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Interorgan Communication Pathways in Physiology: Focus on *Drosophila*

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interorgan communication, interorgan communication network, secreted factor, myokine, adipokine, secretion

Abstract

Studies in mammals and *Drosophila* have demonstrated the existence and significance of secreted factors involved in communication between distal organs. In this review, primarily focusing on *Drosophila*, we examine the known interorgan communication factors and their functions, physiological inducers, and integration in regulating physiology. Moreover, we describe how organ-sensing screens in *Drosophila* can systematically identify novel conserved interorgan communication factors. Finally, we discuss how interorgan communication enabled and evolved as a result of specialization of organs. Together, we anticipate that future studies will establish a model for metazoan interorgan communication network (ICN) and how it is deregulated in disease.

INTRODUCTION

Organ functions are highly specialized. For example, nutrients are taken up through the gut; sensed, processed, stored, and released by the liver and adipose tissues; and utilized by the peripheral organs. Nutrients are used by the skeletal muscle and heart for contraction, by the brain for behavior, by the kidney for water balance and waste disposal, by the gonads for reproduction, and by other tissues for growth (**Figure 1**) (136, 148). In addition, each organ depends on other organs. For instance, increased physiological demands such as exercise, brain activity, growth, and disease require increased nutrient uptake by the gut and nutrient release (sugars, fats, ketone body) by the liver and adipose tissues (136, 148). Because organ functions are interdependent, it is important to understand how organs communicate their states to each other. In this review, we focus on the identification of factors that mediate communication between organs. In particular, we focus on the fruit fly *Drosophila melanogaster*, which offers the advantages of having organ systems with similar functions to humans, and powerful genetic tools. Importantly, many of the *Drosophila* organ communication factors identified to date have human orthologs.

IDENTIFICATION OF INTERORGAN COMMUNICATION FACTORS IN MAMMALS

Experiments in mammals and other vertebrates have identified important interorgan communication factors. As a number of recent reviews (34, 37, 65, 107, 117) have described mammalian

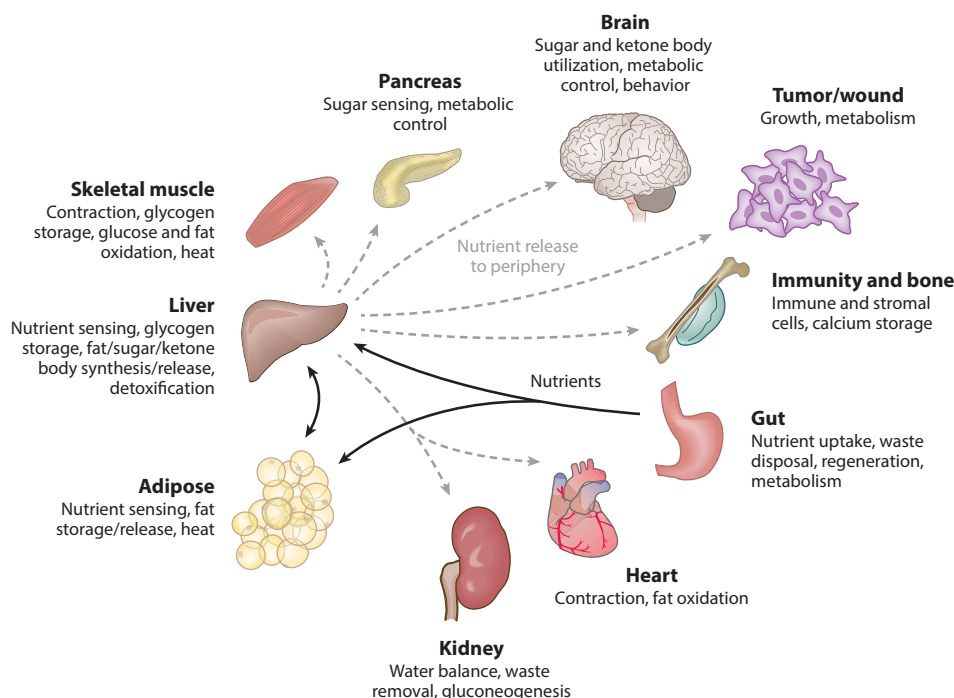


Figure 1

A simplified view of organ specialization and integration in mammals (136, 148). Nutrients are taken up by the gut (black arrows) and then sensed, processed, stored, and released to peripheral organs by the liver and adipose tissues (gray dashed arrows). Increased physiological demands enhance nutrient traffic to certain organs. For instance, during exercise, muscles require increased fatty acids and glucose from the liver and adipose tissues.

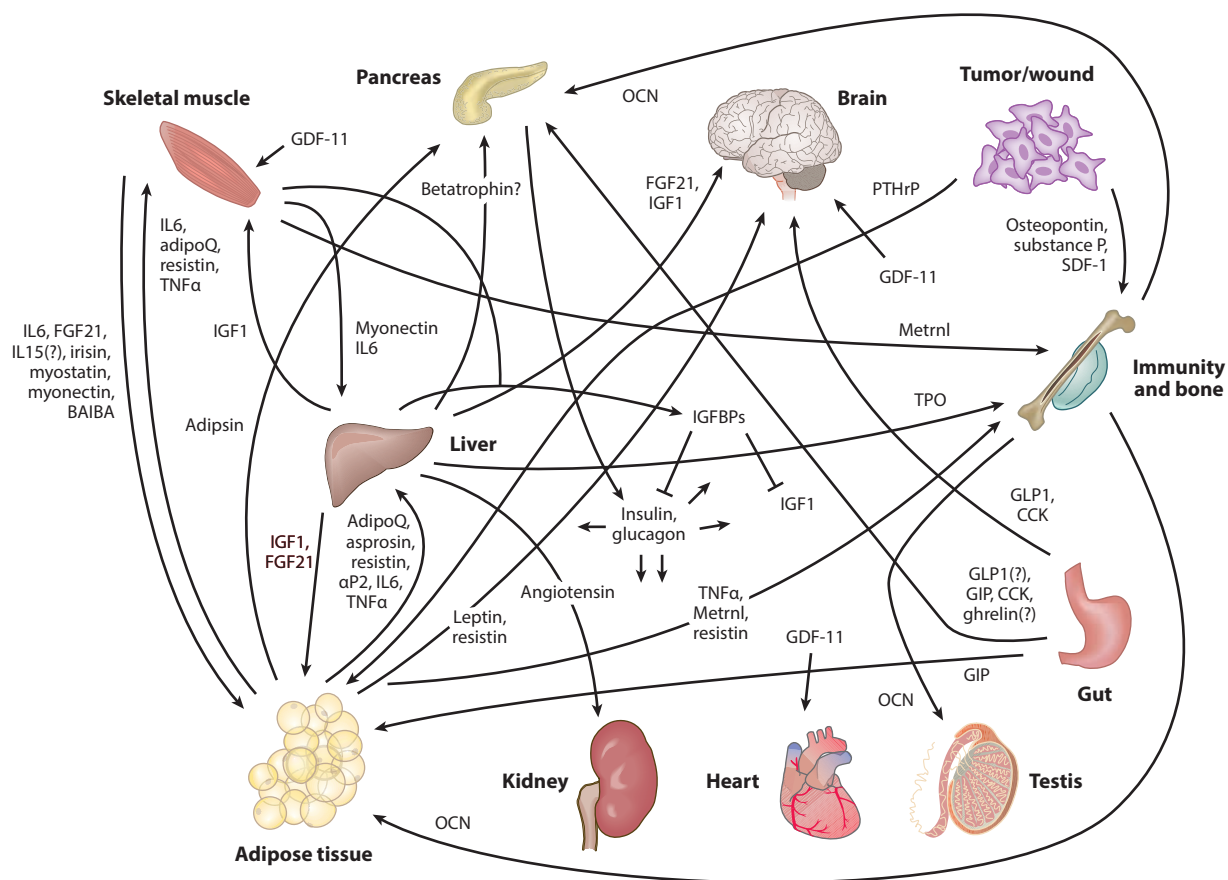


Figure 2

Selected recent examples of mammalian interorgan communication factors, their origins, and destinations; also see **Table 1**. Selected recent references for these factors: adipoQ (adiponectin) (154), adipon (89), angiotensin (55), aP2 (19), asprosin (126), BAIBA (β -aminoisobutyric acid) (124), betatrophin (53, 157), CCK (cholecystokinin) (84, 88, 120), FGF21 (42), GDF-11 (growth differentiation factor 11; tissue source is unclear) (39, 67, 90, 113, 138), ghrelin (94, 97), GIP (gastric inhibitory polypeptide) (18), GLP1 (glucagon-like peptide-1) (36, 140), glucagon (136, 148), IGF1 (insulin growth factor 1) (13, 24), IGF1 (insulin growth factor binding proteins) (61), IL6 (112, 128), IL15 (112), insulin (136, 148), irisin (12), leptin (2, 100, 144, 158), metnrl (meterorin-like) (119), myonectin (133), myostatin (95), OCN (osteocalcin) (79, 106), osteopontin (93), PTHrP (parathyroid hormone related protein) (70), resistin (8, 64, 101, 130, 143), SDF-1 (116), substance P (59), TNF α (tumor necrosis factor α) (46, 60, 142), and TPO (thrombopoietin; also made by kidney) (31, 68).

systemic factors in detail, here we highlight only a few recent examples (see **Figure 2**, **Table 1**, and references therein for an overview). Adipose tissue and muscle-derived growth factors and cytokines—adipokines and myokines, respectively—have been recently recognized for their roles in organ cross talk (107). For instance, regulated by stored nutrients, the adipokine leptin is secreted from adipose tissue and acts on neuroendocrine organs via the leptin receptor (2, 144, 158). Also, fibronectin type III domain-containing protein 5 (FNDC5) transmembrane protein cleavage product irisin is derived from muscle during exercise and regulates adipose tissue browning and metabolism (12). In addition, transforming growth factor (TGF)- β family member growth differentiation factor 11 (GDF-11) regulates the aging heart, muscle stem cells, and brain vasculature (67, 90, 113, 138, but see controversy in 39, 132). Interestingly, parathyroid hormone related

TGF: transforming growth factor

Table 1 Selected recent examples of mammalian interorgan communication factors, their origins, and destinations (also see Figure 2)

Factor	Communication axes	Reference(s)
Irisin	Muscle → adipose tissue	12
Myostatin	Muscle → adipose tissue	95
IL6	Muscle → adipose tissue, liver	112, 128
IL15 (?)	Muscle → adipose tissue	112
Myonectin	Muscle → adipose tissue, liver	133
BAIBA (β -aminoisobutyric acid)	Muscle → adipose tissue	124
FGF21	Muscle → adipose tissue	42
AdipoQ (adiponectin)	Adipose tissue → muscle, liver	154
Asprosin	Adipose tissue → liver	126
Resistin	Adipose tissue/blood monocytes → muscle, brain, liver	8, 64, 101, 130, 143
IGF1	Liver → adipose tissue, muscle	13, 24
Adipsin	Adipose tissue → pancreas	89
aP2	Adipose tissue → liver	19
Leptin	Adipose tissue → brain	2, 100, 144, 158
Betatrophin (?)	Liver? Adipose tissue? → pancreas?	53, 157
Angiotensin	Liver → kidney	55
Insulin growth factor binding protein	Pancreas → multiple organs	136, 148
Glucagon	Pancreas → multiple organs	136, 148
Insulin-s	Liver, muscle → bind to insulin, insulin growth factors	61
Metnrl (meterorin-like)	Adipose tissue, muscle → immune system	119
TNF α	Adipose tissue → immune system, muscle, liver	46, 60, 142
GLP1 (glucagon-like peptide-1)	Gut → pancreas?, brain	35, 136
GIP (gastric inhibitory polypeptide)	Gut → pancreas	18
CCK (cholecystokinin)	Gut → pancreas, brain	84, 88, 120
Ghrelin	Gut → pancreas?	94, 97
PTHrP	Tumor → adipose tissue	70
GDF-11	Unclear organ source → muscle, heart, brain	39, 67, 90, 113, 132, 138
TPO (thrombopoietin)	Kidney, liver → bone/hematopoiesis	31, 68
Osteopontin	Tumor → bone/immunity	93
Substance P	Tumor → bone	59
SDF-1	Wound → bone	116
OCN (osteocalcin)	Bone → testis, adipose tissue	79, 106

protein (PTHrP) released systemically from tumors regulates adipose tissue wasting, or cachexia, through the G-protein-coupled PTH receptor (70).

A number of questions for future studies remain. For instance, the nature of the irisin receptor (151) and the organ source of GDF-11 (90) are unclear. In addition, could systemic factors also have a local function? For example, leptin may be sensed by neurons within the adipose tissue (100), whereas the intestine-derived peptide cholecystokinin (CCK) might regulate insulin secretion (88) via local release from pancreatic neurons (120). Also, tissue-specific loss-of-function studies of the incretin glucagon-like peptide 1 (GLP-1) receptor suggest that postprandial gut-derived GLP-1 may increase insulin secretion not systemically through the circulation as previously proposed

but instead through paracrine mechanisms (neurons near the gut, other pancreatic cells, etc.) (36, 140). Moreover, the physiological relevance of stomach-derived peptide ghrelin to food uptake, postprandial insulin secretion, and its systemic role (ghrelin can be secreted by the pancreatic islets themselves) has been questioned (94, 97). Finally, the question of conservation of a mouse-secreted factor and its mechanism of action to humans needs to be addressed. For example, cysteine-rich cytokine resistin is derived from adipocytes in the mouse, whereas in humans, resistin is found in blood monocytes but not in adipocytes (130).

Studies in nonprimate mammalian systems have been instrumental in identifying interorgan communication factors, and advantages include the availability of tissues and cells for biochemistry and proteomics, and the likelihood of a given factor to be conserved to humans. Loss-of-function genetic studies are essential to show the function of a systemic factor. For example, overexpression of angiopoietin-like protein 8 (ANGPTL8) betatrophin was reported to induce β -cell proliferation (157); however, betatrophin knockouts showed no phenotype on β -cell proliferation (53). In addition, the roles of many secreted proteins in interorgan communication remain to be investigated. Human normal and diseased blood contains thousands of proteins (40, 87). Moreover, human adipocytes (80) and myocytes (57) secrete hundreds of proteins *in vitro*. A number of these proteins have poorly characterized functions, and we expect some to have signaling functions. However, large-scale systematic *in vivo* functional studies (genetic screens) are challenging in mammals. Thus, invertebrate genetic model systems such as *Drosophila* are expected to contribute significantly to discoveries in interorgan communication.

In this review, we describe *Drosophila* as a genetic model system for understanding principles of interorgan communication. We present the secreted factors, their physiological inducers, mechanisms of action, and how they are integrated together to regulate physiology. Also, based on evolutionary considerations, we describe how interorgan communication enabled and evolved as a result of specialization of organs. Finally, we discuss how future studies in *Drosophila* may lead to an interorgan communication network (ICN) (37) conserved to humans and deregulated in disease.

DROSOPHILA AS A MODEL SYSTEM TO DISSECT INTERORGAN COMMUNICATION

Drosophila Has Functionally Equivalent Organ Systems to Mammals

Drosophila is an emerging model system for studying interorgan communication. Importantly, *Drosophila* has functionally similar organs to the human digestive tract, gonads, liver and adipose tissue [fat bodies (FBs) and oenocytes in flies], muscle, brain, and others (Figure 3) (4, 35, 81, 109). In addition, like in mammals, *Drosophila* organs are specialized and integrated. For instance, nutrients are taken up through the gut; sensed, processed, stored, and released by FBs and oenocytes; and utilized by the peripheral organs. Nutrients are used by the muscle and heart for contraction, by the brain for behavior, by the gonads for reproduction, and by developing organs (imaginal discs) and other tissues for growth (Figure 4). Moreover, increased physiological demands such as exercise, brain activity, growth, and disease require increased nutrient uptake by the gut and nutrient release by the FBs and oenocytes (4, 35, 81, 109).

Drosophila proceeds through embryonic, larval, pupal, and adult life stages. Both larva and adults have FBs, oenocytes, muscles, heart, brain, and gut (4, 35, 81, 109). However, the physiological and environmental differences between the stages lead to additional specialized organs. For instance, larvae have an actively developing hematopoietic system, dividing muscle precursors, a brain containing dividing neural precursors, and developing adult organs (imaginal discs), including wings, eyes, gonads, and others. By contrast, adults have a fully developed nondividing brain,

FBs: fat bodies



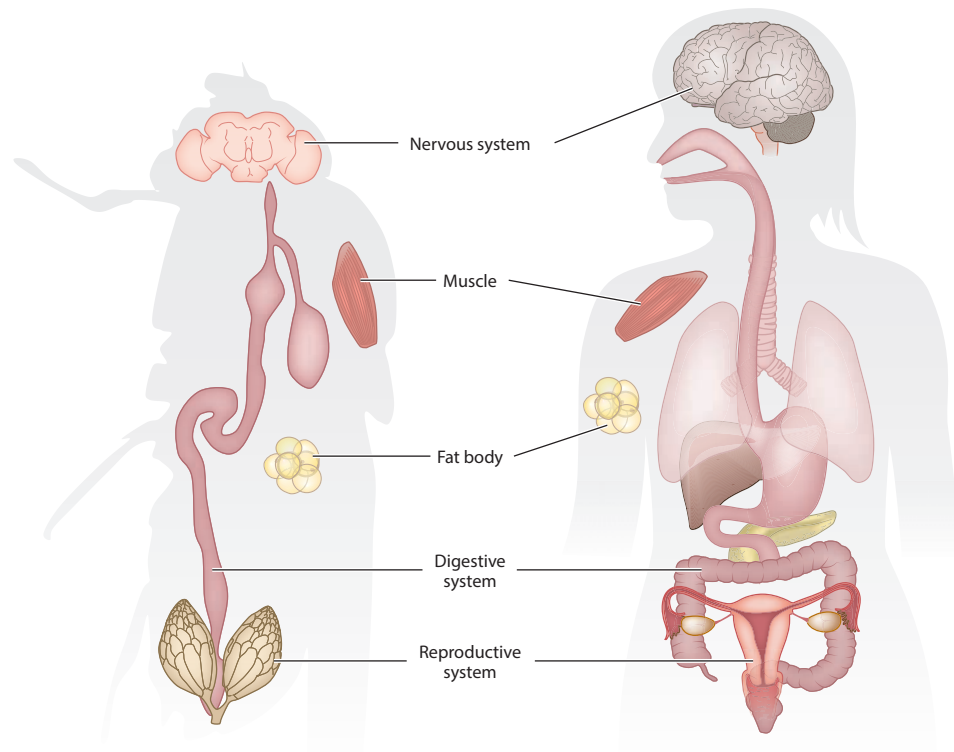


Figure 3

Drosophila melanogaster has functionally equivalent organ systems to the human liver/adipose tissues (fat bodies and oenocytes in *Drosophila*), gut, brain, muscle, gonads, and others (4, 17, 35, 81, 109). This allows the study of interorgan communication using the powerful genetic tools available in flies.

hematopoietic cells, muscles, wings, eyes, and gonads, but have dividing stem cells in the gut and gonads (4, 17, 35, 81, 109). In sum, larvae are a model for growing, developing organisms, whereas adults are a model for homeostatic regulation of metabolism, reproduction, tissue homeostasis, and aging.

***Drosophila* Interorgan Communication Factors**

A number of conserved interorgan communication factors have been identified over the years—many recently—in *Drosophila* larva and adults using genetic approaches (summarized in **Table 2** and **Figures 5–9**).

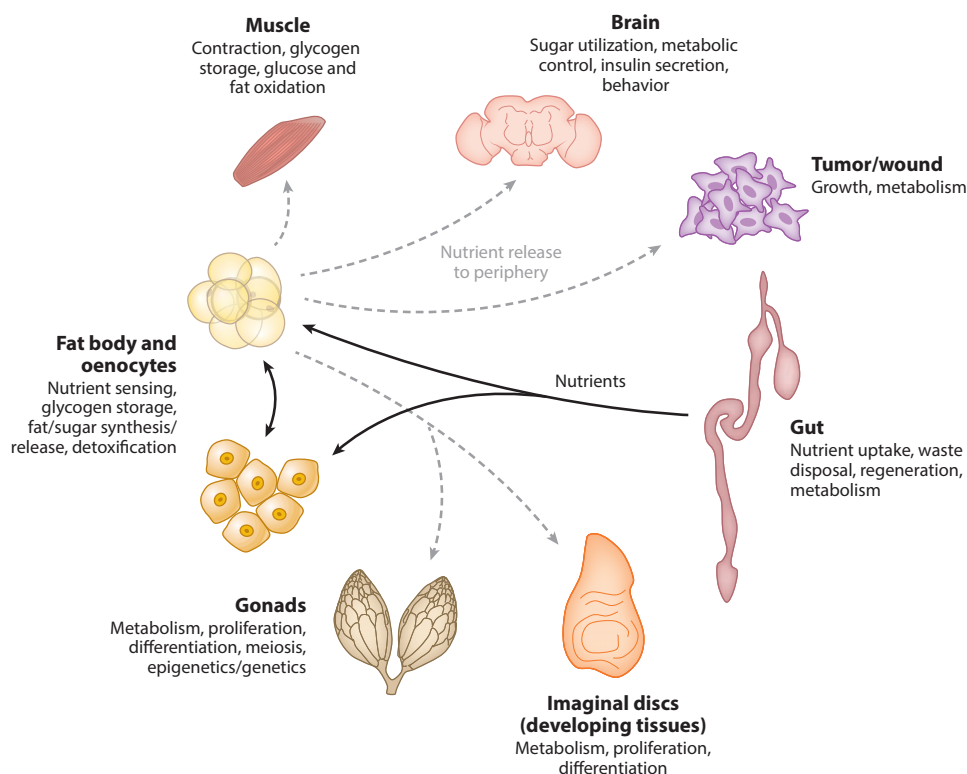
***Drosophila* Brain-Derived Systemic Factors**

Drosophila brain-derived systemic factors include insulin-like peptides, secreted decoy of InR, and γ -aminobutyric acid.

***Drosophila* insulin-like peptides 2, 3, and 5.** *Drosophila* insulin-like peptides (Dilps) and mammalian insulin and insulin-like growth factors (IGFs) are homologous (15, 102, 152). In mammals,

Dilps: *Drosophila* insulin-like peptides

IGFs: insulin-like growth factors

**Figure 4**

A simplified view of organ specialization and integration in *Drosophila* (4, 17, 35, 81, 109).

insulin is produced by β -cells, whereas in *Drosophila*, Dilps 2, 3, and 5 are secreted from median neurosecretory cells [insulin-producing cells (IPCs)] of the brain (15, 62, 102, 127, 152). Insulin and Dilps act through the highly homologous insulin receptor (InR) on all organs to increase growth, nutrient storage, and anabolism (15, 62, 102, 127, 152). In adults, Dilps also regulate germline stem cells (GSCs) (75) and aging (145). It will be important to discover the functional differences between *Drosophila* Dilps (102).

Secreted decoy of InR. Secreted decoy of InR (SDR) is an extracellular Dilp binding protein that is orthologous to InR. In *Drosophila* larva, SDR is secreted from glial cells on the surface of the brain. SDR binds to and inhibits Dilp function, negatively regulates growth, and is necessary for starvation resistance (104). It is not clear what regulates SDR secretion (104). In mammals, soluble decoy versions of transmembrane receptors have been identified (91); soluble InR can be generated by transcript termination before the transmembrane domain (149).

γ -aminobutyric acid. Larval olfaction induces secretion of the neurotransmitter γ -aminobutyric acid (GABA) into the hemolymph (insect functional equivalent of blood) (4, 109) from brain neurons (135). GABA targets the GABA_B metabotropic receptor on the hematopoietic lymph gland, induces intracellular calcium signaling, and preserves hematopoietic progenitor cells, suggesting that environmental sensing can be translated into a change in physiology of an organism. It

IPCs:

insulin-producing cells

GSCs: germline stem cells

Hemolymph:

insect equivalent of vertebrate blood; bathes organs and provides a medium for interorgan communication

Table 2 *Drosophila* interorgan communication factors

<i>Drosophila</i> factor	Mammalian ortholog	Developmental stage	Physiological inducer	Origin	Destination	Receptor	Effect	Questions	Reference(s)
Dilp2, 3, 5	Insulin	Larvae and adults	Food uptake	IPCs	All organs	InR	Increased growth, nutrient storage, anabolism; regulation of germline stem cells, aging	Why are there so many insulins in <i>Drosophila</i> ?	15, 62, 75, 102, 127, 145, 152
Dilp6	Insulin	Larvae and adults	Cessation of feeding (pupariation, starvation)	FB	Oenocytes, imaginal discs, IPCs (?)	InR	Take up lipids (oocytes), promote growth (imaginal discs), decrease Dilp secretion	Relationship to other insulins? Paracrine from local FB?	7, 21, 105, 139
Impl2	IGFBP7	Larvae and adults	ISC overproliferation; muscle mitochondrial damage; starvation	Gut, muscle, FB	Blood, organs	Insulin	Binding to insulin (inhibits insulin)	Relationship to other insulin binding proteins?	41, 74, 108
SDR	InR (soluble)	Larvae	Unknown	Brain glia	Blood, organs	Insulin	Binding to insulin (inhibits insulin)	Relationship to other insulin binding proteins? Inducer?	104
Ucp2	Leptin	Larvae and adults	Dietary sugar/fat	FB	Neurons regulating IPCs	Dome	Increase insulin secretion	Presence in blood? Crossing of BBB? Sensing by peripheral neurons? Additional FB-derived signals in response to other nutrients? Relationship to CCHa2 and GBPs?	118
Egr	TNF- α	Larvae and possibly adults	Low dietary protein (through TACE induction)	FB	IPCs, FB	Gmrd	Decrease insulin secretion; decrease growth; and (in high sugar conditions) increase insulin resistance (larva). Increase TAG upon protein starvation (adult).	BBB crossing? Hemolymph interacting proteins? Is insulin affected in adults? How is TACE induced downstream of TOR? Functional homology to AdipoQ?	1, 134

Dilp8	Insulin/rexin family	Larvae	Injury/tumors	Injured organs (imaginal discs)	Lgr3 neurons	Lgr3?	Inhibition of insulin and PTTH/JH signaling to inhibit growth and pupariation	Is endogenous Dilp8 present in blood? Crossing of BBB? Functions in adults? Is Lgr3 is the bona fide Dilp8 receptor?	26, 27, 48, 49, 147
Lst	NMU?	Adults	Food restriction	CC cells	IPCs	LstR (CG9918)?	Decrease insulin secretion	Presence in blood? Other sites of limostatin action? Is LstR the bona fide Lst receptor?	3
AKH	Glucagon	Larvae and adults	Starvation	CC cells	All organs	AKHR	Metabolism; increased catabolism of sugar and fat in fat body; regulation of life span, food search, sleep, resistance to oxidative stress	Systemic factors regulating AKH?	47, 51, 66, 69, 78, 96, 150
Myo	Myostatin, GDF11	Adults	?	Muscle	FB	Babo? Wit?	Decrease FB nucleolar size and rRNA; increase life span	Physiological inducer? Presence in blood? Relationship to Daw?	32
Daw	TGF- β	Larvae and adults	Dietary sugar	FB, muscle, others?	Gut, FB, muscle	Babo/Punt	Gut digestive enzymes repression; metabolism; pH equilibrium; muscle protein homeostasis	Local or systemic factor (present in many organs)? Relationship to myoglianin?	6, 23, 50, 82
Hh	Shh and other mammalian Hh proteins	Larvae	Starvation	Gut and possibly imaginal discs?	FB, prothoracic gland	Ptc	Growth and development; lipid release from FB	Local secretion from neurons on FB?	92, 110, 125
JH	?	Larvae and adults	Mating (adult females), other	Corpora allata	Several organs	Gce/Met	Increased growth, metabolism; increased proliferation of intestinal stem cells; regulation of insulin signaling	Mammalian ortholog?	43, 63, 98, 121

(Continued)

Table 2 (Continued)

<i>Drosophila</i> factor	Mammalian ortholog	Developmental stage	Physiological inducer	Origin	Destination	Receptor	Effect	Questions	Reference(s)
GABA	GABA	Larvae	Olfaction	Brain neurons	Lymph gland	GABA-B-R	Preservation of hematopoietic progenitor cells	Role in mammals? Other roles of systemic GABA?	135
PGRPs	PGRPs	Adults	Aging-associated FB inflammation	FB	Gut	PGRP-LC	Altered gut inflammation and increased intestinal stem cell proliferation	Are PGRPs acting directly or indirectly on the gut?	135
GBPs	EGF?	Larvae	Dietary sugar, lipids, and proteins	FB	IPCs	?	Increase insulin secretion	Direct action? Neural circuitry and receptor? Mechanism of BBB crossing? Similar mammalian mechanisms? Relationship to Upd2 and CCHa2	72
CCHa2	?	Larvae, adult (feeding)	Dietary sugar and proteins	FB?, gut?	IPCs, brain	CCHa2R	Increase insulin secretion, induce feeding	Produced from FB or gut? Mechanism of BBB crossing? Presence in hemolymph? Do lipids induce CCHa2? Similar mammalian mechanisms? Relationship to Upd2 and GBPs?	122, 129

Abbreviations: AKH, adipokinetic hormone; AKHR, AKH receptor; BBB, blood-brain barrier; CC, *Drosophila corpora cardiaca*; Daw, dawdle; Dilp, *Drosophila* insulin-like protein; EGF, epidermal growth factor; FB, fat body; GABA, γ -aminobutyric acid; GBPs, growth-blocking peptides; Hh, hedgehog; IPCs, insulin-producing cells; InR, insulin receptor; ISC, intestinal stem cell; JH, juvenile hormone; Lst, limostatin; Myo, myoglianin; NMU, neuromedin U; PGRPs, peptidoglycan recognition proteins; PTTH, prothoracicotropic hormone; SDR, secreted decoy of insulin; Shh, sonic hedgehog.

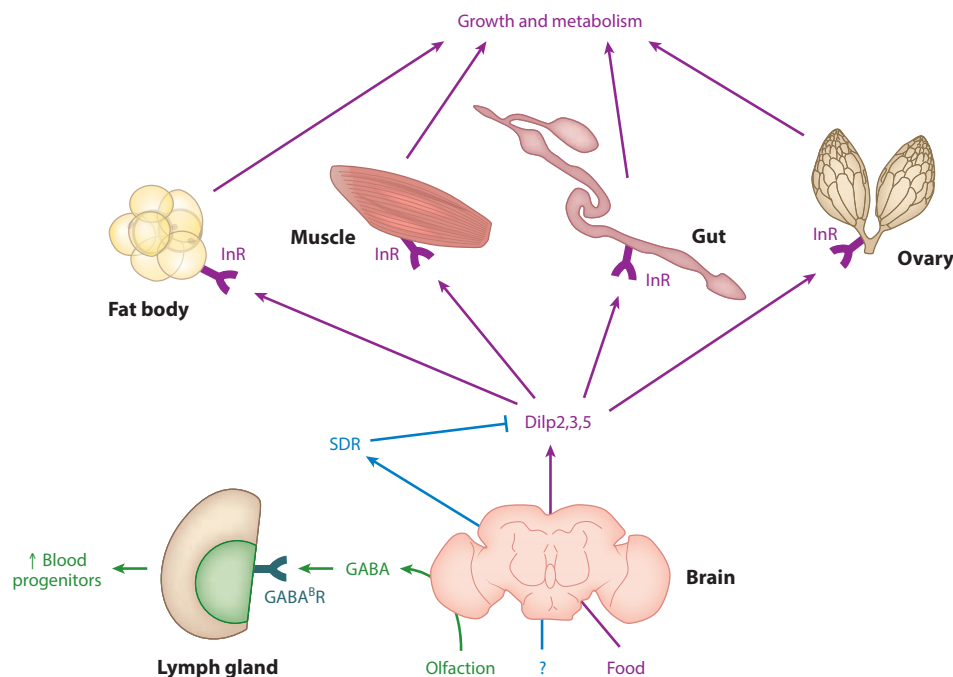


Figure 5

Drosophila central nervous system-derived systemic factors include the Dilps (*Drosophila* insulin-like proteins), SDR [secreted decoy of insulin receptor (InR)], and GABA (γ -aminobutyric acid). SDR binds to and negatively regulates Dilps. Dilps are secreted from insulin-producing cells (IPCs) and act through InR found in most tissues to regulate growth and metabolism. Note that not all organs on which Dilps act are shown. GABA is produced by the brain to preserve hematopoietic progenitor cells. Data from References 15, 62, 75, 102, 104, 127, 135, 145, and 152.

raises the questions of whether similar mechanisms operate in mammals and whether systemic brain-derived GABA has additional roles (135).

Drosophila Fat Body-Derived Systemic Factors

Drosophila FB-derived systemic factors include unpaired-2, eiger, growth-blocking peptides, CCHamide-2, dawdle, ImpL2, peptidoglycan recognition proteins, and Dilp6.

Unpaired-2. High fat and sugar diets induce secretion of unpaired-2 (Upd2) from FBs. Upd2 is a JAK/STAT cytokine and sensed by its receptor domeless (dome) on neurons adjacent to the IPCs to positively regulate Dilp secretion (**Figure 6**). Dilp secretion in turn promotes growth in larva and nutrient storage in larva and adults. Interestingly, Upd2 is the structural and functional ortholog of mammalian leptin (118). A number of questions remain. First, what is the mechanism of Upd2 secretion from the FB in response to diet, given that Upd2 has no signal peptide (118)? Second, is Upd2 a systemically secreted factor: Is it present in the hemolymph (blood)? How does Upd2 cross the blood-brain barrier (BBB)? Also, in mammals, leptin may be sensed by adipose tissue neurons (100); does *Drosophila* have neurons innervating the FB, and can it sense Upd2? Neuronal mechanisms of Upd2 sensing remain to be clarified (118). Finally, FB amino acids

JAK/STAT:
janus kinase/signal
transducer and
activator of
transcription
BBB: blood-brain
barrier

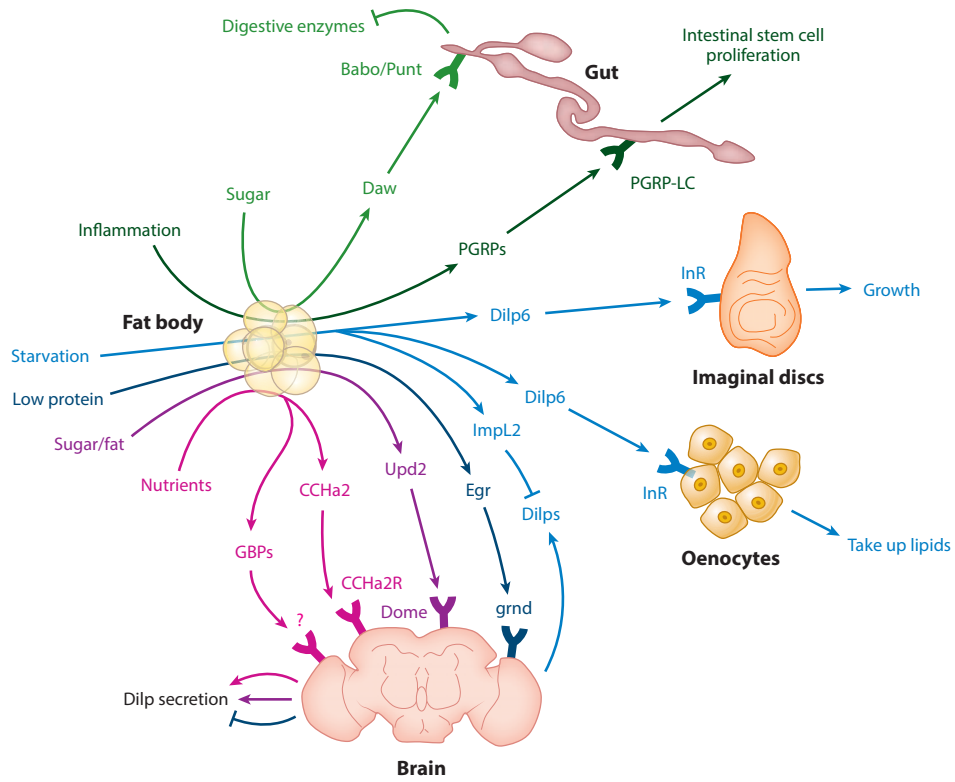


Figure 6

Drosophila fat body (FB)-derived systemic factors include the transforming growth factor (TGF)-related Daw (dawdle), PGRPs (peptidoglycan recognition proteins), Dilp6 (*Drosophila* insulin-like protein 6), ImpL2, GBPs (growth-blocking peptides), CCHa2 (CCHamide2), Egr (Eiger), and leptin-like Upd2 (unpaired-2). Daw acts through the receptor Babo/Punt to regulate metabolism, gut digestive enzymes, pH equilibrium, and Dilp (*Drosophila* insulin-like protein) secretion (not shown as it may be indirect). It is not clear whether Daw is a systemic factor, as it is found in multiple organs. PGRPs are secreted by age-inflamed FBs and act directly or indirectly to regulate gut inflammation and stem cell proliferation. Upd2 regulates insulin secretion through the receptor dome (domeless). Egr negatively regulates insulin secretion through the receptor Grnd (Grindelwald). GBP1/2 induces Dilp secretion through unknown mechanisms. CCHa2 induces Dilp secretion through the CCHa2 receptor. CCHa2 may also be produced by the gut (not shown). Dilp6 acts through insulin receptor (InR) on oenocytes and imaginal discs to regulate lipid uptake and growth, respectively. Dilp6 may also regulate insulin secretion (not shown). Also, ImpL2 is secreted from larval FBs upon starvation to inhibit extracellular Dilp. Data from References 1, 6, 7, 21–23, 50, 58, 72, 105, 118, 122, 129, and 139.

regulate insulin secretion (28) independent of Upd2 (118), suggesting that additional FB-derived signals exist.

Eiger. Eiger (Egr) is a tumor necrosis factor (TNF)-family cytokine expressed as a transmembrane protein. In larvae, low protein diet induces Egr secretion from FBs into the hemolymph through inhibition of TOR (target of rapamycin) and induction of TNF α -converting enzyme (TACE), which cleaves Egr from the membrane (1). Egr binds to IPCs through the Grindelwald (Grnd) receptor, which acts through the Jun N-terminal kinase (JNK) pathway to inhibit Dilp2/5

TNF: tumor necrosis factor
JNK: Jun N-terminal kinase

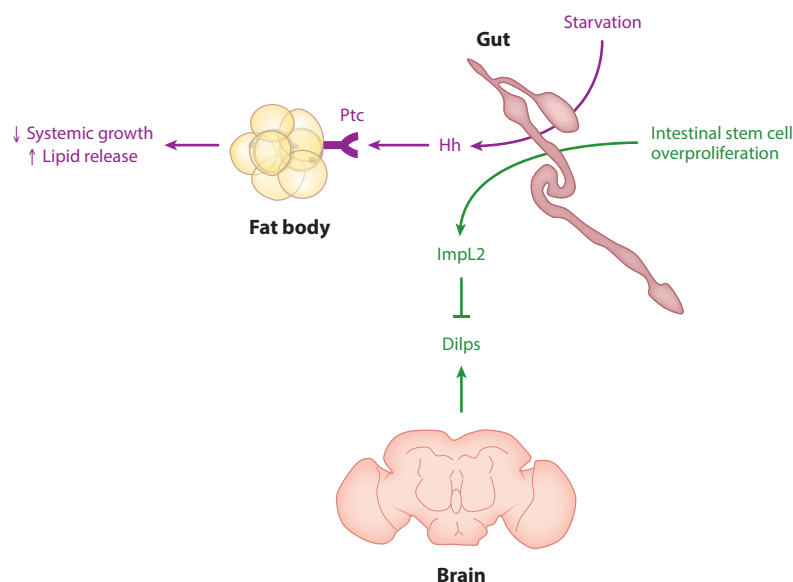


Figure 7

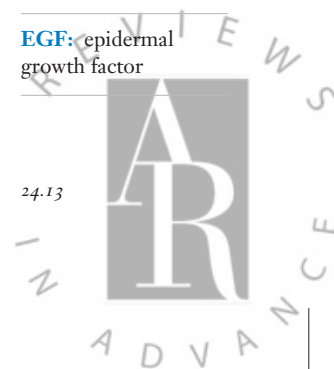
The *Drosophila* gut-derived factors are the insulin growth factor binding protein (IGFBP)-like factor ImpL2 and Hh (hedgehog). ImpL2 is secreted from the gut upon intestinal stem cell overproliferation and binds to and inhibits Dilps (*Drosophila* insulin-like proteins). Hh binds to Ptc (patched) on fat bodies and the prothoracic gland (not shown) to regulate growth and lipid mobilization. CCHa2 (CCHamide2) may also be produced by the gut (not shown). Data from References 74, 122, 125.

mRNA expression and larval growth (1). In addition, under high sugar diet, Grnd signaling in FBs induces insulin resistance. In adult flies, Egr induces TAG storage under starvation; however, it remains to be seen whether this occurs through insulin secretion. Intriguingly, treatment of mammalian islets with $\text{TNF}\alpha$ reduces insulin mRNA expression (1). Issues for future study include mechanisms of Egr crossing of BBB, Egr-interacting proteins in the hemolymph, and mechanisms of TACE induction downstream of TOR (1). In addition, mammalian $\text{TNF}\alpha$ forms a similar protein structure to adiponectin (134), which raises the question of whether fly FB-derived Egr is an adiponectin ortholog. This question can be addressed using rescue of *egr* mutants by expressing human adiponectin, as done previously for Upd2-leptin (118).

Growth-blocking peptides. Growth-blocking peptides (GBPs) are epidermal growth factor (EGF)-like cytokines and immune regulators without known receptors. Dietary lipids, proteins, and sugars induce larval FB GBP1/2, which act on IPCs to induce Dilp secretion and growth (72, 146). Future studies may determine whether GBPs act directly on the brain, their neural circuitry and receptors, or the mechanism of BBB crossing, and whether similar mechanisms exist in adult flies and mammals (72, 146).

CCHamide-2. CCHamide-2 (CCHa2) is a neuropeptide acting on G-protein-coupled CCHa2 receptor (122). Proteins and sugars induce larval FB CCHa2, which acts on IPCs to induce Dilp secretion and growth (129). In adults and larva, CCHa2 regulates feeding (122). However, it is unclear whether CCHa2 is produced by the gut, brain, or FB (122). Future studies may determine the mechanism of BBB crossing, whether CCHa2 is present in the hemolymph, whether lipids

EGF: epidermal growth factor



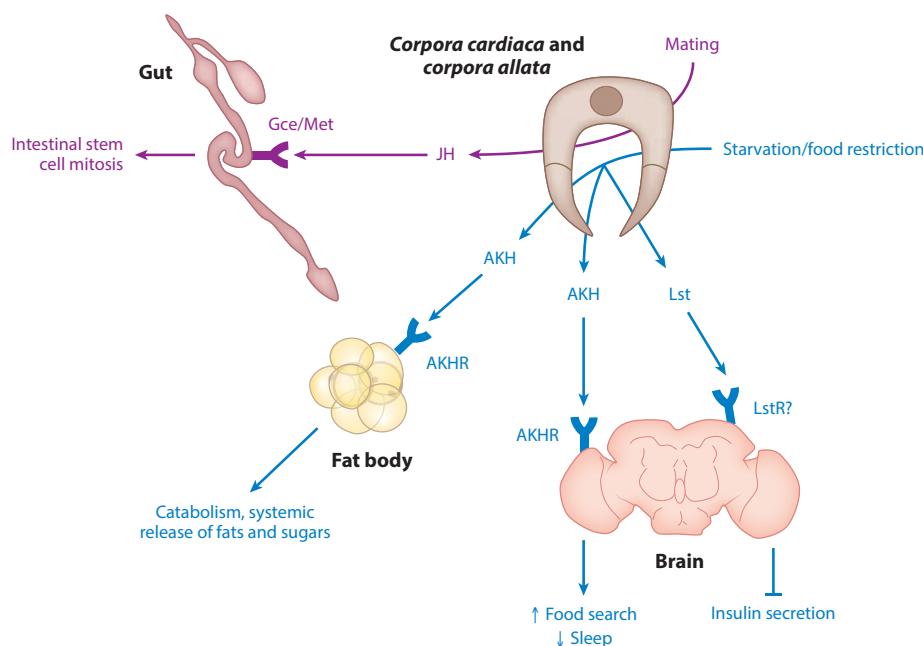


Figure 8

Drosophila corpora cardiaca (CC)- and *corpora allata* (CA)-derived factors are glucagon-like AKH (adipokinetic hormone), JH (juvenile hormone), and NMU (neuromedin U)-like Lst (limostatin). AKH is secreted by CC cells and acts through the AKHR (AKH receptor) found in many tissues to regulate growth and metabolism. Lst is secreted from CC cells and acts through its putative receptor LstR on insulin-producing cells to decrease Dilp (*Drosophila* insulin-like protein) secretion. JH is secreted from CA cells and acts through the receptor Met found in several organs to regulate growth and metabolism. Note that CC/CA cells are found close to the esophagus, proventriculus, and brain in adults and brain in larva. Although JH and AKH have other target organs, selected organs and functions discussed in the text are shown for simplicity. Data from References 3, 29, 43, 47, 51, 63, 66, 69, 78, 96, 98, 121, and 150.

induce CCHa2, and whether similar mechanisms exist in adult flies and mammals (129). Also, what is the relationship between Upd2, GBPs, and CCHa2, given their induction by similar nutrients (72, 118, 129)?

Dawdle. In adults, the TGF- β /activin-like ligand dawdle (Daw) is induced primarily in FBs by dietary sugar. Directly or indirectly, Daw acts through Baboon (Babo)^C/Punt receptors on intestinal enterocytes to phosphorylate Smad-2, which then represses the transcription of digestive enzymes. Thus, adult FB-derived Daw acts as a negative feedback to repress digestion (23). Also, Daw from adult muscle can negatively regulate muscle protein homeostasis and directly or indirectly positively regulate insulin secretion (6). Finally, larval Daw from several organs positively regulates insulin secretion and affects systemic metabolism, including triacylglycerol, glucose, and glycogen storage, mitochondrial genes, and hemolymph pH (50). Together, these studies suggest that Daw is an important regulator of metabolism (6, 23, 50). Future studies may address whether Daw acts as a local or a systemic factor, as it is found in many organs (50). Studies of Daw in the hemolymph may address this question. Mammalian activin signaling also regulates mitochondrial activity and organ growth (82), suggesting a number of further studies.

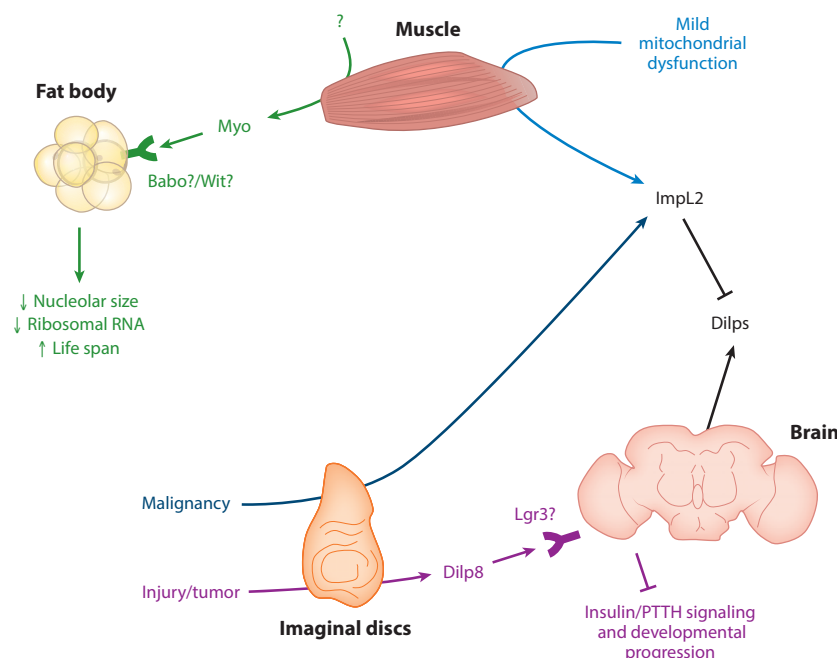


Figure 9

Muscle-derived Myo (myoglianin) may act through Babo or Wit receptors to decrease fat body nucleolar size and ribosomal RNA and increase life span. ImpL2 is secreted from muscle upon mild mitochondrial dysfunction. Injured imaginal discs secrete Dilp8 (*Drosophila* insulin-like protein 8), which acts on Lgr3 (leucine rich repeat-containing G-protein-coupled receptor 3)-positive neurons to inhibit insulin and prothoracicotropic hormone (PTTH) signaling and developmental progression. Also, ImpL2 is secreted by malignant *scrib* and *scrib Ras^{V12}* tumor-like larval imaginal discs transplanted to adults. Data from References 26, 27, 32, 41, 48, 49, 108, and 147.

ImpL2. ImpL2 is an immunoglobulin-superfamily member similar to mammalian IGFBP7 (58). It binds to Dilps extracellularly and inhibits insulin signaling. Starvation induces expression of *Drosophila* larval FB ImpL2, thereby increasing survival (58).

Peptidoglycan recognition proteins. Peptidoglycan recognition proteins (PGRPs) are immune factors that act through PGRP-LC receptor and the immune deficiency (IMD) pathway (22). In adults, old age-associated FB inflammation causes secretion of PGRPs, which act on the gut to alter inflammation and increase intestinal stem cell proliferation. It is not clear whether PGRPs act directly or indirectly on the gut (e.g., by acting on immune cells) (22). PGRPs are conserved (38), raising the question of whether similar mechanisms operate in mammals.

Dilp6. In larvae, the IGF-like factor Dilp6 is induced in the FB upon cessation of feeding—before/during pupariation or starvation. The induction is dependent on the FOXO transcription factor and the metamorphosis steroid hormone ecdysone (153). Dilp6 promotes growth of imaginal discs that give rise to adult organs. As this happens in the absence of other Dilps and food intake, Dilp6 acts as a switch between energy storage and growth of organs (105, 139). In adults, FB-derived Dilp6 acts through the InR to regulate turnover of lipids from FBs to oenocytes and oenocyte lipid uptake. This is important for starvation resistance (21). In addition, Dilp6 may

IGFBP: IGF binding protein

Ecdysone: insect hormone produced by the prothoracic gland that induces molting and pupariation

ISC: intestinal stem cell

AKH: adipokinetic hormone

directly or indirectly regulate insulin secretion (7). Dilp6 has similarities to mammalian IGFs (139).

***Drosophila* Gut-Derived Systemic Factors**

Drosophila gut-derived systemic factors include hedgehog and ImpL2.

Hedgehog. Hedgehog (Hh) was previously known as a paracrine developmental regulator. In *Drosophila* larva, starvation induces gut Hh, which is secreted into the hemolymph bound to lipoproteins. Hh targets the FB through the Patched (Ptc) receptor to negatively regulate systemic growth and positively regulate lipid release due to starvation, thus affecting larval sensitivity to starvation. Moreover, Hh integrates growth and metamorphosis by acting on the prothoracic gland to reduce ecdysone production, thus negatively regulating pupariation (125). The gut has been proposed to be the major source of Hh acting on FBs because FBs have little to no Hh mRNA and reduction of Hh in the gut results in reduction of Hh protein in FBs (125). However, it is possible that neurons that innervate the FB could be a source of Hh, as neurons and enterocytes can both produce Hh (56) and knockdown of Hh in neurons results in at least a twofold reduction in hemolymph Hh (125). It would be interesting to address whether mammalian sonic hedgehog (Shh) and other Hh proteins have similar roles, as Shh is detected in the blood (110, 125).

ImpL2. In adults, Hippo pathway-induced intestinal stem cell (ISC) hyperproliferation causes production of Dilp-inhibitor ImpL2 from the gut. This results in decreased Dilp signaling; nutrient uptake from hemolymph; nutrient storage; and ovary, muscle, and FB atrophy. In the FB, energy stores are depleted, and hemolymph sugar levels rise (74). Interestingly, in the gut hyperplasia itself, insulin signaling and nutrient consumption increases through upregulation of insulin and glycolysis pathway components, including Dilp3 (74), which may bind poorly to ImpL2 (104). It would be interesting to determine whether related mechanisms occur during physiological processes involving cell proliferation and mammalian cancer cachexia (74).

***Drosophila Corpora Cardiacac*– and *Corpora Allata*–Derived Systemic Factors**

The following three factors are produced by the *corpora cardiacac* (CC) and *corpora allata* (CA) endocrine gland complex, which is located close to the brain, esophagus, and proventriculus in adults, and brain in larvae (29, 43).

Adipokinetic hormone. Adipokinetic hormone (AKH) is an endocrine peptide produced by CC cells that acts on the AKH receptor (AKHR) in multiple tissues in both larva and adults. AKH regulates metabolism in an opposing way to Dilps by acting to promote catabolism and systemic release of fats and sugars from FBs (47, 51, 69, 78). In addition, AKH signaling regulates life span, food search behavior, sleep, and resistance to oxidative stress (47, 66, 78, 96, 150). Future studies may identify systemic factors that regulate AKH signaling. Interestingly, AKH and CC cells have been likened to the mammalian glucagon and α -cell system, respectively (47, 69).

Limostatin. Limostatin (Lst) is a novel protein secreted by CC cells in response to food restriction in adult *Drosophila*. Lst acts as a secretin, as it decreases insulin secretion by acting through the G-protein-coupled CG9918/LstR receptor on IPCs (3). However, binding experiments using purified Lst and CG9918 proteins will need to be performed to demonstrate that CG9918 is the bona fide LstR. Also, whether Lst is present in fly hemolymph is not known. Moreover,

future studies may address whether Lst acts on CC cells themselves and on the FB. Interestingly, mammalian neuromedin U (NMU) and NMU receptors are orthologous to fly Lst signaling (3). However, the mechanisms of NMU action remain to be investigated in detail.

Juvenile hormone. Juvenile hormone (JH) is a sesquiterpenoid molecule secreted by CA cells that regulates larval growth and development and adult reproduction through its Gce/Met receptor (43, 63). Recently, additional functions of JH emerged, including regulation of insulin signaling in larva and intestinal stem cell proliferation in adults (98, 121).

Prothoracicotropic hormone (PTTH): neuropeptide that induces ecdysone release

***Drosophila* Muscle-Derived Systemic Factors**

Drosophila muscle-derived systemic factors include myoglianin and ImpL2

Myoglianin. In addition to Daw (described above) (50), myoglianin (Myo), a related TGF- β family factor, performs a distinct role in regulating physiology. Adult muscle-derived Myo decreases FB nucleolar size and ribosomal RNA, and increases life span (32). The detection of Myo in fly hemolymph would strengthen the conclusion that Myo acts systemically. Although the receptor in this context is unclear, previous work showed that Myo signals through wishful-thinking (Wit) and Babo coreceptors (77). Moreover, the physiological inducer of Myo secretion from muscle is uncharacterized. Also, what is the relationship of Myo to other TGF- β family members also involved in physiology, including Daw as described above (50)?

ImpL2. Moderate mitochondrial perturbation in *Drosophila* adult muscle results in secretion of ImpL2, which inhibits whole-body insulin signaling and increases life span (108). Overall, *Drosophila* systemic insulin signaling is regulated by extracellular binding factors from the periphery, including SDR (104) and ImpL2 (74, 108). What is the relationship between these, and does secretion of ImpL2 and SDR from different organs have diverse effects on physiology? Interestingly, SDR and ImpL2 bind to different Dilps in vitro: Dilp3 binds well to SDR but poorly to ImpL2 (104).

***Drosophila* Imaginal Disc-Derived Systemic Factors**

Drosophila imaginal disc-derived systemic factors include Dilp8, ImpL2, and possibly Hh.

Dilp8. Dilp8 is a relaxin/insulin/IGF-like peptide. In larva, changes in imaginal disc growth caused by injury or overproliferation induce secretion of Dilp8 from imaginal discs. Dilp8 delays entry to pupariation and growth of other imaginal discs, thereby acting as a signal for developmental consistency (27, 48). Dilp8 may directly or indirectly bind to leucine rich repeat-containing G-protein-coupled receptor 3 (Lgr3) in four neurons in the brain pars intercerebralis. These neurons delay growth and pupariation by inhibiting prothoracicotropic hormone (PTTH; 153) neurons and thus JH production, as well as Dilp3 and 5 secretion from IPCs (26, 49, 147). Issues for future studies include detection of endogenous Dilp8 in the hemolymph, Dilp8 functions in adult animals, and Dilp8 crossing of the BBB as well as whether Lgr3 is the bona fide Dilp8 receptor (49, 147). Of note, it is not clear whether Lgr3 is the bona fide Dilp8 receptor (49); in vitro binding assays using purified Lgr3 and Dilp8 proteins need to be done. Dilp8 is related to mammalian relaxin, insulin, and IGF, whereas Lgr3 is a relaxin-type receptor. This raises the possibility that a similar mechanism occurs in mammals (26, 27, 48, 49, 147).



ImpL2. Tumor-like malignant *scrib* and *scrib Ras^{V12}* larval imaginal discs transplanted to adults secrete ImpL2, which inhibits systemic Dilps (41). This results in ovary, muscle, and FB atrophy in a phenotype similar to that resulting from ImpL2 secretion from overproliferating ISCs described above (41, 74).

Hedgehog. Larval imaginal discs have been suggested to secrete Hh into the fly hemolymph (92). It remains to be investigated whether imaginal disc-derived Hh has a physiological function on distal organs.

ROBUST READOUTS FOR FUNDAMENTAL ORGAN FUNCTIONS ARE ESSENTIAL FOR SYSTEMATIC DISCOVERY OF NOVEL FACTORS

Systematic genetic screens aimed at discovering interorgan communication factors have not been done in any organism. Therefore, we expect that many molecules involved in organ communication under physiological and pathological conditions remain to be identified. Indeed, a number of connections between organs remain uncharacterized. These include muscle to GSCs, gut to GSCs, FBs to GSCs, digestive tract to muscle, brain to adipose tissue (non-neural), and others. For instance, in humans, adult-onset muscle dystrophies (111) and poor nutrition (45) are associated with poor fertility. Moreover, *Drosophila* FBs regulate GSCs in response to nutrients through unknown signals (5). Importantly, approximately half of fly hemolymph proteins and 30–40% of fly-secreted proteins have unknown or poorly characterized functions, and most have no known functions in interorgan communication (I.A. Droujinine, Y. Hu, J.M. Asara, N. Perrimon, unpublished results). We expect that a fraction of these proteins have a signaling role in organ communication.

The factor and its source and destination can be determined from a perturbation or at homeostasis by bioinformatics, biochemistry, RNA sequencing, organ transplants, parabiosis (25), or genetic screens. In an organ-sensing screen, secreted factors are mutated in one organ, and an organ function is measured in another (**Figure 10**) (37). *Drosophila* organ-specific perturbations can be achieved using the Gal4/UAS system driving the expression of a secreted factor cDNA, RNAi, or Cas9/CRISPR (86, 103, 114). Cas9 proteins with dead nuclease activity (dCas9) fused to

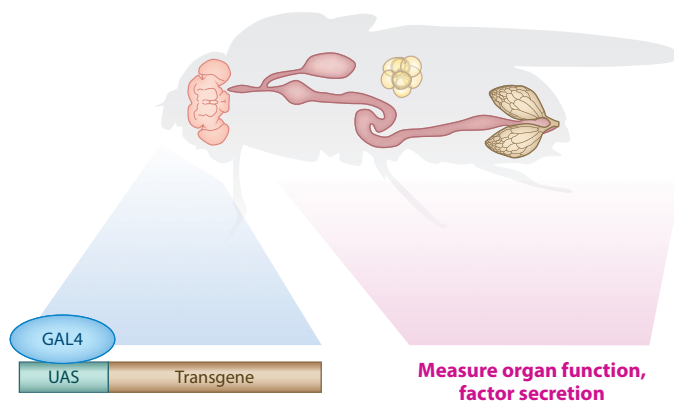


Figure 10

Design of an organ-sensing screen in *Drosophila*. The Gal4-UAS system drives the tissue-specific expression of a transgene (RNA interference), cDNA, or Cas9, and the function of a distal organ is measured. Alternatively, secretion of a key systemic factor can be measured to address questions about the integration of pathways in interorgan communication.

either transcriptional activators (dCas9-a) or repressors (dCas9-i) can be used for gene activation and repression in cells expressing the sgRNAs (86). For a successful organ-sensing screen (37), a critical parameter is a robust distal organ function readout.

There are a number of basic organ functions that have been measured in the organ communication literature (**Table 3** and references therein). For instance, fatty acid (FA) and sugar metabolism in FBs, Dilp retention in IPCs, and systemic growth have been popular readouts, given their simplicity, widespread reagent availability, and physiological relevance (e.g., see 118). However, a significant number of organ functions have been largely overlooked in *Drosophila* (**Table 3**). These include heat generation (30) (see Evolutionary Considerations below) and detoxification by FBs; behavioral control by the central nervous system (CNS); cell division, growth, differentiation, chromosomal stability, and cell migration associated with tumors and wounds; and waste production by the digestive system. In addition, a number of organs have not been extensively studied, including the reproductive system, oenocytes, Malpighian tubules, trachea, and the heart. Thus, it is important to develop assays for these key tissues, as they may reveal novel biological pathways and/or be more sensitive readouts than are the current ones. In conclusion, systematic screens that measure robust organ function readouts in response to secreted factor perturbation identify novel interorgan communication pathways.

SYSTEMS BIOLOGY OF INTERORGAN COMMUNICATION: COORDINATED REGULATION OF SYSTEMIC FACTORS AND PHYSIOLOGY

In the above sections, we have reviewed the *Drosophila* interorgan communication factors, their physiological inducers, and outputs. After elucidating the pathways involved in interorgan communication, the challenge is to determine how these pathways integrate with each other in coordinating body function, integration meaning two or more pathways interacting to regulate systemic physiology. For example, dietary restriction pathways interact with FA turnover in life-span regulation through unclear systemic factors (66). Also, high-fat-diet-induced heart toxicity is rescued by inhibition of TOR and promotion of lipid breakdown in FBs through unknown secreted factors (11). These systems biology interorgan communication questions are best addressed in *Drosophila*, given its powerful genetic tools.

Most, if not all, integration studies so far have been centered on the regulation of Dilp (insulin) signaling by secreted factors (**Figure 11**). Dietary nutrients induce FB secretion of Upd2, GBPs, and CCHa2, which positively regulate IPC Dilp secretion to promote nutrient storage and growth (72, 118, 129). The opposing physiological condition of starvation induces Egr secretion from FBs and Lst secretion from *corpora cardiaca* to inhibit Dilp secretion from IPCs, thus reducing nutrient storage and promoting breakdown (1, 3). In addition, developing organ (imaginal disc) growth perturbation in the form of an injury or tumor causes secretion of Dilp8 to negatively regulate IPC Dilp secretion and slowing down the growth of the organism (26, 27, 48, 49, 147). Also, imaginal disc malignancy, ISC overproliferation, mild muscle mitochondrial dysfunction, and FB starvation induce secretion of ImpL2, which inhibits Dilps extracellularly (41, 58, 74, 108). Induction of ImpL2 in these contexts makes sense because tumors are quickly dividing and growing tissues that require increased nutrient release from storage organs like FBs and decreased nutrient uptake to other organs (41, 74). Reduced insulin signaling promotes mitophagy of defective mitochondria (108), and extracellular inhibition of Dilps provides another level of regulation of insulin signaling during starvation (58). Together, these studies illustrate how various secreted systemic factors integrate information about overall organism status from multiple organs and translate this information to a key interorgan communication factor (in this situation, insulin).

Organ-sensing

screen: experimental approach for identifying systemic factors through systematic genetic perturbation in one tissue and scoring the effect on another tissue

FA: fatty acid

CNS: central nervous system





Table 3 Selected *Drosophila* organ functions in interorgan communication

<i>Drosophila</i> organ	Mammalian functional equivalent	Possible functions in interorgan communication	What has been measured in <i>Drosophila</i> ?	Selected references
Insulin-producing cells	Pancreatic β -cells	Insulin storage and secretion; nutrient sensing; secreted factor sensing; electrical activity; synapses	Insulin storage and secretion; nutrient sensing; secreted factor sensing; synapses	3, 15, 26, 27, 33, 48, 49, 62, 72, 75, 102, 118, 127, 129, 145, 147, 152
<i>Corpora cardiaca</i> and <i>corpora allata</i>	Pancreatic α -cells and other specialized endocrine glands?	AKH/glucagon and other factor storage and secretion; nutrient sensing; secreted factor sensing	AKH/glucagon and Lst storage and secretion	3, 43, 47, 51, 63, 66, 69, 78, 96, 98, 121, 150
Muscle	Muscle	Contraction; glycogen storage; protein homeostasis; glucose, and FA turnover; heat generation; mitochondria; interaction with immune system; secreted factor production; secreted factor sensing	Contraction; protein homeostasis; glucose and FA turnover; mitochondria; secreted factor production (e.g., Myo, ImpL2)	4, 30, 32, 33, 66, 81, 108, 109, 156
Fat body	Adipose tissue and liver	Nutrient sensing; glycogen, glucose and FA synthesis, storage and release; heat generation; detoxification; mitochondria; protein homeostasis; interaction with immune system; secreted factor production; secreted factor sensing	Nutrient sensing; glucose and FA synthesis, storage and release; mitochondria; protein homeostasis; interaction with the immune system; secreted factor production (Upd2, Daw, PGRPs, Dilp6, ImpL2, GBPs, CCHa2); secreted factor sensing (Myo, Dilps, AKH)	4, 6, 7, 17, 21–23, 30, 32, 33, 35, 47, 50, 51, 58, 66, 69, 72, 78, 81, 105, 109, 118, 129, 139
Oenocyte	Liver	Nutrient sensing; sugar and FA homeostasis; detoxification; cuticular hydrocarbon production; secreted factor production; secreted factor sensing	Nutrient sensing; sugar and FA homeostasis; secreted factor sensing (Dilp6)	10, 21, 54, 81, 109, 118

Digestive system	Digestive system	Digestion; nutrient uptake; nutrient sensing; glucose, FA, and protein metabolism; detoxification/waste excretion; regeneration and stem cell proliferation; host-microbiome interactions; interaction with immune system; secreted factor production; secreted factor sensing	Digestion; nutrient uptake; nutrient sensing; glucose and FA metabolism; stem cell proliferation; interaction with the immune system; secreted factor production (ImpL2, Hh) secreted factor sensing (Daw, PGRPs)	4, 17, 23, 35, 74, 81, 109, 125, 135, 141
Reproductive system	Reproductive system	Cell division, growth, and migration; germline stem cell proliferation and differentiation; meiosis; epigenetic inheritance; glucose, FA, and protein metabolism; mitochondria; secreted factor production; secreted factor sensing	Germline stem cell proliferation; secreted factor sensing (insulin)	5, 75, 155
Central nervous system	Central nervous system	Outside environment sensing; interorganism communication; nutrient homeostasis; behavioral control; electrical activity; synapses; neural regulation of organs and immunity; central regulation of glycogen, glucose, FA, and protein homeostasis; mitochondria; secreted factor (including classical hormone) production; secreted factor sensing	Outside environment sensing; nutrient homeostasis; electrical activity; synapses; central regulation of glucose and FA homeostasis; secreted factor production (insulin, SDR, GABA); secreted factor sensing (Upd2, Dilp8, GBPs, CCHa2)	15, 17, 62, 72, 73, 75, 102, 104, 118, 127, 129, 135, 145, 152

(Continued)



Table 3 (Continued)

<i>Drosophila</i> organ	Mammalian functional equivalent	Possible functions in interorgan communication	What has been measured in <i>Drosophila</i> ?	Selected references
Malpighian tubule	Kidney	Water balance; waste removal; glucose, FA, and protein metabolism; regeneration; interaction with immune system; secreted factor production; secreted factor sensing		9, 17, 137
Heart	Heart	Contraction; blood propulsion; glucose, FA, and protein metabolism; mitochondria; secreted factor production; secreted factor sensing	Contraction, lipids (unknown secreted factors)	11, 35
Trachea	Air tract, lungs, trachea, blood vessels for oxygen delivery	Exchange of oxygen, carbon dioxide, and other gases and volatiles between the environment and the body; buoyancy; interaction with immune system; secreted factor production; secreted factor sensing		4, 17, 109
Tumor and wounds	Tumor and wounds	Cell division, growth, differentiation, and migration; glucose, FA, and protein metabolism; nutrient sensing; mitochondria; interaction with immune system; chromosomal stability; secreted factor production; secreted factor sensing	Glucose and FA metabolism; secreted factor production (ImpL2, Dilp8)	26, 27, 41, 48, 49, 74, 147

Abbreviations: AKH, adipokinetic hormone; Daw, dawdle; Dilp, *Drosophila* insulin-like protein; EGF, epidermal growth factor; FA, fatty acid; GBPs, growth-blocking peptides; Hh, hedgehog; Lst, limostatin; Myo, myoglianin; PGRPs, peptidoglycan recognition proteins; SDR, secreted decoy of insulin.

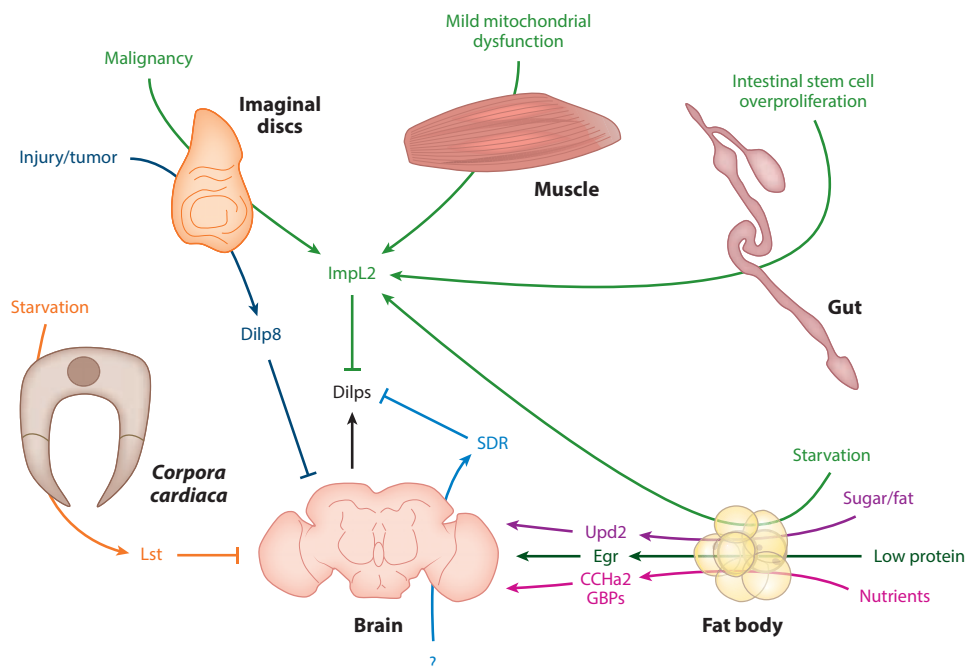


Figure 11

Various interorgan communication factors are integrated to regulate insulin signaling (1, 3, 26, 27, 41, 48, 49, 58, 72, 74, 108, 118, 129, 147). Abbreviations: CCHA2, CCHamide2; Dilp, *Drosophila* insulin-like protein; Egr, Eiger; GBP, growth-blocking peptide; Lst, limostatin; SDR, secreted decoy of insulin receptor; Upd2; unpaired-2.

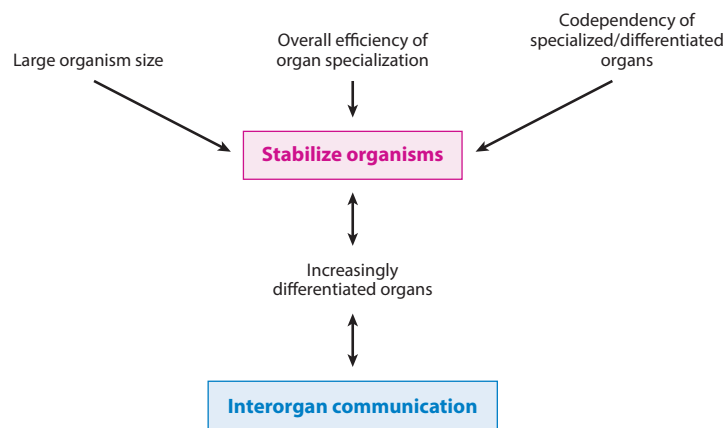
EVOLUTIONARY CONSIDERATIONS

Similarities and Differences Between Flies and Humans

Drosophila is a model system for interorgan communication between organs conserved to humans. Fly FBs and oenocytes (adipose tissue and liver in humans), brain, muscle, digestive system, gonads, and heart have human equivalents (**Figure 3**) (4, 35, 81, 109). A number of interorgan communication factors identified in mammals are conserved to *Drosophila*, including leptin (fly Upd2) (118) and GDF-11 (fly myoglianin) (32) (**Table 2**). However, flies have no bone, blood vessels, adaptive immunity, or potent central thermoregulation (4, 17, 35, 81, 109). Interestingly, *Drosophila* larvae keep their body temperature 0.5°C above that of the medium, suggesting limited thermoregulatory capacity (30).

Interorgan Communication Enabled and Evolved as a Result of Specialization of Organs

The origin of multicellularity has been extensively looked at, whereas evolution and maintenance of multiorgan organisms have been largely overlooked (20, 52, 71). Multicellular organisms are stabilized by the large organism size, efficiency of cell specialization, and codependency of specialized/differentiated cells on each other (52, 83, 99). Stable organisms may lead to increasingly differentiated organs (83). As organs became increasingly differentiated, interorgan communication may have evolved for organs to regulate and coordinate each other's functions (37). Interorgan

**Figure 12**

Interorgan communication enabled and evolved as a result of specialization of organs (20, 37, 52, 71, 83, 99). Large organism size, overall efficiency of organ specialization, and codependency of specialized/differentiated organs stabilize organisms. This leads to increasingly differentiated organs, which results in interorgan communication (e.g., through insulin) enables regulation and coordination of organ functions and ensures organ dependency on the rest of the organism. In turn, interorgan communication leads to increasingly differentiated organs, which stabilize organisms.

communication ensures that differentiated cell/organ functions are carried out faithfully and that cells remain differentiated, specialized, and dependent on the rest of the organism. For example, IPCs are dependent on other organs for nutrients, and other organs are dependent on insulin (102). In turn, interorgan communication leads to increasingly differentiated organs, which stabilize organisms (**Figure 12**). For instance, in the absence of *Drosophila* larval Dilp8, developmental robustness and synchrony are affected (26, 27, 48, 49, 147). Thus, interorgan communication coevolved with multicellularity and is necessary for the evolution of organs.

Potential Properties of Evolved Interorgan Communication Networks

To faithfully execute each organ's function, the action of local signaling networks needs to be limited. For instance, to prevent tumorigenesis, proliferation must be limited to the stem cell niche (131). As hypothesized from network theory (16, 99), in organisms there is a compromise between the number of cell types and connectivity: If there are too many different directly communicating cells, the system becomes unstable. Organs allow the number of cell types that directly interact with each other to be limited (through hierarchy). For example, regulated by other neurons, only IPCs in the brain produce insulin (118). Spatiotemporal segregation of cells and reduction in number and distance of action of competitive and cooperative interactions may increase organism stability (52, 99). In addition, different organs' functions or signaling networks do not interfere with each other. Thus, long-distance communication may connect organs through a limited number of links.

Reorganization of local secreted factor networks (71, 85, 123) may have led to long-distance communication. Developmental pathways, including JAK/STAT (Upd2) (118) and TGF β (Myo, Daw) (23, 32, 50), have physiological functions in interorgan communication. This pleiotropy of pathways may stabilize complex organisms and allow fewer links or system components (99). For example, *Dictyostelium discoideum* dimA has dual functions in responding to secreted DIF-1 and

cell fitness (44). Long-distance signals act on key nodes between organs, affecting organ-specific networks. These nodes can be niche cells, such as neurons that are adjacent to and regulate IPCs in response to Upd2 (118). Alternatively, because developmental ligands are potent regulators of cell fates, such as proliferation, a systemically released binding factor can regulate niche signaling extracellularly (e.g., ImpL2) (37, 58). Hence, interorgan signaling coordinates and limits the action of organ-specific networks. In addition, interorgan communication is a distinguishing feature and necessity of complex organisms.

ICN: interorgan communication network

PERSPECTIVES

After elucidating the pathways involved in interorgan communication, the challenge will be to determine how these pathways integrate with each other in coordinating body function. Given the powerful genetic tools available in *Drosophila*, these questions in systems biology of interorgan communication are best addressed in the fly. In the studies focused on the regulation of insulin signaling by various systemic factors, readouts such as body size, lipid and sugar metabolism, Dilp retention in IPCs, and Dilp secretion have been used (3, 74, 108, 118). From these studies, it is apparent that robust, reliable readouts are essential for understanding the integration of pathways regulating systemic physiology.

An informative and robust readout of pathway integration is the induction or repression of known key secreted physiological regulators, such as AKH, Myo, ImpL2, Upd2, and others (Table 2; Figure 10). Studies may help to elucidate how a change in the physiological state of one organ causes a change in production of a secreted factor. That is, does the secretion of a physiological regulator depend on an unknown systemic signal from another organ? However, many of the described interorgan communication factors have not been detected in the fly hemolymph at endogenous levels. Therefore, it is essential to develop reliable assays for such factors before major screens are undertaken. Moreover, does one systemic factor act through another systemic factor to regulate physiology? For this question, mutants can be made in two or more tissues using Gal4, Q, and LexA systems (14, 76, 115). In conclusion, after identifying the basic components of interorgan communication, studies will be required to investigate how these parts are integrated into the broader interorgan communication network (ICN) in physiology and disease.

Interorgan communication allows and evolved as a result of specialization of organs. Studies in vertebrates and *Drosophila* have identified a number of organ communication factors. Future studies will focus on identifying novel conserved organ communication factors through systematic genetic screens with robust organ function readouts. In addition, it is important to identify how known organ communication pathways are integrated. Together, we anticipate that studies within the next decade will establish a framework ICN that will have implications for evolution, function, and dysfunction of multiorgan organisms.

SUMMARY POINTS

1. A number of mammalian interorgan communication factors have been identified.
2. A number of conserved *Drosophila* interorgan communication factors have been found using organ-specific genetic perturbations. These include Dilp1–8, ImpL2, SDR, Upd2, Egr, Lst, AKH, Myo, Daw, Hh, CCHa2, GBP1/2, JH, and GABA.
3. Interorgan communication evolved as a result of, and enabled, specialization of organs.



FUTURE ISSUES

1. A number of connections between organs remain uncharacterized.
2. Future studies will aim to identify conserved interorgan communication factors using organ-sensing genetic screens.
3. Organ-sensing screens require development of robust organ function readouts.
4. After identifying the key interorgan communication factors, studies will aim to determine how these pathways are integrated with each other into an ICN.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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