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Stress Signaling Between Organs in Metazoa

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Abstract

Many organisms have developed a robust ability to adapt and survive in the face of environmental perturbations that threaten the integrity of their genome, proteome, or metabolome. Studies in multiple model organisms have shown that, in general, when exposed to stress, cells activate a complex prosurvival signaling network that includes immune and DNA damage response genes, chaperones, antioxidant enzymes, structural proteins, metabolic enzymes, and noncoding RNAs. The manner of activation runs the gamut from transcriptional induction of genes to increased stability of transcripts to posttranslational modification of important biosynthetic proteins within the stressed tissue. Superimposed on these largely autonomous effects are nonautonomous responses in which the stressed tissue secretes peptides and other factors that stimulate tissues in different organs to embark on processes that ultimately help the organism as a whole cope with stress. This review focuses on the mechanisms by which tissues in one organ adapt to environmental challenges by regulating stress responses in tissues of different organs.

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INTRODUCTION

Animals frequently encounter stress, defined as any condition that threatens to disrupt the integrity of the proteome, metabolome, or genome. The range of perturbations that can hamper the optimal functioning of the proteome, metabolome, or genome include internal stressors, such as damage to mitochondria and other organelles, as well as external stressors, which may involve alterations in temperature and limited nutrient availability. The effects of these stressors vary widely and can manifest as increased reactive oxygen species (ROS) production; an accumulation of misfolded proteins in the cytosol, mitochondria, or endoplasmic reticulum (ER); impaired energy homeostasis; and ultimately decreased lifespan. When exposed to stress, most tissues are capable of activating compensatory signaling cascades within the tissue aimed at repairing the damage or at least minimizing further damage. In addition, cells and tissues activate nonautonomous stress responses that have either systemic effects or more specific effects on target tissues of different organs (Andreux et al. 2013, Droujinine & Perrimon 2013, Owusu-Ansah & Perrimon 2014). Here, we highlight a range of scenarios in *Drosophila*, *Caenorhabditis elegans*, and vertebrate systems that show how stress signaling emanating from perturbations of the proteome or metabolome is relayed between organs (**Figure 1**).

STRESS SIGNALING BETWEEN ORGANS: THE MAJOR PLAYERS

How the Brain/Nervous System Regulates Stress Responses Between Organs in Invertebrates

Studies in invertebrate model organisms have provided valuable insight into stress-sensitive, interorgan signaling modules involving the brain/nervous system and other organs. In *Drosophila*,

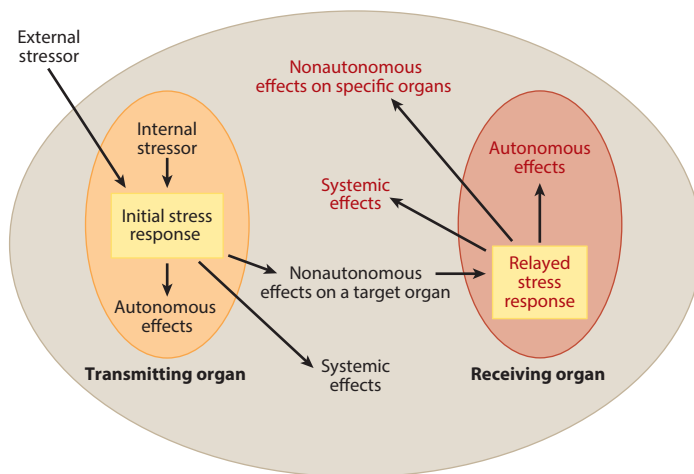


Figure 1

Schematic of stress signaling between organs. An external or internal stimulus is interpreted as a stressful event (or stressor) by an organ or tissue, which causes local activation of a stress response. This may culminate in the activation of genes that exert their effects within (i.e., autonomous effects) or outside the organ/tissue that experienced the stressor. When the stress response is conveyed outside the original organ (the transmitting organ), it may affect the whole organism (i.e., systemic effects) or nonautonomously target a specific organ (the receiving organ) to trigger various autonomous effects. However, in more complex scenarios, the receiving organ may reinterpret and further propagate the stress response systemically or to additional target organs.

most studies have focused on how insulin-like peptides secreted from a group of neurosecretory cells in the brain regulate whole-organism insulin signaling in response to various stressors and other secretory peptides (reviewed in Kannan & Fridell 2013, Nassel et al. 2013). In addition, forced activation of the energy sensor AMPK in the brain/nervous system is reported to up-regulate autophagy in the brain, but also nonautonomously in the gut, and to increase lifespan (Ulgherait et al. 2014). Autophagic gene expression is also evident in the muscle and correlates with a reduction in the accumulation of misfolded protein aggregates there. These effects are associated with a reduction in the levels of mRNA expression of at least two *Drosophila* insulin-like peptides (DILPs) in the brain, as well as altered DILP2 secretion from the insulin-producing cells (IPCs) of the brain. Thus, mimicking energy distress in the nervous system induces a longevity cue involving the activation of autophagy in peripheral tissues.

Another setting in which signaling between the brain/nervous system and a peripheral organ has been observed involves the olfactory and hematopoietic systems. In *Drosophila* larvae, undifferentiated hematopoietic progenitors are maintained in the innermost region of a discrete organ referred to as the lymph gland, whereas differentiated mature cells occur in the outermost layer. Various stressors can trigger premature differentiation of the progenitors (Ferguson & Martinez-Agosto 2014, Mondal et al. 2011, Mukherjee et al. 2011, Owusu-Ansah & Banerjee 2009, Shim et al. 2012, Sinenko et al. 2012). High cytosolic calcium levels are required in the progenitor pool to keep them undifferentiated (Shim et al. 2013). When olfactory receptor neurons are stimulated, they are reported to trigger the release of γ -aminobutyric acid (GABA) from a set of neurosecretory cells in the brain into the circulatory system (Shim et al. 2013). This in turn causes a sustained increase in calcium levels in the hematopoietic progenitor cells in the lymph gland and keeps the progenitor population undifferentiated. Indeed, precocious differentiation of the progenitor population occurs in larvae with mutant odorant receptors or those raised on minimal odor

synthetic media (which contain carbohydrates, nitrogen base, fats, and amino acids but lack the volatile compounds that give the standard cornmeal/molasses-based fly foods their characteristic odor), further emphasizing how odorant receptor activation is linked to *Drosophila* hematopoiesis. Thus, the lack of an appropriate olfactory stimulus or response is perceived as a stressor that is transmitted to the hematopoietic system via GABA.

A series of observations in *C. elegans* has also revealed how the nervous system can regulate proteostasis in adjacent or remote tissues. For instance, defective GABA or enhanced acetylcholine (ACh) signaling in presynaptic motor neurons can perturb protein homeostasis in the postsynaptic muscles (Garcia et al. 2007), and thermosensory neurons can regulate the heat shock response in remote tissues (Prahlaad & Morimoto 2011, Prahlaad et al. 2008). In addition, when mitochondrial function is impaired in the digestive tract by disruption of mitochondrial complex IV using an RNA interference (RNAi) construct targeting cytochrome c oxidase-1 subunit Vb (*cco-1*), the mitochondrial unfolded protein response (UPR^{mito}) is induced in the intestine; surprisingly, UPR^{mito} reporters are induced cell nonautonomously in the intestine even when *cco-1* disruption occurs exclusively in the nervous system (Durieux et al. 2011). Indeed, UPR^{mito} reporters are induced to the same extent in the intestine irrespective of whether mitochondrial perturbation is initiated locally in the gut or distally in the nervous system. Reduction of UBL-5 (a ubiquitin-like protein required for induction of the UPR^{mito}) in the intestine suppresses the extended longevity associated with intestine-specific *cco-1* disruption but not *cco-1* perturbation in the nervous system. Nevertheless, the exact molecule required for propagating the mitochondrial stress response between the different tissues remains unidentified. Similar observations have been made regarding neuronal expression of an activated form of X-box-binding protein 1, XBP-1 (referred to as XBP-1s). XBP-1s upregulates the expression of genes involved in repairing the damage associated with protein misfolding in the ER, as part of the ER unfolded protein response (UPR^{ER}). Neuronal expression of XBP-1s increases lifespan, enhances stress resistance, and activates the UPR^{ER} in peripheral organs as well. Disruption of XBP-1 in distal cells abrogates cell-nonautonomous signaling from the nervous system and suppresses the increased lifespan (Taylor & Dillin 2013). However, the molecular determinant(s) that propagates this interorgan signaling module is unknown, although it has been shown to involve the release of neurotransmitters (Taylor & Dillin 2013).

Regulation of Nonautonomous Stress Signaling in Vertebrates by the Brain and Nervous System

Similar to observations in invertebrate systems, the brain/nervous system has been implicated in regulating cellular proteotoxic stress signaling between tissues, in vertebrate systems. Indeed, the ability of adrenocorticotrophic hormone (ACTH) released from the pituitary gland to regulate Hsp70 expression in the adrenal cortex has long been observed in rodents (Blake et al. 1991, 1993; Udelsman et al. 1994). More than half a century ago, a brain-derived peptide referred to as ACTH was shown to be released in response to various stresses experienced by the body (De Groot & Harris 1950). Subsequently, corticotrophin-releasing factor (CRF) was identified as the factor that stimulates the release of ACTH from the pituitary gland (Guillemin & Rosenberg 1955, Saffran et al. 1955). Because these hormones engage a signaling axis that regulates whole-organism physiology in response to stress, the role of the brain in communicating stress responses between vertebrate tissues was essentially established.

The brain influences whole-organism stress signaling in response to increased aerobic physical activity. Regular exercise causes the release of endorphins and other peptides that are purported to promote cognitive function and a sense of well-being (Arida et al. 2015, Dinas et al. 2011). Regular exercise is associated with the release of a host of humoral factors that enhance neuronal plasticity

and promote stress resistance in the brain and other organs. One of the factors released is BDNF (brain-derived neurotrophic factor), which enhances mitochondrial biogenesis through activation of PGC-1 α and thus promotes dendritic spine formation and maintenance in hippocampal neurons (Cheng et al. 2012). Other exercise-induced stress-responsive neural circuits involving serotonin have also been identified. These serve primarily to limit the negative emotional consequences of the stressors (Amat et al. 2005, Baratta et al. 2009).

In addition, the melanocortin system of the mediobasal hypothalamus has emerged as a major orchestrator of energy intake and body weight. Within the arcuate nucleus, two neuronal populations regulate energy homeostasis. They are referred to as the proopiomelanocortin (POMC) and neuropeptide-Y-agouti-related-protein (NPY-AgRP) neurons (Williams & Elmquist 2012). Activation of the NPY-AgRP axis promotes hyperphagia and suppresses energy expenditure; this can be counteracted by the activation of POMC cells by leptin, which promotes satiety and feeding cessation (Nasrallah & Horvath 2014). Thus, interventions that specifically perturb the activation or inhibition of POMC or NPY-AgRP neurons can impair systemic energy balance. Indeed, ER stress in the hypothalamus has been linked to leptin resistance and diet-induced obesity (Ozcan et al. 2009, Won et al. 2009, Zhang et al. 2008).

Interestingly, in mice, overexpression of XBP-1s exclusively in POMC neurons protects against diet-induced obesity and results in a cell-nonautonomous expression of XBP-1s mRNA and its target genes in the liver (Williams et al. 2014). Hepatic expression of XBP-1s has been shown to induce the XBP-1s target gene, UDP-galactose-4-epimerase (*Gale*), which in turn leads to reduced hepatic glucose release and an overall decrease in circulating glucose levels (Deng et al. 2013). The metabolic phenotypes observed for POMC-specific expression of XBP-1s parallel those for liver-specific expression. However, as with the analogous observations in *C. elegans*, the mechanism for this interorgan signaling circuit is unknown (Taylor & Dillin 2013). Altogether, these results add to the growing evidence that the nervous system has a fundamental role in regulating proteotoxic stress across distal organs. Accordingly, therapeutic strategies that target the nervous system may alleviate disease pathology in peripheral organs as well.

Integrating Stress Responses Between Adipose Tissue and Other Tissues and Organs in Invertebrates

In *Drosophila*, glycogen and triacylglycerol are stored in the fat body, which performs functions analogous to the liver and adipose tissue in vertebrates. Metabolism is regulated by a variety of metabolic signaling cascades that impinge on insulin, adipokinetic hormone (the glucagon ortholog in *Drosophila*), and the adiponectin receptor, although the exact ortholog of adiponectin itself remains elusive (it is likely, based on the conservation of the adiponectin receptor, that an adiponectin-like ligand exists in *Drosophila*; future studies are required to clarify this issue) (Caers et al. 2012, Katewa et al. 2012, Kim & Rulifson 2004, Kwak et al. 2013, Laws et al. 2015). The importance of the fat body in relaying physiological signals to other tissues was established more than a decade ago, when restricting the import of amino acids into the fat body was reported to impair systemic insulin signaling and growth by causing the retention of DILPs in the IPCs of the brain (Colombani et al. 2003, Martin et al. 2000). This spurred the hypothesis that a humoral factor secreted by the fat body regulates DILP secretion from the brain. Accordingly, subsequent studies identified the importance of TOR signaling, RNA polymerase III activity, the transcription factor DREF, and the JAK-STAT ligand Unpaired 2 (Upd2) in mediating the effect of the fat body-derived signal(s) on organismal growth and physiology (Geminard et al. 2009, Killip & Grewal 2012, Marshall et al. 2012, Rajan & Perrimon 2012). The fat body also secretes peptides in response to infection and during development. For instance, it secretes an extracellular matrix

Table 1 Selected stress-dependent signaling circuits in *Drosophila*

Signaling molecule	Source	Target	Reference(s)
Adipokinetic hormone	Corpora cardiaca cells of the ring gland	Systemic	Kim & Rulifson 2004
Dawdle	Fat body	Midgut	Chng et al. 2014
GABA (γ-aminobutyric acid)	Olfactory neurons in the brain	Lymph gland	Shim et al. 2013
Hedgehog	Gut	Fat body	Rodenfels et al. 2014
ImpL2	Multiple organs	Systemic	Alic et al. 2011, Owusu-Ansah et al. 2013, Ghosh et al. 2014, Figueroa-Clarevega & Bilder 2015, Kwon et al. 2015
Insulin-like peptides 2 and 5	Insulin-producing cells in the brain	Systemic	Reviewed by Kannan & Fridell 2013, Nassel et al. 2013
Insulin-like peptide 6	Fat body	Systemic	Andersen et al. 2013, Okamoto et al. 2009, Slaidina et al. 2009
Limostatin	Gut	Brain	Alfa et al. 2015
Myoglianin	Muscle	Fat body	Demontis et al. 2014
Neural lazarillo	Fat body	Systemic	Hull-Thompson et al. 2009, Pasco & Leopold 2012
Peptidoglycan recognition proteins	Fat body	Midgut	Chen et al. 2014
Secreted decoy of InR	Glia	Systemic	Okamoto et al. 2013
Unpaired 2	Fat body	Brain	Rajan & Perrimon 2012
Unpaired 3	Macrophages	Systemic	Woodcock et al. 2014

enzyme that regulates trachea development and antimicrobial peptides to combat bacterial and fungal infections (Mabery & Schneider 2010, Schmid et al. 2014). However, we devote most of this section to discussing how communication between the fat body and other tissues and organs regulates organismal physiology under metabolic stress or other adverse environmental conditions.

As a case in point, DILP6 is strongly upregulated in the fat body during starvation and the late larval and pupal periods. When *dilp6* function is disrupted, flies become more sensitive to starvation and pupal growth is significantly impaired. These phenotypes can be rescued by expression of DILP6 in the fat body, emphasizing the importance of this tissue in coordinating organismal response to starvation and determining adult body size (Andersen et al. 2013, Okamoto et al. 2009, Slaidina et al. 2009).

More and more peptides are emerging as regulators of DILP secretion or function, especially in the fat body (**Table 1**). For instance, a peptide dubbed secreted decoy of insulin receptor (SDR) antagonizes insulin signaling (Okamoto et al. 2013). In addition, Upd2, a ligand of the *Drosophila* JAK-STAT pathway, is reportedly induced in the fat body during the fed state (Rajan & Perrimon 2012). Disruption of *upd2* function in the fat body inhibits growth and perturbs energy metabolism and secretion of DILPs. In addition, RNAi-mediated knockdown of adiponectin receptor function in IPCs impairs glucose and lipid homeostasis (Kwak et al. 2013), suggesting the existence of a *Drosophila* adiponectin. Furthermore, a high-sugar diet (HSD) inhibits *Drosophila* larva growth as a result of resistance to DILPs in peripheral tissues (Pasco & Leopold 2012). This has been attributed to the production and secretion of the lipocalin Neural Lazarillo (NLaz)—an ortholog of the vertebrate Retinol Binding Protein 4 (RBP4)—from the fat body, which represses systemic

insulin signaling. *NLaz* is strongly induced when larvae are fed a HSD, and *NLaz* null mutants are refractory to HSD-induced DILP resistance. As evidence that the fat body is the major organ that regulates HSD-induced insulin resistance, RNAi-mediated disruption of *NLaz* in the fat body recapitulates the phenotype of *NLaz* null mutants (Pasco & Leopold 2012). Interestingly, flies with impaired *NLaz* function have reduced lifespans and are sensitive to stress, whereas overexpression of *NLaz* enhances stress resistance and extends longevity (Hull-Thompson et al. 2009). However, it is unclear how *NLaz* impairs insulin secretion. It will be interesting to assess whether SDR, Upd2, *NLaz*, and adiponectin signaling act in concert or in parallel to regulate DILP secretion from IPCs.

Alterations in intracellular calcium concentrations in the fat body can regulate lipid metabolism. When components of the store-operated calcium entry channel are disrupted in the fat body, decreasing intracellular calcium levels, flies respond by releasing short neuropeptide F (sNPF) from the brain, which increases feeding and culminates in the upregulation of obesogenic genes in the fat body (Baumbach et al. 2014). As a consequence, total body fat increases without affecting circulating glucose, trehalose, or even stored glycogen levels. Overexpression of sNPF in the brain is sufficient to recapitulate the increased fat content of flies, confirming the importance of sNPF in mediating the obesogenic signal between the brain and fat body. However, future studies must identify what the exact messenger between the fat body and brain is and whether an analogous calcium-dependent adipocyte-brain signaling axis operates in mammalian systems.

It has long been observed that flies fed a HSD (which can trigger insulin resistance and hyperglycemia) downregulate the expression of amylases in the intestine in a phenomenon referred to as glucose repression (Benkel & Hickey 1986, Hickey & Benkel 1982). Recent observations have revealed that the fat body plays a role in regulating this phenomenon. Chng et al. (2014) have shown that glucose repression is more extensive than previously reported: In addition to amylase genes, genes that encode products with lipase, oxidoreductase, and glucose transporter activity are also repressed. Ingestion of nutritious sugars induces Dawdle, the transforming growth factor β (TGF- β) ligand, in the fat body; Dawdle is then presumably released into circulation to activate TGF- β /Activin/Smad2 signaling in the midgut, which downregulates the expression of many digestive enzymes. This phenomenon is not observed for sweet-tasting sugars with no nutritional value. Thus, by repressing TGF- β signaling in the midgut to reduce the expression of amylases and lipases and, consequently, the amount of nutrients absorbed; the fat body helps avert the potentially catastrophic events of hyperglycemia and increased fat accumulation (Musselman et al. 2011). Notably, Activin signaling has also been implicated in the regulation of sugar metabolism and pH balance (Ghosh & O'Connor 2014).

Additionally, as flies age, the fat body mounts an inflammatory response that can be transmitted to the intestine. The inflammatory response in the fat body impairs immune deficiency (IMD) signaling in the midgut, culminating in midgut hyperplasia (Chen et al. 2014). This is caused by an age-dependent downregulation of lamin B in the fat body and the subsequent secretion of peptidoglycan recognition proteins, resulting in enhanced IMD signaling in the fat body but impaired IMD signaling in the midgut.

One of the enabling characteristics that sustains the hallmarks of cancer is the elevation of proinflammatory cytokines that impact tumor prognosis and trigger organismal responses (Hanahan & Weinberg 2011). The cellular and molecular underpinnings of this phenomenon remain largely unresolved. A recent report in *Drosophila*, which uncovered a tumor suppressor role for the fat body, may shed some light on this problem. When epithelial tumors are generated in *Drosophila*, they cause a systemic immune response involving TNF- α activation in hemocytes and culminating in Toll activation in the fat body (Parisi et al. 2014). This, in turn, restricts tumor growth by triggering apoptosis/cell death. TNF- α is a well-characterized Toll-like receptor

Table 2 Selected stress-dependent signaling circuits in vertebrates

Signaling molecule	Source	Target	Reference(s)
Adenosine	Unknown	Adipose tissue	Gnad et al. 2014
Adiponectin	Adipose tissue	Systemic	Koh et al. 2007, Wang et al. 2013
Adipsin/C3a	Adipose tissue	β cells of pancreas	Lo et al. 2014
BAIBA (β -aminoisobutyric acid)	Myocytes	Adipocytes	Roberts et al. 2014
FGF-21	Liver, adipose tissue, skeletal muscle	Adipose tissue	Reviewed by Itoh 2014, Kim & Lee 2014
GDF11	Unknown	Cardiac and skeletal muscle tissue	Loffredo et al. 2013, Sinha et al. 2014
IGF-1	Skeletal muscle	Skeletal muscle	Ruas et al. 2012
Interleukin 6	Skeletal muscle	Muscle and other organs	Reviewed by Pedersen & Febbraio 2012
Irisin	Skeletal muscle	Adipose tissue	Bostrom et al. 2012
MANF	Cardiac tissue	Cardiac tissue	Glembotski et al. 2012, Tadimalla et al. 2008
Meteorin-like	Skeletal muscle and adipose tissue	Adipose tissue	Rao et al. 2014
Osteocalcin	Bone	Adipose tissue and pancreas	Lee et al. 2007
PTHrP	Tumors	Adipose tissue	Kir et al. 2014

(TLR)/NF- κ B target in mammals and is induced during inflammatory situations such as a high tumor burden (Balkwill 2009). Accordingly, it will be interesting to investigate whether a similar situation occurs in mammals and whether TLRs are similarly required to restrain tumor growth, especially in tissues analogous to the fat body, such as white adipose tissue (WAT) and the liver.

Conveying Metabolic Stress Signals from the Adipose Tissue to Other Tissues and Organs in Vertebrates

Besides its role as a master regulator of metabolism, adipose tissue secretes adipokines and other molecules with autocrine, paracrine, and endocrine functions. For instance, leptin, adiponectin, resistin, adipsin, visfatin, vaspin, fibroblast growth factor 21 (FGF-21), retinol-binding protein-4, and a host of complement factors and cytokines are secreted by adipose tissue in response to metabolic stress, immune stimulation, and other stimuli (Table 2).

FGF-21 has emerged as a major adipokine that is induced to confer tolerance to multiple stressors (reviewed by Itoh 2014, Kim & Lee 2014). It stimulates the formation of beige adipocytes in WAT after chronic exposure to cold. This is an important adaptive response, as beige adipocytes can pursue a thermogenic program similar to that of brown adipose tissue (BAT) by expressing uncoupling protein 1 (UCP-1), a mitochondrial protein notable for its role in generating heat in an ATP-consuming reaction (Barbatelli et al. 2010). During cold acclimatization, FGF-21 is induced through activation of a cAMP-dependent signaling cascade in adipose tissue and acts in an autocrine/paracrine manner to stimulate PGC-1 α activity. This results in the transcriptional upregulation of UCP-1 and other thermogenic genes in specific fat depots. For this reason, mice deficient in FGF-21 adapt poorly to chronic cold exposure and produce fewer beige adipocytes

(Barbatelli et al. 2010, Fisher et al. 2012, Hondares et al. 2011). Thus, in this context, FGF-21 enables the organism to adapt to the stress of hypothermia by increasing the amount of heat generated in the adipose tissue.

FGF-21 also augments the effect of another adipokine: adiponectin. Produced in WAT, adiponectin functions similarly to FGF-21, regulating systemic lipid and glucose homeostasis. The metabolic benefits associated with FGF-21 in skeletal muscle and liver are abrogated in mice lacking adiponectin, and FGF-21 can stimulate the expression and secretion of adiponectin to raise circulating serum levels (Lin et al. 2013). Thus, adiponectin is critical for potentiating the glycemic and insulin-sensitizing effects of FGF-21 (Holland et al. 2013).

In addition to being the source of FGF-21, adipose tissue can respond to systemic FGF-21 signals that emanate from the liver. This happens during fasting, when FGF-21 is induced by PPAR α in the liver, where it acts in an autocrine manner to increase ketogenesis. In addition, FGF-21 from the liver upregulates the two predominant lipases in adipocytes—hormone-sensitive lipase and adipose triglyceride lipase—to increase lipolysis in WAT. Nonesterified fatty acids (NEFA) such as oleate and linoleate can activate PPAR α to increase FGF-21 expression (Mai et al. 2009; Mai et al. 2010). This leads to a mechanism in which fasting causes the release of NEFA from adipose tissue, which activates PPAR α in the liver to stimulate FGF-21 induction. This in turn further increases lipolysis in adipocytes, resulting in a feed forward loop that efficiently mobilizes lipids for metabolism during starvation.

Adipsin is another adipokine involved in energy homeostasis. Also referred to as complement D, it can be processed into several biologically active peptides with important immune-related functions (Cook et al. 1987, Ricklin et al. 2010, Rosen et al. 1989). It is also involved in regulating organismic responses to metabolic stress. C3a—one of the biologically active peptides derived from adipsin—stimulates insulin secretion from pancreatic β cells when circulating glucose levels are high (Lo et al. 2014). Consequently, although mice lacking adipsin fare just as well as wild-type mice when fed a regular diet, glucose homeostasis is significantly impaired when they are fed a high-fat diet (HFD). Importantly, because C3a does not trigger the release of insulin from β cells when the glucose concentration is low, it can readily be exploited for therapeutic purposes; as its inherent negative feedback mechanism will likely curtail the development of hypoglycemia, a possible side effect.

Stresses that inhibit the proper folding and oligomerization of adiponectin in the ER down-regulate systemic adiponectin signaling and accelerate the development of metabolic diseases such as obesity and diabetes (Zhou & Liu 2010). This has been attributed to the various stable oligomeric isoforms in which serum adiponectin can exist, each with distinct biological activities and properties (Schraw et al. 2008, Tsao et al. 2003). The three major oligomers are the trimeric, hexameric, and multimeric high-molecular-weight (HMW) forms (Pajvani et al. 2003, Tsao et al. 2002, Waki et al. 2003), with the HMW form being the most potent in improving glucose homeostasis and forestalling diabetes (Basu et al. 2007, Hara et al. 2002, Pajvani et al. 2004, Waki et al. 2003). A conserved cysteine residue at the N terminus of adiponectin (Cys³⁹ in mice and Cys³⁶ in humans) is required for the formation of an intermolecular disulfide bond critical for adiponectin multimerization (Frizzell et al. 2009, Schraw et al. 2008, Waki et al. 2003), and the disulfide bond A oxidoreductase-like protein (DsbA-L) is required for multimerization of adiponectin (Zhou et al. 2010). Consequently, mice overexpressing DsbA-L in their adipocytes are refractory to diet-induced insulin resistance (Liu et al. 2012, Zhou et al. 2010). Because cysteine is very sensitive to oxidation, acting as a redox sensor in many proteins, it is tempting to speculate that mild oxidative stress resulting from mitochondrial perturbation may enhance multimerization of adiponectin to ultimately promote glucose homeostasis (Cremers & Jakob

2013, Groitl & Jakob 2014). However, severe mitochondrial injury that generates high levels of ROS may increase the amount of misfolded proteins and trigger ER stress, as well as impair secretion of adiponectin (Koh et al. 2007, Ristow & Zarse 2010, Tapia 2006). In any case, it is evident that mitochondrial dysfunction in adipocytes is coupled to systemic energy homeostasis via its effect on adiponectin secretion (Koh et al. 2007, Wang et al. 2013).

Crosstalk Between Stressed *Drosophila* Muscles and Other Organs

The flight muscles of *Drosophila* are structurally very similar to skeletal muscles in vertebrates. Although primarily required for propelling the flies during flight, recent evidence shows that they can regulate systemic stress responses, at least in part, through the secretion of signaling peptides that act in an autocrine or endocrine manner. When mitochondrial function is perturbed in flight muscles, the muscles activate a battery of cytoprotective genes that help repair the effect of stress or at least limit the extent of damage (Owusu-Ansah et al. 2013). Indeed, it is possible to carefully control the amount of mitochondrial damage such that the compensatory stress responses are potent enough to decrease age-related climbing defects and extend lifespan relative to wild-type controls (Owusu-Ansah et al. 2013). Under these conditions, insulin signaling is dampened in both muscle and nonmuscle tissue. In addition, one of the genes transcriptionally activated in response to slight mitochondrial distress in flight muscles is *ImpL2*, which can antagonize insulin signaling. *ImpL2*, originally identified as an imaginal disc growth factor, binds DILP2 and DILP5 to sequester them from circulation; in this respect, it has functions analogous to mammalian insulin-like growth factor-binding proteins (IGFBPs) (Alic et al. 2011). *ImpL2* induction is required for the extended longevity associated with mitochondrial perturbation, and when *ImpL2* is expressed specifically in muscles, evidence of insulin repression is observed in muscles as well as other tissues, providing strong evidence that mitochondrial injury in muscles results in the upregulation of an insulin-antagonizing molecule to limit insulin signaling locally and in distal tissues as well.

ImpL2 is also induced in larval somatic muscles when ribosome synthesis is impaired (Ghosh et al. 2014). This, together with reduced DILP release from the IPCs, limits insulin signaling across the whole organism. RNA polymerase I (Pol I), acting in concert with a Pol I-specific transcription initiation factor (TIF-IA), is required for transcribing ribosomal RNA genes. Increasing TIF-IA levels in muscle partially restores systemic insulin signaling. The repression of insulin release evident when ribosome synthesis is inhibited in muscles is observed in other contexts as well. When FOXO is overexpressed in flight muscles, insulin secretion from IPCs is repressed, culminating in an age-dependent delay in the accumulation of misfolded protein aggregates in muscles and other tissue (Demontis & Perrimon 2010). Similar results are obtained when components of the TGF- β signaling pathway are impaired in muscles (Bai et al. 2013). Although it is unclear whether *ImpL2* is also involved in these processes, it is evident that multiple stressful perturbations of *Drosophila* muscles repress insulin signaling nonautonomously. Ghosh et al. (2014) have posited that the extent of ribosome synthesis in larval muscles may be a sentinel for the regulation of organism-wide responses to insulin signaling, such that when muscle ribosome synthesis is suppressed, an endocrine response involving *ImpL2* and diminished DILP release is activated to inhibit systemic insulin signaling. It will be interesting to test this hypothesis in adult flight muscles, under conditions in which mitochondrial function or components of TGF- β signaling are impaired (**Figure 2**).

Finally, muscle-restricted overexpression of the transcription factor Mnt preserves climbing ability and extends longevity in *Drosophila* (Demontis et al. 2014). This is coupled with downregulation of nucleolar components in muscles and a nonautonomous reduction in ribosomal RNA (rRNA) levels in the fat body. These phenotypes are reported to be triggered by Mnt-dependent

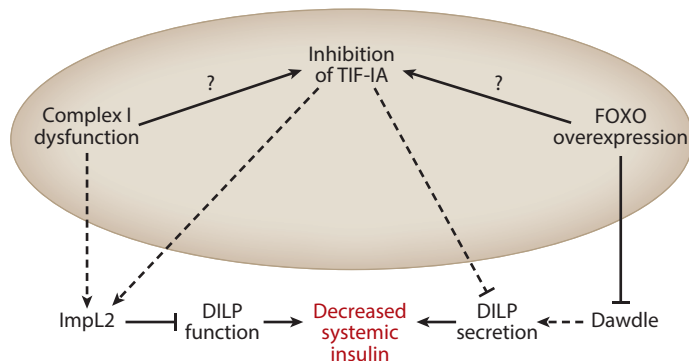


Figure 2

Regulation of systemic insulin signaling as a result of stressful stimuli originating in muscles. Disruption of mitochondrial complex I results in the upregulation of the insulin-antagonizing peptide, ImpL2, which can bind to circulating DILPs to suppress systemic insulin signaling. Dawdle promotes secretion of DILPs from IPCs. Accordingly, FOXO overexpression, which represses Dawdle expression, inhibits the secretion of DILPs, culminating in impaired systemic insulin signaling. Inhibition of TIF-IA, which regulates ribosome biogenesis, results in the retention of DILPs by IPCs and the induction of ImpL2 in muscles. It remains to be tested whether either complex I inhibition or FOXO overexpression in muscles also inhibits TIF-IA to downregulate systemic insulin signaling. Abbreviations: DILP, *Drosophila* insulin-like peptide; IPC, insulin-producing cell; TIF, transcription initiation factor.

upregulation of myoglianin, another TGF- β ortholog. Overexpression or RNAi-mediated disruption of myoglianin expression result in the systemic downregulation or upregulation of rRNA respectively, further demonstrating how physiological stresses in *Drosophila* muscles can be communicated to other tissues.

Myokines Transmit Stress Signals Between Muscles and Other Organs

Skeletal muscles encounter a constant onslaught of both internal and external stressors that make it necessary to swiftly and efficiently communicate with other organs to mount a coordinated and system-wide response to cope with stress. The idea that muscles can secrete growth factors, cytokines, and other peptides to regulate signaling events in the muscle itself or distant organs has gained traction during the past decade with the identification of hundreds of molecules that satisfy these criteria (Bortoluzzi et al. 2006). Some of the secreted factors identified are myostatin, LIF, IL-6, IL-7, BDNF, IGF-1, FGF-2, FGF-21, FSTL-1, irisin, and meteorin-like (Metrnl). In this section, we focus on a few myokines that help relay muscle stressors to other organs.

IL-6 is a myokine that is induced and/or secreted upon exposure to multiple stresses, including oxidative stress, hyperthermia, extracellular adenosine, ADP or ATP, and reduced intramuscular glycogen (reviewed in Pedersen & Febbraio 2012). These stresses engage a range of signaling cascades, including the β -adrenergic and TLR pathways as well as the stress-activated kinase pathways of JNK and p38, leading to the induction of IL-6 (Frost et al. 2006, Patel et al. 2012, Whitham et al. 2012). In general, IL-6 activates compensatory or restorative processes to confer tolerance to or enable recovery from stress, respectively. For instance, IL-6 stimulates muscle compensatory hypertrophy by enhancing the proliferation of satellite cells, which is followed by myonuclear accretion in preexisting myofibers (Serrano et al. 2008). In addition, it enhances lipid catabolism by increasing lipolysis and fatty acid oxidation (van Hall et al. 2003). The increased

circulating IL-6 levels that occur as a result of exercise enhance levels of glucagon-like peptide-1 (GLP-1), which stimulates insulin secretion (Ellingsgaard et al. 2011). Accordingly, IL-6 knockout mice develop glucose intolerance and obesity. Because IL-6 signaling can trigger phosphorylation of STAT-3, and STAT-3 activation can stimulate mitochondrial respiration (Gough et al. 2009, Kishimoto 2005, Serrano et al. 2008), it will be interesting to examine if some of the beneficial effects of IL-6 result from STAT-3-mediated enhancement of mitochondrial respiration.

Impaired autophagy, mitochondrial dysfunction, or ectopic expression of UCP-1 in skeletal muscles leads to FGF-21 induction in muscles (Crooks et al. 2014, Keipert et al. 2014, Kim et al. 2013, Suomalainen et al. 2011, Tynismaa et al. 2010). In a mouse model of mitochondrial myopathy, increased plasma FGF-21 levels are associated with a reduction in hepatic fat content and adipocyte size, as well as resistance to HFD-induced obesity (Tynismaa et al. 2010). However, overexpression of UCP-1 in the skeletal muscles of mice (henceforth referred to as UCP-1-SM mice) reduces muscle mass, increases circulating FGF-21 levels approximately fivefold, and triggers the activation of a compensatory stress response involving eIF2 α /ATF4 in muscles (Keipert et al. 2014). This is associated with enhanced respiratory capacity and expression of BAT markers in WAT. Of note, UCP-1 expression increases in primary white adipocytes treated with serum from UCP-1-SM mice. Thus, in response to some stressors, skeletal muscles can secrete FGF-21 to induce browning of WAT.

Exercise-mediated induction of PGC-1 α expression in muscle increases expression of fibronectin type III domain containing 5 (FNDC5), a glycosylated membrane protein that can be further cleaved into a potent myokine, dubbed irisin. Irisin stimulates the development of beige adipocytes in WAT, increasing energy expenditure and protecting against diet-induced insulin resistance and obesity (Bostrom et al. 2012, Zhang et al. 2014). Regular endurance exercise has long been known to improve cognitive function at least in part by enhancing neurogenesis (Cotman et al. 2007, Mattson 2012). Recently, exercise-induced upregulation of FNDC5 was shown to enhance BDNF expression in the hippocampus of mice; indeed, PGC-1 α can stimulate neuronal FNDC5 and BDNF expression (Wrann et al. 2013). It remains to be determined whether FNDC5 regulates BDNF expression, through irisin or another peptide derived from FNDC5. Nevertheless, these findings establish a molecular link between PGC-1 α and FNDC5 postexercise, in the hippocampus.

PGC-1 α 4, a splice isoform of PGC-1 α , is upregulated in response to resistance training (Ruas et al. 2012); and induces and represses IGF1 and myostatin, respectively, culminating in muscle hypertrophy. Besides the autocrine effects of IGF1 and myostatin, the expression of PGC-1 α 4 in muscles alters whole-body energy expenditure (Ruas et al. 2012). Recently, a secreted protein, meteorin-like (Metrl), which is induced in muscle after exercise and in adipose tissue upon cold exposure, was shown to be induced in response to muscle-specific PGC-1 α 4 overexpression (Rao et al. 2014). Metrl boosts energy expenditure, enhances glucose tolerance in obese mice, increases the expression of genes associated with beige fat thermogenesis, and stimulates an anti-inflammatory response in adipose tissue. These effects result from an eosinophil-dependent upregulation of IL-4 expression, which promotes alternative activation of macrophages localized in adipose tissue. As alternatively activated macrophages enhance insulin action and protect adipocytes from inflammation (Odegaard & Chawla 2011), both irisin and meteorin-like have therapeutic potential for metabolic diseases.

Finally, several muscle-derived factors, such as FGF-2, IGF-1, IL-5, myostatin, and osteonectin, have notable effects on bone metabolism (Bortoluzzi et al. 2006, Chan et al. 2007, Elkasrawy & Hamrick 2010, Franchimont et al. 2005, Hamrick et al. 2010, Jorgensen et al. 2009, Nielsen et al. 2007). Some of these factors are secreted in response to muscle contraction, resistance exercise, myotube hypertrophy, or stresses that injure the muscle. A particularly important peptide

secreted from both human and rat myotubes is osteonectin, a 40-kDa protein also referred to as secreted protein acidic and rich in cysteine (SPARC) or basement membrane protein 40 (BM-40) (Termine et al. 1981). Although osteonectin has been implicated in mineralization during bone formation, a definitive role for osteonectin secreted from muscles has yet to be determined (Termine et al. 1981).

The Role of the Intestine in Stress-Mediated Interorgan Communication in *Drosophila*

As one of the first barriers to the *milieu interieur*, the digestive tract encounters a plethora of aggressions. Tissue injury, infection, ER stress, and oxidative stress can trigger intestinal stem cell proliferation and/or intestinal dysplasia in fly guts (Apidianakis et al. 2009, Hochmuth et al. 2011, Wang et al. 2014). Indeed, the gut is home to both beneficial and harmful microorganisms. Accordingly, the effect of the gut microbiota on the physiology of the digestive tract, intestinal stem cell activity, and the overall health of the animal has sparked considerable interest. Excellent reviews describing this subject have been published elsewhere (Berrilli et al. 2012, Lee & Brey 2013). We draw attention to a few key studies that emphasize how the digestive tract may be intimately involved in stress-dependent organ-to-organ communication.

In *Drosophila*, enterobacterial infection or increased ROS production in the intestine triggers antimicrobial peptide (AMP) responses in the fat body through a signaling network involving nitric oxide, *Drosophila* orthologs of the AP-1 transcription factor, and NF- κ B (Wu et al. 2012). Because stimulating ROS production is sufficient to trigger the gut-to-fat body communication network, it is plausible that other ROS-generating stresses in the gut, such as impaired mitochondrial function, may also signal to the fat body through this mechanism. Another stress-activated transcription factor that can induce AMP responses even in the absence of infection is FOXO (Becker et al. 2010). AMP genes are upregulated upon starvation; this response is abrogated in *foxo* null mutants but enhanced when FOXO is overexpressed. The FOXO-mediated induction of AMPs appears to be conserved in mammalian cells, as mammalian orthologs of AMPs, such as defensin α -1 (also known as DEFA1), defensin β -1 (DEFB1), and defensin β -3 (DEFB103A), are upregulated in several human cell lines when insulin signaling is suppressed (and, consequently, FOXO is activated) (Becker et al. 2010). These results suggest that many stresses that impair insulin signaling may feed into the AMP-dependent, infection-mediated stress responses described in the gut.

Stem cells residing in the *Drosophila* adult midgut are capable of differentiating into at least two principal cell types of the digestive tract, secretory enteroendocrine (EE) cells or absorptive enterocytes (ECs). Peptides secreted from either EEs or ECs in response to various physiological changes can also initiate crosstalk between the gut and other organs. Limostatin produced from EEs was recently identified as a peptide that suppresses insulin secretion from IPCs (Alfa et al. 2015). Tachykinin, also produced by EEs, regulates lipid metabolism locally in the gut, affects the growth of EEs, and alters systemic lipid storage (Amcheslavsky et al. 2014, Song et al. 2014). Additionally, ECs in larval intestines secrete a lipoprotein-associated form of Hedgehog (Hh) that signals the fat body to modulate growth and developmental timing; and circulating Hh is required for mobilizing fat body triacylglycerol (TAG) stores during starvation (Rodenfels et al. 2014). Furthermore, overexpression of Yorkie (the *Drosophila* ortholog of Yap1) in intestinal stem cells, results in degeneration of the ovary, fat body, and muscle, as a result of systemic inhibition of insulin/IGF signaling caused by upregulation of the secreted insulin/IGF antagonist ImpL2 from the hyperproliferating gut (Figueroa-Clarevega & Bilder 2015, Kwon et al. 2015). Altogether, these results highlight the potential of gut-secreted peptides in coordinating the response of other organs to stressful perturbations in the gut.

Stress Signaling Axes Involving the Gut and Other Organs in Vertebrates

The gut and brain communicate extensively with each other via neural and hormonal cues in response to varying stresses. As in *Drosophila*, the microbiota localized to the vertebrate gut has major physiological consequences. As a case in point, *Helicobacter pylori* is a gram-negative bacterium that infects up to half of the world's population and has been linked to the development of gastric cancer. Oxidative stress is a prominent component of the pathophysiology of *H. pylori* infection. Although there may be multiple reasons why *H. pylori* infection induces oxidative stress, *H. pylori* strains with an active copy of cytotoxin-associated gene A (*cagA*) produce higher levels of ROS and cause more DNA damage (Chaturvedi et al. 2011). Similarly, strains with a functional vacuolating cytotoxin A (VacA) protein stimulate ROS generation in eosinophils.

ROS generated in the gut may damage DNA and activate redox-sensitive signaling cascades, which in turn may promote tumor formation or the development of inflammatory bowel disease (IBD) (Circu & Aw 2011). Moreover, the presence of the *cagA* gene is associated with increased expression of the proinflammatory cytokines TNF- α and IL-8 (Augusto et al. 2007). These observations indicate that by causing oxidative stress in the gastrointestinal tract, *H. pylori* infection can trigger the activation of proinflammatory cytokines, the effects of which may be relayed to internal organs.

The intestinal microbiota also includes probiotic or beneficial microorganisms that can alter cytokine secretion profiles in a way that can be salutary for the host (Thomas & Versalovic 2010). A recent report revealed that even viruses can be amicable: for instance, the murine norovirus (MNV)—a common enteric RNA virus—triggers transcriptional changes in the gut consistent with activation of antiviral type I interferon signaling (Kernbauer et al. 2014).

Other observations highlight how ER stress impacts the gut. Unresolved ER stress can hasten the depletion of intestinal epithelial stem cells by promoting their progression to the transit-amplifying state (Heijmans et al. 2013). Transit-amplifying cells are incapable of self-renewal but undergo cell division for a few cycles prior to terminal differentiation. In addition, XBP-1 suppresses tumor formation (Niederreiter et al. 2013), and its deletion creates a proinflammatory environment in the intestinal epithelium that increases susceptibility to the development of IBD (Kaser et al. 2008). In perhaps another example of how stress signaling may be propagated between tissues, IBD is associated with the development of osteoporosis (Targownik et al. 2013). However, further studies are required to establish whether proinflammatory cytokines induced in response to ER stress and IBD are secreted into serum to activate stress-signaling cascades in osteoblasts (bone cells) to trigger osteoporosis.

OTHER SCENARIOS

Up to this point, the focus of this review has been on tissues and organs with prominent roles in initiating or at least mediating nonautonomous stress signaling. In this section, we summarize observations from other scenarios, highlighting additional and perhaps less-characterized avenues by which stress signaling between tissues may be regulated.

Skeletal development and function has long been known to be influenced by FGF-23, which is secreted from bone tissue and can inhibit the reabsorption of phosphate ions from the kidney, thus affecting whole-organism phosphate homeostasis. Growing evidence implicates the skeletal system in conveying signals from the bone to tissues that regulate energy homeostasis in response to environmental cues. This process is at least partly mediated by osteocalcin, an acidic, calcium-binding, bone-remodeling protein synthesized primarily by osteoblasts during bone formation. Some osteocalcin is released into circulation, where it subsequently targets pancreatic β cells and

adipocytes to stimulate insulin and adiponectin expression, respectively (Lee et al. 2007). Mice deficient in osteocalcin have impaired glucose homeostasis and are obese, providing firm evidence of how the skeletal system can regulate energy homeostasis through this protein. In addition, osteocalcin enhances the synthesis of several enzymes involved in testosterone biosynthesis but does not alter the expression of Cyp19, an enzyme required for converting testosterone to estradiol. As a result, it stimulates the production of testosterone by the testes but has no effect on estrogen levels (Karsenty 2011). Changes in plasma levels of IL-6 and TNF- α regulate the expression or activity of osteocalcin (Li & Stashenko 1992). Therefore, endurance exercise and other physiological stresses that alter IL-6 or TNF- α secretory profiles are likely to regulate systemic energy homeostasis or male fertility, at least in part, by modulating the activity of osteocalcin.

The success story regarding the study of myokines from skeletal muscles has impelled researchers to examine secretory factors from cardiac muscles (cardiomyokines). ER stress can be induced as a result of cardiac ischemia or when cardiomyocytes are cultured under hypoxic conditions (Doroudgar et al. 2009, Thuerlauf et al. 2006). Although ischemia can disrupt protein folding in the ER of cardiomyocytes, it appears that the secretion of some cardiomyokines actually increases when ER homeostasis is impaired. When ER stress is induced, ATF6 is activated and stimulates transcription of genes with ER stress response elements in their promoter regions. Among the genes induced in response to ATF6 activation are cardiomyokines, an example of which is MANF (mesencephalic astrocyte-derived neurotrophic factor, also referred to as arginine-rich mutated in early tumors, or ARMET) (Tadimalla et al. 2008). In ischemic cardiomyocytes or in the hearts of mice with a myocardial ischemic/reperfusion injury, overexpression of MANF suppresses cell death and tissue damage, respectively (Glembotski et al. 2012, Tadimalla et al. 2008). However, given that MANF, as the acronym suggests, is also a neurotrophic factor, the possibility that it can be secreted from ischemic hearts to regulate events in the nervous system, in addition to its apparent autocrine/paracrine effects, cannot be excluded. Future studies should help elucidate the exact mechanism(s) by which MANF regulates stress signaling in response to cardiac ischemia.

The importance of secretory factors in modulating cardiac physiology has also been shown in a study in which cardiomyocyte hypertrophy was reversed as a result of exposure to humoral factors from young mice (Loffredo et al. 2013). Subsequent proteomic, metabolomic, and lipidomic analyses identified growth differentiation factor 11 (GDF11, a member of the TGF- β family) as a secretory factor that is elevated in young mice relative to old. Where exactly GDF11 is secreted is unclear, as it is expressed in multiple tissues, but its expression in the spleen is particularly high in young versus old mice. It has therefore been hypothesized that a decline in production or secretion of GDF11 by the spleen may account for the reduction in circulatory levels with age. Restoring GDF11 expression in old mice was reported to reverse age-related hypertrophy. Recent studies have also shown that the reduction in GDF11 levels with age impairs skeletal muscle function; GDF11 supplementation increases the number of muscle satellite cells and improves muscle function in old mice (Sinha et al. 2014). However, an independent group recently reported that GDF11 expression actually increases with age and inhibits muscle regeneration (Brun & Rudnicki 2015, Eggerman et al. 2015). In spite of the disagreement on the regenerative properties of GDF11, GDF11 does appear to have antiaging effects by repressing cell growth pathways—which is also supported by observations in *Drosophila* (Demontis et al. 2014).

It was recently shown in *Drosophila* that macrophages play a role in the systemic response of flies fed a HFD (Woodcock et al. 2014). Flies raised on a HFD activate the JAK-STAT pathway systemically and display insulin resistance and a shorter lifespan. Interestingly, the enhanced activation of JAK-STAT signaling results from the JNK-mediated production of one of its ligands, Upd3, in macrophages. Disruption of Upd3 function in macrophages suppresses insulin resistance

and partially restores the decreased longevity of flies fed a HFD. Notably, both insulin resistance and cytokine production are attenuated in mice with JNK-deficient macrophages (Han et al. 2013). Accordingly, it may be possible to exploit this HFD-induced JNK-cytokine signaling axis for therapeutic purposes.

When germline cells of *C. elegans* are ablated, stress resistance and lifespan increase in a phenomenon referred to as gonadal longevity. This phenomenon is mediated by HSF-1, FOXO (DAF-16), the FOXA ortholog PHA-4, and the nuclear receptors DAF-12 and NHR-80. These factors act in concert to enhance lipolysis activity and the proteostasis network across the whole organism (Shemesh et al. 2013). Although the phenomenon has not yet been described in other systems, it provides a sterling example of how gonads can regulate stress responses in other tissues.

FUTURE PROSPECTS

Identifying Signaling Peptides that Regulate Nonautonomous Stress Signaling

A strategy that has proven extremely successful in identifying myokines induced in response to PGC-1 α activation may be employed to identify the secretory peptides that help communicate stress responses between transmitting and receiving organs (**Figure 1**). By using a combination of Affymetrix GeneChip microarrays and software that can predict candidate proteins targeted for secretion (Emanuelsson et al. 2007), it was possible to identify several proteins that may be secreted in response to PGC-1 α expression. Further metabolic and biochemical characterization identified irisin as the peptide that is secreted from muscles to induce a thermogenic program in adipocytes (Bostrom et al. 2012). This robust approach was also used to identify meteorin-like as a secretory factor induced in response to PGC-1 α 4 expression in muscles (Rao et al. 2014) and MANF and regulator of calcineurin 1 (RCAN1) as factors induced as a result of XBP-1 overexpression in cardiac tissue (Belmont et al. 2008, Glembofski et al. 2012).

Extending such an approach to invertebrate model organisms such as *Drosophila* and *C. elegans* is likely to prove even more successful; because the extensive arsenal of tools available makes further characterization of putative candidates more feasible than in a mouse model. For instance, in *Drosophila* a particular transcription factor can be overexpressed specifically in the transmitting organ using the Gal4-UAS system, and then RNA-seq coupled with algorithms that predict secretory peptides can be used to detect all putative secretory factors that are induced above a particular cutoff point. Subsequently, RNAi can be used to disrupt expression of each of the putative secretory factors in the transmitting organ, and then the appropriate phenotypes can be scored in the target organ or by means of whole-organism metabolic assays. Because of large-scale efforts, more than 50,000 transgenic UAS-RNAi lines are now publicly available at multiple *Drosophila* stock centers (Perrimon et al. 2010). This means that even candidates assigned a low priority, perhaps as a result of induction close to an artificially selected cutoff point, can readily be tested. This approach can be further expanded by using techniques that probe gene and protein expression via ribosome profiling and mass spectrometry, respectively.

Another approach for identifying peptides that regulate interorgan stress responses in *Drosophila* is to analyze the compositional changes of the hemolymph—an interstitial fluid that bathes the fly's organs. Hemolymph may be composed of more than 700 proteins, and the concentration of some of these proteins changes in response to dietary conditions (Handke et al. 2013). It is possible to analyze compositional changes in the hemolymph using mass spectrometry. If a factor's concentration increases, RNAi can be used to disrupt its expression in the transmitting organ, and then the appropriate phenotype(s) can be scored in the receiving organ. Alternatively, if the phenotype to be scored is very robust and can be assessed in a relatively facile assay, a

more labor-intensive but completely unbiased approach can be employed: RNAi can be used to knock down the expression of all putative secretory factors (i.e., the secretome) in the transmitting organ, and the appropriate phenotype can be scored. In both scenarios, genes perturbed via RNAi in the transmitting organ that reduce expression of the reporter in the receiving organ will emerge as strong candidates. Further characterization of the effects of their overexpression should help determine which of the streamlined candidate(s) actually regulate interorgan stress signaling.

The Advent of Metabolites as Regulators of Interorgan Stress Responses

Metabolites are also emerging as regulators of nonautonomous stress signaling modules. As a case in point, β -aminoisobutyric acid (BAIBA), which is secreted from myocytes overexpressing PGC-1 α , induces expression of brown adipocyte-specific genes when added to adipocytes (Roberts et al. 2014). Further studies have revealed that serum levels of BAIBA increase in mice subjected to exercise or mice overexpressing PGC-1 α in their skeletal muscles (Roberts et al. 2014). In line with previous observations of mice with impaired leptin function, BAIBA reduces weight gain and improves glucose homeostasis in mice (Begriche et al. 2008). Furthermore, in mice, it enhances β -oxidation in the liver and stimulates a brown adipocyte gene expression signature in human induced pluripotent stem cells primed to differentiate into white adipocytes (Roberts et al. 2014). Finally, in humans, plasma levels of BAIBA are inversely correlated with cardiovascular risk factors such as fasting glucose, triglyceride, and cholesterol levels, highlighting the translational potential of BAIBA (Roberts et al. 2014). Notably, adenosine has recently been shown to activate BAT (Gnad et al. 2014). As GABA, 2-deoxycytidine, and cytosine also increase as a result of forced expression of PGC-1 α , it is clear that additional metabolites that relay stress responses between tissues and organs are likely to be identified in the future.

In invertebrate model organisms, metabolomic approaches are being explored to identify metabolites that may help convey the physiological state of one organ to another or even modulate the whole aging process (Chintapalli et al. 2013). In a particularly illuminating example, when long-lived *C. elegans* mutants were metabolically profiled, six compounds were found to be associated with increased lifespan (Patti et al. 2014). Further studies in humans revealed that the amounts of two of these compounds are altered in aged quadriceps muscles (Patti et al. 2014). However, as with many metabolomics studies, a causal relationship could not be established. Nonetheless, compounds identified this way can readily be tested in *C. elegans* or *Drosophila* for lifespan-promoting effects.

CONCLUSION

In this review, we describe some of the mechanisms by which tissues communicate under stress conditions. Although we are only at the beginning of having a unified view of these processes, some uniting themes have emerged, for example, the role of XBP-1 in conveying stress signals associated with beneficial effects in both *C. elegans* and mice (Taylor & Dillin 2013, Williams et al. 2014). Importantly, the ultimate challenge will be to understand how the many signals emanating from various tissues and organs are integrated at the single cell and organismal levels, and how cells integrate so many signals that appear to converge on very similar processes: protein synthesis, substrate utilization, glucose homeostasis, and lipid storage.

As we move forward, many fundamental questions remain to be addressed. To cite only a few, the recent observation that different splice isoforms of PGC-1 α regulate muscle function and myokine expression differently, coupled with the isoform-specific characteristics observed for the UPR^{ER} transducer ATF6, is likely to spur new questions (Bostrom et al. 2012; Rao et al. 2014;

Ruas et al. 2012; Thuerlauf et al. 2004, 2007). To what extent do stresses in various transmitting organs regulate different isoforms of specific secretory peptides? Can a transmitting organ regulate isoforms of a particular signaling peptide to respond to different degrees or types of stresses? In addition, studies on stress signaling between organs should help resolve how microenvironmental stresses in tumors are relayed to other clinically normal organs. It is well known that tumor hypoxia activates hypoxia inducible factor (HIF-1), which in turn upregulates VEGF to stimulate angiogenesis. Along similar lines, it is tempting to speculate whether impaired ER homeostasis also contributes to nonautonomous tumor effects via activation of XBP-1. Indeed, Wnt processing and secretion are impaired as a result of ER stress induced by tumor hypoxia (Verras et al. 2008). The loss of adipose tissue that occurs during cancer cachexia results from tumor-derived parathyroid-hormone-related protein (PTHrP), which enhances expression of thermogenic genes in adipose tissue (Kir et al. 2014). These observations underscore how, eventually, extending these studies to tumors is likely to uncover novel therapeutic opportunities. Finally, moving forward, one challenge that needs to be addressed is how to deal with variability in phenotypes resulting from subtle differences in genetic background or from animals raised in different facilities (Adams et al. 2013, Dutchak et al. 2012, Fisher et al. 2010, Hotta et al. 2009).

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Errata

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