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Drosophila as a Model for Interorgan Communication: Lessons from Studies on Energy Homeostasis

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Current studies of physiological communication between *Drosophila* organs are beginning to address the fundamental problem of how nutrients regulate organismal growth, stem cell behavior, immunity, and aging. Advances in the *Drosophila* genetic tool kit will allow the design of genetic screens to systematically identify factors involved in organ communication.

Understanding the genetic basis of heredity, the organization of cells and their signaling pathways, and the mechanisms of development, physiology, homeostasis, and aging are among the most important questions in biology. *Drosophila*, as a model system, has contributed fundamental insights into many of these processes. Here we argue that *Drosophila* is a prime genetic model for investigating the "integrative physiology" of an organism, i.e., analyzing the function of an organ in the context of its interaction with others.

For an organism to function effectively under varying environmental conditions, its organ systems must adapt to maintain a steady state, a process referred to as "homeostasis." Such homeostasis is exemplified in desert animals like camels, which have evolved physiological strategies that alter their water metabolism in accordance with its availability, hence permitting the animal to survive for weeks without drinking water. Other striking examples include hibernating animals, such as the ground squirrel, that slow their metabolic rates, leading to a reduction in body temperature in response to decreased food availability in winter. These stratagems are made possible by communication between organs, those that sense the environmental conditions such as light, temperature, nutrients, or pathogens (the "sensor" organs) and those that respond to signals from the "sensors" and maintain physiological homeostasis.

The coordination of food intake and utilization of nutrient stores with energy requirements is a key homeostatic mechanism in an organism referred to as "energy homeostasis." Our understanding of the interplay between the different organ systems involved in maintaining energy homeostasis has largely originated from studies in model organisms such as the mouse. For instance, murine models led to the discovery of Leptin, a molecule that regulates systemic energy homeostasis by linking the animal's fat stores with caloric intake. Leptin functions as a "satiety" signal that is released from the adipose tissue in proportion to fat stores and that impinges on the hypothalamic brain circuits to increase energy expenditure and inhibit feeding (Farooqi and O'Rahilly, 2009). Humans with rare loss-of-function mutations in the Leptin gene are clinically obese due to abnormalities in energy expenditure and increased food intake; such symptoms can be reversed by Leptin replacement therapy. Studies such as these reveal the importance of coordination between organ systems for homeostasis.

In this Essay, we argue that *Drosophila* is an emerging model system for studying interorgan communication. Below, we introduce the role of different organ systems in *Drosophila* involved in energy homeostasis. We highlight a number of recent studies that provide insights on how the flies' nutritional status intersects with other fundamental biological processes such as the control of tissue and organismal growth, cell proliferation, circadian rhythm, immunity, and aging. Finally, we discuss how recent advances in the *Drosophila* genetic tool kit enable the design of screens to identify new signaling systems involved in organ communication.

Organ Systems in *Drosophila*

Fruit flies have organ systems that regulate food intake and energy metabolism, facilitate responses to pathogens, and maintain a circadian rhythm. Flies are quite different from mammals in that they have an open circulatory system (the hemolymph) and do not have organs such as the pancreas and liver. Nevertheless, they have clusters of cells and tissues that are functionally analogous to their well-organized counterparts in mammals (Figure 1). Specifically, the fat body (FB) functions as the white adipose tissue and mediates many of the effects of nutrition on the other organs. It stores fats in the form of triacylglycerols and stores sugars in the form of glycogen. Circulating sugar levels are maintained by a group of median neurosecretory cells (mNSCs; akin to pancreatic beta cells) located in the brain that release *Drosophila* insulin-like peptides (Dilps) in response to increased circulating sugars and results in their storage as glycogen in the FB (Rulifson et al., 2002). Conversely, the FB signals back to the mNSCs to control Dilp secretion; this feedback forms part of a core mNSC circuit that is essential for maintaining glucose homeostasis. In addition, recent studies have shown that the fly skeletal muscles are involved in the regulation of systemic growth (Demontis and Perrimon, 2009), as well as metabolism and aging (Demontis and Perrimon, 2010).

In mammals, the brain functions as a key integrator of various physiological states from other organs to maintain homeostasis. In the next section, we will discuss in particular some studies that

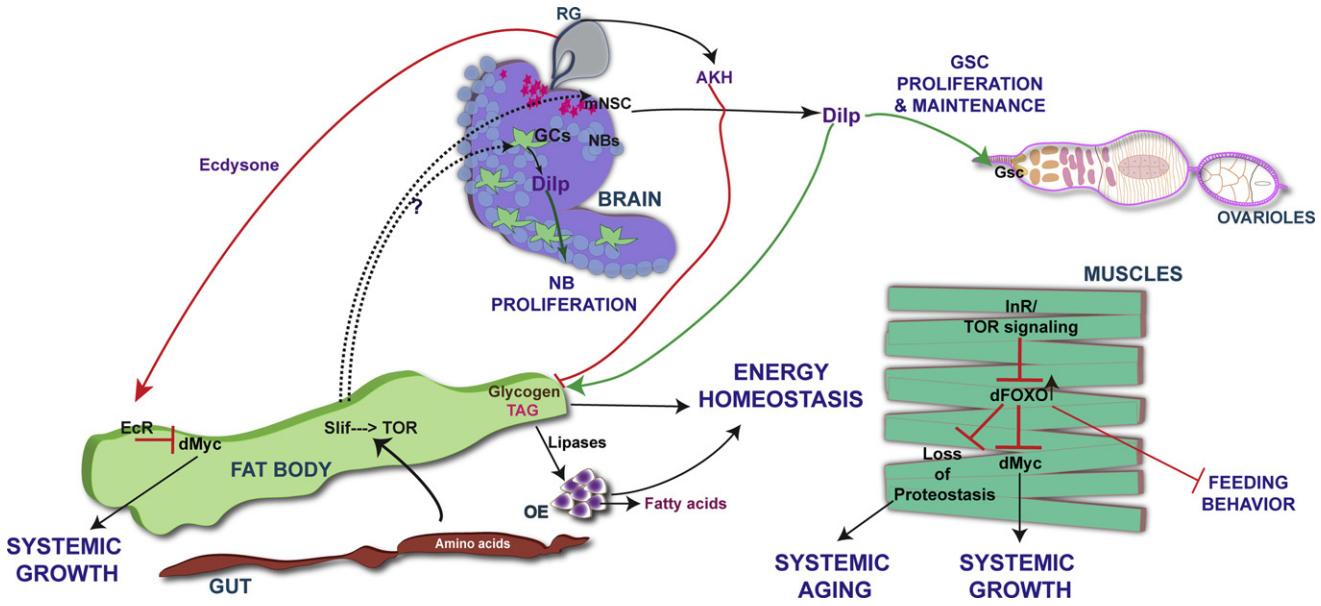

Figure 1. Interorgan Communication and the Coordination of Energy Status with Biological Processes
Tissue/organ names are in blue. The outcome of the interactions is represented in green. Hormone names are in purple. AKH: adipokinetic hormone; Dilp: *Drosophila* insulin-like peptide; GC: glial cells; GSC: germline stem cells; mNSC: median neurosecretory cells; NB: neuroblasts; OE: oenocytes; RG: ring gland; TAG: triacylglycerol.

demonstrate how various organs in *Drosophila*, such as the FB and muscles, can signal their physiological state to the brain.

Coordination of the Energy Status of the Fly with Biological Processes

Regulation of Systemic Growth

Drosophila has been used extensively as a model to answer questions pertaining to the physiology of growth control, in particular the coordination of nutritional availability with growth and maturation. The fly transitions through different stages (embryo, three larval instars, pupa, and adult) during its 10 days of development. During each transition, pulses of 20-hydroxyecdysone (ecdysone is a steroid thta signals through nuclear hormone receptors) are released from the prothoracic gland (PG). The PG is part of the *Drosophila* ring gland, and it "senses" that the organism has reached a critical weight appropriate for transitioning to the next developmental stage. Ecdysone, released by the PG, impinges on the FB where it upregulates the transcription factor dFOXO, which in turn inhibits insulin-like signaling (IIS). In addition, ecdysone inhibits dMyc—a transcription factor regulating the G1-S cell-cycle transition—in the FB, which in turn inhibits systemic growth (Delanoue et al., 2010). dMyc plays a similar role in regulating systemic growth in fly skeletal muscles (Demontis and Perrimon, 2009). When IIS is inhibited in the muscles, it results in dFOXO activation, which downregulates dMyc. This reduction in dMyc activation in the muscle results in reduced growth of not only the muscles but also other larval tissues, most likely due to reduced feeding.

The FB has a key role as a nutritional sensor during systemic growth. Knocking out the amino acid transporter *slimfast* (*slif*) in the FB results in systemic reduction of growth (Colombani et al., 2003). It has been demonstrated that the FB, via a yet-unknown signal, controls systemic growth by remotely controlling Dilp secretion from the mNSCs. Secreted Dilp promotes growth in peripheral tissues by activating the IIS pathway.

Stem Cell Proliferation

Systemic IIS also couples nutritional availability with stem cell behavior. Recent work has reported that when *slif* is inactivated in the FB, it results in reduced entry of neuroblast (NB; multipotent neural cells) into the mitotic state (Sousa-Nunes et al., 2011). The mitogenic signal derived from the FB also activates Dilp secretion in glial cells, which in turn controls the exit of the NBs from quiescence (Chell and Brand, 2010; Sousa-Nunes et al., 2011). Dilps, secreted by mNSCs, humorally regulate the proliferation and self-renewal of *Drosophila* germline stem cells. Ablation of Dilp-producing mNSCs results in the reduction in egg production and vitellogenesis (LaFever and Drummond-Barbosa, 2005). These studies illustrate how the nutritional state of an organism impinges on stem cell proliferation and reproductive potential.

Aging

IIS has been extensively investigated for its role in organismal aging. Strikingly, the activation of dFOXO in skeletal muscles is able to decelerate systemic aging (Demontis and Perrimon, 2010), reducing accumulation of protein aggregates in aged flies, decreasing feeding, and reducing Dilp secretion from the mNSCs. Likewise, FB dFOXO can influence aging via effects on Dilp secretion from mNSCs. The mechanism by which the release of Dilp affects protein aggregation, as well as how reduced feeding impacts aging, remains to be clarified.

Circadian Rhythm

Brain regions that regulate the sleep-wake cycle in the fly have been identified, and the molecular cascade of circadian components in flies exhibits a high level of conservation with mammals. Recent work highlights an intriguing link between the circadian clocks and energy homeostasis.

Flies exhibit a rhythmic feeding behavior pattern that is independent of exposure to light (Xu et al., 2008) but is mediated by rhythmic oscillations of the circadian machinery in the FB. Disruption of this "peripheral clock" results in increased feeding and starvation sensitivity (Xu et al., 2008). Also, it has been shown that starvation suppresses sleep in *Drosophila* (Keene et al., 2010). Altogether, these studies suggest that in *Drosophila*, as in mammals, two homeostatic processes of sleep and feeding are tightly interrelated.

Immunity

Innate immunity in *Drosophila* is mediated by the evolutionarily conserved Toll and IMD pathways. Given that an effective immune response is an energy-intensive process, recent studies have examined the interaction between innate immunity and metabolic homeostasis. Toll pathway activation during infection counteracts the action of IIS on dFOXO subcellular localization in the FB. Toll activation drives the nuclear accumulation and therefore activation of dFOXO, resulting in growth inhibition (DiAngelo et al., 2009). In addition, epidermal DNA damage induces an innate immune response, which in turn represses Dilp transcription in the mNSCs. This repression allows the animal to adapt to the stress induced by DNA damage at the expense of systemic growth, resulting in increased survival poststress (Karpac et al., 2011). Such studies demonstrate the interaction between immunity and growth homeostasis in fruit flies.

Genetic Screens to Identify Factors Involved in Organ Communication

The selected examples described above exemplify the power of *Drosophila* as a model to garner a comprehensive understanding of integrative physiology. Further, they underscore the importance of organ communication mechanisms that allow tissues to sense the physiological status of others, which in turn may affect their own physiology, growth, proliferation, and aging (Figure 1). The next few years should prove to be a golden age for *Drosophila* as a model for integrative physiology since powerful tools for tissue-specific transgenic RNAi that allow knockdown of every gene in the genome are now available or are being built. In addition, new systems for binary expression such as the Q system have been developed, allowing conditional perturbations of different genes in different tissues (Potter et al., 2010).

Thus, to identify communication pathways between tissues, one could first examine how genetic changes in one tissue (Tissue A; e.g., muscle) affect gene expression in another tissue (Tissue B; e.g., fat body and brain). Next-generation sequencing methods in particular can now be systematically applied to examine these effects. Such studies may reveal how biological processes observed in Tissue A, such as decreased cellular metabolism and mitochondrial dysfunction, influence processes such as cell proliferation and aging in Tissue B. Further, one could then use some of the genes expressed in Tissue B in response to Tissue A perturbation as sensors in genetic screens. In particular, screening for knockdown and/or overexpression of the putative secreted proteins in *Drosophila*, i.e., the "secretome," by overexpression or knockdown in Tissue A and by studying its effects on Tissue B will be insightful. For instance, in Tissue A the UAS/GAL4 system (Brand and Perrimon, 1993) can be used to regulate expression of the secretome (e.g., *Tissue-A-GAL4>UAS*-secreted protein-RNAi); this can be combined with a GFP reporter of a gene in Tissue B that is known to be responsive to perturbations in Tissue A (e.g., *Tissue-B "sensor" promoter-QF>QUAS-GFP*). Such screens will allow the identification of genes that function in Tissue A to influence the physiology of Tissue B.

Altogether, given the sophisticated genetic tools and characterization of interactions between organ systems, *Drosophila* is poised to broaden our knowledge regarding the "integrative physiology" of organisms.

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