling leads to elevated lipid levels via increased SREBP-FAS function [84]. This increased insulin-TOR signaling also leads to increased PGC-1 levels and mitochondrial biogenesis [80]. Thus, altered TOR signaling can modulate both basal lipid metabolism and HFD-induced obesity via changes in lipid metabolism and mitochondrial function, although the relationship between these processes still needs resolution and clarification.

Although insulin-TOR signaling can act as a nexus for these key lipid and mitochondrial regulators, it is not clear how they function in the lipid-heart relationship. Furthermore, little is known yet about the possible functions of the insulin-TOR pathway and the novel lipid and mitochondrial mediators in cardiac dysfunction caused by a HFD. Future work will determine the intricate relationship between the insulin-TOR pathways and lipid and mitochondrial regulatory genes in controlling HFD-related changes of cardiac structure and function. A basic genetic understanding of how fat accumulation causes cardiac dysfunction will serve as a prototype for similar studies in mammals, and thus is likely of significant impact to human health.

Obesity, TOR Signaling and Aging

The genetic influence on the rapidly expanding epidemic type 2 diabetes in the human, especially the Western populations, has been evident for some time, but only recently has it been given widespread attention. Furthermore, the frequency of type 2 diabetes increases with age, which suggests that metabolic homeostasis is more sensitive to disturbances later in life as a result of accumulating changes that predispose the organism to metabolic dysregulation [23,84,87-89]. However, the roles of the different tissues, timing and the pathways that contribute to age-dependent changes in metabolism are not completely known. Conversely, recent studies have shown that moderate reduction of TOR signaling can increase lifespan and block some age-dependent diseases, possibly by altering metabolism or mitochondrial function via a Dietary Restriction (DR)-like mechanism [23,84,87-89]. Although TOR is implicated in the DR response and metabolic homeostasis, many important areas remain to be studied. We need to understand how metabolism is altered with age and what dietary stimuli and pathways are capable of modulating these changes.

Concluding Remarks

Drosophila is a suitable genetic model to analyze the effects of HFD obesity and related diseases. Future studies will exploit the fly's genetic versatility and simple characteristics to study functional changes by a HFD and determine how the genetic components of the insulin-TOR pathways affect this organism's metabolism and aging by HFD. Determining the role of the insulin and TOR pathways in peripheral tissues and IPC in the context of lipotoxicity, the tissue communication that occurs via cellular and physiological feedback by insulin-TOR signaling, and the timing of the HFD effects all remain critical areas of research.

Box 1

Insulin-TOR Origins and Evolution

Given the importance of the insulin-TOR pathway interactions and the early evolutionary potential for developing obesity and diabetes [9], it is important to understand the possible origins of insulin and TOR pathways. The TOR pathway is evolutionarily more ancient than the insulin/IGF system as it predates insulin/IGF by approximately 1 billion years [90]. TOR is present in primitive plants, yeast, and animals, while the insulin/IGF system is essentially restricted to the animal kingdom (Figure I). We propose that the ancestral function of TOR is to reallocate energy stores for different growth options as a short-term adaptation to malnutrition and perhaps arose coinciding with increased energy availability due to increased atmospheric oxygen [91]. This idea is consistent with a shift to different utilization conditions depending on environmental status. A system that could integrate and balance these short-term fluctuations while minimizing loss of growth would provide a large evolutionary advantage. Significantly, the first recorded appearance of TOR in the evolutionary history of the yeast, plant, and animal kingdoms is in species that can alternate between unicellular and multicellular forms that typically depends on nutrient conditions. It is known that the transition from unicellularity to multicellularity evolved in different phyla multiple times [92]. Included in these phyla are slime molds (*Dictyostelium discoideum*, *Myxococcus spp.*), green algae (*Volvox carterii*), and yeast (*Mucor racemosus*). Under starvation conditions, these organisms can aggregate to form fruiting bodies that allow for greater dispersal of the spores to increase their chance of survival [93-96]. This effect is observed in dimorphic fungi (*Mucor racemosus*), whereby fermentation is used in the unicellular stage, while respiration is used in the multicellular fruiting body stage. It is known that rapamycin treatment of yeast (*Saccharomyces cerevisiae*) can regulate genes involved in the transition from fermentation to respiration (diauxic shift) [97-100]. This association between metabolic state and cellular status suggests that an early benefit of TOR function may have been to regulate the alternation between different metabolic states and thus TOR may have been involved in the transition between unicellularity and multicellularity.

Figure I. Appearance of insulin and TOR during evolution. This phylogenetic tree shows the relationships of the major groups of organisms. The tree is constructed from comparative analysis of the sequence of bases on RNA molecules from organisms in each group (adapted from [101]).

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Figure 1.

Simplified model of nutrient signaling pathways influencing metabolic responses. InR and TOR pathway components are virtually all unique orthologous genes in *Drosophila*. TOR signaling also receives inputs from the energy sensing AMPK. Future studies will elucidate how the components of the InR-TOR signaling pathway modulate fat accumulation due to high levels of dietary fats, using the versatility and genetic simplicity of the *Drosophila* model. Unlike the complexity and interrelation between these pathways in mammals, *Drosophila* is ideal to study their role in controlling complex traits like HFD effects on disease.