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The Insect Fat Body Integrates Nutritional State, Immunity, Reproduction, and Stress Through Shared Regulatory Networks

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ABSTRACT

The insect fat body is conventionally described through discrete functions: nutrient storage, metabolic regulation, immune effector production, vitellogenic support, detoxification, and endocrine signaling. This partitioning is experimentally convenient but biologically incomplete because many of these functions occupy the same tissue, use overlapping molecular machinery, and change simultaneously as nutritional, reproductive, infectious, developmental, and environmental conditions shift. The resulting problem is not simply pathway cross-talk. A regulatory input that promotes one output may constrain another because substrate accessibility, translational capacity, cellular state, endocrine context, or inter-organ feedback changes with physiological state. This article develops a molecular systems interpretation in which the fat body is treated as a conditional regulatory interface rather than a collection of independent pathways. Evidence from dipteran, lepidopteran, coleopteran, hemipteran, and orthopteran systems shows that nutrient sensing, insulin/IGF signaling, AMP-activated protein kinase, autophagy, lipid-droplet regulation, juvenile hormone, ecdysteroid signaling, immune activation, and xenobiotic-responsive transcription intersect with fat-body function, but their effects are strongly contingent on taxon, developmental stage, sex, diet, infection, and environmental state. Particularly informative discordances include increased stored lipid with impaired starvation performance, post-feeding lipogenic flux without corresponding increases in lipogenic transcript abundance, and reproductive molecular outputs that do not necessarily predict realized fecundity. A proposed systems model therefore distinguishes physiological demand, regulatory state, tissue capacity, accessible resource pools, and realized organismal output. The model generates testable predictions about simultaneous-demand constraints, state-dependent regulatory effects, cross-level feedback, and the conditions under which molecular measurements fail to predict physiological performance.

Keywords: Fat body, Nutrient sensing, Immunometabolism, Vitellogenesis, Endocrine signaling, Metabolic stress

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Introduction

The insect fat body combines functions that vertebrate physiology distributes among several organs. It stores and mobilizes carbohydrate and lipid reserves, supports systemic nutrient homeostasis, produces immune effectors, contributes to reproductive provisioning, participates in detoxification, and exchanges endocrine information with

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other tissues. These activities are not merely colocated: immune activation can reorganize metabolism, while simultaneous reproductive and immune demands can expose limits in the translational machinery of the same tissue [1–3]. Treating these activities as independent modules therefore obscures a central systems problem: fat-body output at any moment depends on which demands coincide and on whether the resources and cellular machinery required by those demands are mutually compatible.

A pathway-centred account is also insufficient because the same canonical signals do not produce identical functional consequences across insect contexts. Fat-body biology encompasses conserved molecular motifs, but their deployment differs with developmental stage, feeding strategy, reproductive mode, pathogen exposure, and environmental history [1]. A molecular interaction observed under larval starvation cannot automatically be transferred to a blood-fed adult female, and a transcriptional response to infection cannot be interpreted as evidence that metabolic flux or organismal performance changed in the same direction.

This article therefore develops a proposed conditional systems model of fat-body regulation. Its purpose is not to replace pathway-specific mechanisms with a universal master network. Instead, it distinguishes five analytical quantities that are often conflated: physiological demand, regulatory state, tissue capacity, accessible resource pools, and realized output. The model asks when shared regulatory nodes coordinate several functions, when they create antagonistic demands, and when apparently contradictory molecular and organismal measurements reflect different levels of the same physiological system.

Functional organization of the fat body

The fat body should first be understood as a functionally heterogeneous tissue whose regulatory organization changes across insect life histories. Nutritional regulation of growth illustrates this point. Insulin/IGF, target-of-rapamycin, steroid, and nutrient-sensing mechanisms recur broadly, yet insects differ in how nutritional information is coupled to growth and developmental timing [4]. Conserved pathway names therefore do not imply identical regulatory architecture. For a systems model, the relevant unit is not the presence of a signaling component but the state-dependent relationship between that component and a particular physiological output.

Tissue-specific perturbation demonstrates how local fat-body regulation can propagate systemically. In *Drosophila melanogaster*, inactivation of E2F/Dp activity in fat-body cells altered carbohydrate metabolism, reduced circulating trehalose and lipid stores, and generated organism-level viability defects that could be partly rescued nutritionally [5]. This establishes that a transcriptional regulator operating within the fat body can influence whole-organism metabolic state. It does not establish E2F as a universal metabolic controller; rather, it provides a mechanistic example of how local cell state can become a systems-level constraint.

Functional organization also includes responses that are often discussed separately from nutrient physiology. In *Spodoptera exigua*, P450 and UDP-glycosyltransferase genes show strong tissue specificity and chemically dependent transcriptional responses to insecticides [6]. The pattern is important precisely because it is not uniform: different compounds do not activate an interchangeable detoxification program. Moreover, transcript induction cannot by itself demonstrate detoxification flux or resistance. The fat body is therefore better represented as a tissue containing partially overlapping functional programs whose regulatory meaning depends on both the initiating demand and the level at which the response is measured.

Nutrient sensing and storage

Nutritional state is dynamic rather than binary. Metabolomic analysis of *D. melanogaster* showed rapid remodeling during the transition from fasting to refeeding, while chronic high-sugar feeding reduced some of the metabolic contrast between hunger and satiety [7]. These data establish rapid organismal metabolic plasticity, although they do not assign every measured metabolite change specifically to the fat body. For a systems interpretation, they nevertheless demonstrate that a fixed molecular reading taken at one nutritional state cannot be assumed to describe the regulatory landscape after feeding.

Trehalose metabolism provides a complementary form of control. Loss of trehalose synthesis in developing *Drosophila* destabilizes circulating glucose homeostasis and increases sensitivity to dietary composition [8]. Trehalose therefore functions not only as stored carbohydrate but as a buffering mechanism capable of reducing variation in internal nutrient conditions. Such buffering is relevant to fat-body systems regulation because downstream signaling can respond to the stability and accessibility of substrates rather than simply their total abundance.

Metabolic compensation further complicates single-node interpretations. In adult female *Aedes aegypti*, pyruvate kinase activity varies with nutritional condition, and RNA interference against pyruvate kinase produces compensatory changes in carbon and nitrogen metabolism revealed by stable-isotope tracing [9]. Survival effects were conditional rather than uniform. A molecular perturbation may therefore expose alternative routes through the network without establishing that the perturbed enzyme is rate-limiting under every feeding state.

The distinction between molecular abundance and metabolic flux is especially clear in the blood-feeding bug *Rhodnius prolixus*. A blood meal strongly increases de novo lipogenesis in the fat body, yet acetyl-CoA carboxylase transcript and protein abundance do not rise in parallel with that flux [10]. Consequently, transcriptomics alone may misidentify both the magnitude and direction of physiological allocation. Substrate supply, pre-existing enzyme abundance, post-translational regulation, or interacting pathways may dominate the realized metabolic response.

Storage abundance likewise cannot be equated with effective energy availability. Silencing autophagy-related genes ATG6 or ATG8 in *R. prolixus* produces greater triacylglycerol accumulation during prolonged starvation while simultaneously impairing locomotor performance and survival [11]. The apparent paradox disappears when stored reserves and mobilizable reserves are treated as distinct systems variables. A large lipid pool can coexist with poor physiological access to that pool.

Lipid-droplet regulation is itself state dependent. In the Colorado potato beetle, LSD-family lipid-droplet proteins display different expression and functional relationships across larval, adult, starvation, and diapause contexts [12]. These findings argue against treating lipid storage as one invariant program. Developmental state and environmental history alter both the storage architecture and the likely consequences of manipulating it.

Several studies identify explicit molecular bridges between nutrient state and endocrine control. In *Bombyx mori* and *Drosophila*, 20-hydroxyecdysone activates an AMPK–PP2A axis that antagonizes insulin/IGF signaling in the fat body during developmental transitions, restricting growth rate [13]. This is evidence for a defined cross-talk mechanism, but not for a unique route through which steroid signaling regulates IIS. In *Drosophila*, nutrient stress also activates fat-body AMPK–p53 signaling, represses the adipokine Upd2, modifies systemic insulin signaling, and changes autophagic responses [14]. Here, intracellular energetic stress is translated into inter-organ endocrine information.

Developmental state can determine whether these regulatory motifs produce the same functional outcome. Around the larval commitment to metamorphosis, *Drosophila* changes its starvation response through ecdysteroid-dependent metabolic remodeling and ImpL2-mediated modulation of insulin signaling [15]. After commitment, conserving circulating and stored fuels becomes particularly important for completing development. This context illustrates why a systems model must include developmental state explicitly: the same nutritional deficit can have different regulatory consequences before and after a life-history transition.

Immune signaling

Immune regulation provides some of the clearest evidence that fat-body functions cannot be interpreted independently of physiological state. In mated female *D. melanogaster*, Sex Peptide-dependent reproductive signaling increases juvenile-hormone activity, and this endocrine change contributes mechanistically to reduced resistance against bacterial infection [16]. The result demonstrates an endocrine connection between reproduction and immunity in this system. It does not establish that juvenile hormone is inherently immunosuppressive in all insects or that reproductive investment always produces the same immune consequence.

Environmental information can also reach immune physiology through multi-organ signaling. In *Drosophila* larvae, integrated carbon-dioxide and hypoxia sensing influences immune-cell development through communication involving neural pathways and the fat body [17]. The observation expands the regulatory role of the fat body beyond direct nutrient or pathogen sensing: environmental state may alter immunity through indirect inter-organ signals. Laboratory gas exposures, however, should not be converted into claims about field-level hypoxia responses without ecological validation.

Even within the immune response, the regulatory architecture is context dependent. Allele-specific transcriptomic analysis of *Drosophila* fat body showed that the relative contribution of cis- and trans-regulatory divergence changes with infection type, with different patterns following Gram-negative and Gram-positive bacterial challenges [18]. Thus, “the immune transcriptional state” is not a single reproducible configuration independent of pathogen and genotype.

A similar conditionality appears at the interface between metabolism and immunity. Increased insulin signaling specifically in the fat body of *Anopheles stephensi* alters metabolite profiles and enhances several responses to bacterial and *Plasmodium falciparum* challenge [19]. Yet the same manipulation illustrates why molecular outputs cannot be substituted for whole-organism reproductive success: increased vitellogenin expression did not necessarily translate into greater fecundity, and metabolic consequences changed with age. IIS is therefore appropriately treated as a shared regulatory interface whose consequences depend on state, rather than as a uniformly beneficial or detrimental switch.

Reproductive support

Reproductive support by the fat body is often represented primarily through vitellogenin synthesis, but this understates both its regulatory complexity and its taxonomic diversity. Juvenile hormone, ecdysteroids, insulin-like signaling, and nutritional pathways contribute differently to female reproduction across insect orders [20]. The fat body must therefore be positioned within the reproductive system as a conditional metabolic and biosynthetic partner rather than as a uniform vitellogenin factory.

In the migratory locust, juvenile hormone demonstrates how reproductive signaling can modify the cellular capacity of the fat body itself. JH signaling through Met and Taiman activates Cdk6 and E2f1, promotes fat-body cell polyploidization, and supports vitellogenin production and ovarian maturation [21]. The significance for systems regulation is that reproductive demand can alter the machinery available to satisfy that demand. Cellular state is therefore not merely an output of endocrine signaling; it can determine how much biosynthetic work the tissue can perform. This mechanism is well supported in adult female locusts but should not be extrapolated automatically to other orders.

Reproductive output also depends on how lipid metabolism is partitioned between tissues. In *D. melanogaster*, manipulation of the nuclear receptor dHNF4 produces tissue-dependent consequences. Fat-body overexpression decreases triacylglycerol stores and impairs oogenesis, whereas ovarian manipulation produces a different combination of egg-production and offspring outcomes [22]. Such discordance warns against treating an upstream metabolic regulator as intrinsically pro- or anti-reproductive. The physiological consequence depends on where, when, and how strongly the node is perturbed.

Mating history adds a temporal dimension. A single mating can produce persistent suppression of antibacterial defense in female *D. melanogaster* for at least several days, whereas a second mating does not simply intensify the immune reduction [23]. Reproductive state is therefore better represented as a history-dependent physiological condition than as an instantaneous binary event. Age, endocrine history, nutrient use, and infection timing may all alter the downstream phenotype.

Taken together, the evidence supports a distinction between reproductive demand, fat-body biosynthetic capacity, metabolic support, and realized reproductive output. These quantities can covary, but they need not do so. Increased vitellogenic signaling does not guarantee greater fecundity; increased lipid storage does not guarantee greater reproductive accessibility; and stronger endocrine activation may simultaneously alter immune competence. The proposed systems model therefore treats reproduction not as one competing output but as a structured demand that can modify the regulatory state and capacity of the tissue that supports it.

The reproductive evidence is easiest to interpret when endocrine activation, cellular capacity, metabolic support, immune consequence, and realized reproductive performance are kept analytically separate. The conditionality and failure modes of those relationships are therefore summarized in **Table 1** rather than collapsed into a single reproduction-versus-immunity axis.

Table 1. Reproductive support is partitioned across endocrine drive, fat-body capacity, metabolic accessibility, and realized output

	Endocrine entry	
Reproductive-support dimension	**Endocrine activation of reproductive programming**	**JH-linked expansion of biosynthetic capacity**
Observable support	Juvenile-hormone, ecdysteroid, and nutrient-signaling control of reproductive processes	Met/Taiman-dependent Cdk6/E2f1 activation, fat-body polyploidization, vitellogenin production, ovarian maturation
Consequence for reproduction	Reproductive demand enters the fat body through taxon- and state-dependent endocrine routes	Reproductive signaling can alter the cellular capacity available for biosynthesis

Limit on transfer	The dominant hormonal route is not interchangeable among insect groups	Mechanism is directly established in a hemimetabolous locust, not as a universal insect program
Taxonomic or physiological setting	Female insects; hormonal hierarchy differs among orders	Reproductively maturing female locusts
Experiment needed	Test regulatory nodes within the endocrine architecture of the focal taxon rather than assuming a conserved hierarchy	Separate endocrine activation from tissue-capacity measurements in cross-taxon experiments

Tissue and metabolic realization		
Reproductive-support dimension	**Lipid-regulatory state versus oogenesis**	**Vitellogenic molecular output versus realized reproduction**
Observable support	Tissue-specific manipulation of dHNF4 changes lipid stores and reproductive phenotypes differently	Vitellogenin can increase without a corresponding increase in fecundity
Consequence for reproduction	The effect of a regulatory node depends on the tissue in which it is altered	Molecular reproductive markers are intermediate outputs, not substitutes for reproductive performance
Limit on transfer	Strong experimental perturbation may not reproduce physiological variation in endogenous signaling	Age and constitutive pathway activation alter interpretation
Taxonomic or physiological setting	Drosophila fat body and ovary	Adult female mosquito under altered fat-body insulin signaling
Experiment needed	Use tissue-specific perturbations and measure both stored lipid and reproductive output	Pair molecular readouts with egg production, developmental success, or other appropriate organismal endpoints

Persistence and mismatch		
Reproductive-support dimension	**Persistent post-mating physiological state**	**demand–capacity mismatch (proposed)**
Observable support	Infection resistance remains reduced for days after one mating, whereas another mating is not simply additive	Defined by simultaneous reproductive demand together with constrained translation, mobilization, or metabolic support
Consequence for reproduction	Reproductive history can alter the future response capacity of the fat body–immune system	Reproductive signaling may exceed the tissue capacity available to realize all requested outputs simultaneously
Limit on transfer	Persistence and magnitude are species-, age-, and challenge-dependent	This is an integrative systems classification, not an independently validated universal state
Taxonomic or physiological setting	Adult female Drosophila	Any system in which reproductive biosynthesis coincides with other high-cost functions
Experiment needed	Use longitudinal rather than single-time-point designs when testing reproductive–immune coupling	Test factorial combinations of reproduction, nutrition, and infection while measuring capacity and realized outputs separately

A purely linear reproductive pathway cannot represent the evidence above because reproductive endocrine signaling changes fat-body cellular state, metabolic support can influence reproductive output, and reproduction can feed back onto immune competence. **Figure 1** therefore organizes these relationships as a nested capacity-and-feedback field, while visibly separating directly supported links from the broader synthesis proposed here.

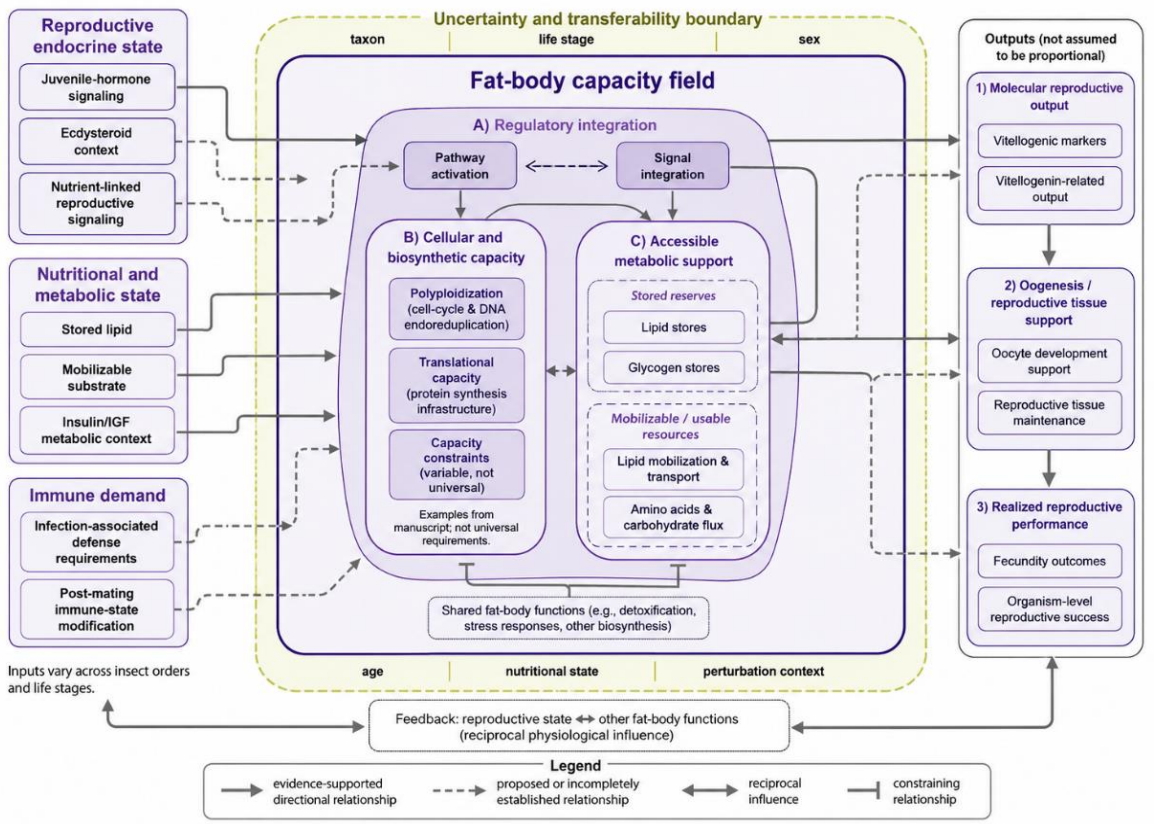


Figure 1. Reproductive demand can modify the capacity of the fat body that must simultaneously support metabolism and immune defense

The figure represents reproductive support as a nested, state-dependent process rather than a single vitellogenic pathway. The left side separates reproductive endocrine inputs from nutritional and immune contexts. The central nested field distinguishes regulatory activation, fat-body cellular/biosynthetic capacity, and metabolic accessibility. Evidence-supported directional relationships include juvenile-hormone-dependent regulation of reproductive machinery, tissue-specific metabolic effects on oogenesis, and reproductive-state effects on immune defense. A distinct output region separates molecular reproductive products from realized organismal reproductive performance because those levels can diverge. Solid arrows denote relationships directly demonstrated within the cited evidence base; bidirectional connectors denote experimentally supported or manuscript-required reciprocal physiological influence; dashed arrows denote conditional relationships incorporated into the proposed systems synthesis rather than universal mechanisms. Blunt-ended connectors identify capacity constraints only where simultaneous demands can interfere with output. A boundary band around the central field indicates that taxon, sex, life stage, nutritional condition, age, and experimental perturbation limit transfer between systems. JH, juvenile hormone; IIS, insulin/IGF signaling.

Stress and detoxification

Stress responses provide a useful test of whether a fat-body phenotype is a regulatory cause, a compensatory response, or simply a consequence of damage. After freezing in *Drosophila melanogaster* larvae, conspicuous fat-body disintegration develops after the primary injury rather than preceding it [24]. Tissue disruption should therefore not automatically be assigned causal status merely because it correlates with mortality. In a systems model, stress-associated molecular or structural changes require temporal ordering before they can be classified as drivers of physiological failure.

Regulatory responses to starvation and diapause also differ among candidate signaling components. In *Leptinotarsa decemlineata*, calcium-associated proteins including calmodulin, calcineurin B, and regucalcin show distinct state-dependent expression and functional relationships with lipid accumulation [25]. These observations do not support a generic “calcium stress pathway.” Instead, they indicate that superficially related molecular nodes can carry different information depending on developmental and metabolic state.

Molecular multifunctionality further blurs conventional boundaries between stress, immunity, and metabolism. Loss of *Drosophila* STING reduces lipid stores and increases sensitivity to starvation and oxidative stress, while biochemical evidence links the protein to lipid-synthetic machinery [26]. This establishes an insect-specific metabolic role for an immune-associated protein, but it does not justify importing the mammalian interferon-STING paradigm into insect fat-body biology.

Detoxification presents an analogous interpretive problem. Fat-body P450 and UGT transcription in *S. exigua* varies among insecticides, with some compounds producing substantially different expression profiles [6]. Expression therefore documents chemical-responsive regulation rather than successful detoxification itself. Together, these studies require stress biology to be resolved at several levels: initiating challenge, regulatory response, metabolic consequence, tissue damage, and organismal performance.

Shared regulatory nodes

A shared regulatory node is most useful conceptually when it is defined by conditional influence across physiological domains, not simply by expression in the fat body. Lipid composition illustrates this principle. In adult *Drosophila*, perturbing phosphatidylethanolamine synthesis in fat cells alters insulin sensitivity, lipoprotein-dependent communication with the brain, and hunger-driven feeding, while restoring the relevant fat-body pathway can modify the phenotype under chronic high-sugar feeding [27]. Membrane-lipid state can therefore function as both a metabolic property and an inter-organ signal determinant.

Shared regulation can also be reciprocal. Adipokinetic hormone signaling in *Drosophila* acts through different target tissues and changes daily activity through temporally distinct routes that include feedback between endocrine, neural, and fat-body components [28]. Such architecture cannot be represented accurately as an endocrine signal flowing irreversibly toward a passive metabolic tissue.

Other candidate shared nodes demonstrate the importance of context. During developmental transitions, 20-hydroxyecdysone can activate AMPK–PP2A signaling and antagonize IIS [13]. In adult female *Anopheles stephensi*, increasing fat-body IIS alters both metabolic and immune outputs, but the direction and magnitude of individual outcomes vary with age and physiological endpoint [19]. These findings support recurring interfaces among energy sensing, endocrine signaling, immunity, and organismal state; they do not establish one conserved hierarchy.

The proposed systems interpretation therefore distinguishes node identity from node function. A molecule or pathway becomes a systems-level interface only when its effect is conditioned by the state of other demands, downstream capacities, or feedback partners. Consequently, apparently conflicting findings need not imply experimental inconsistency. They may indicate that the same regulatory node occupies different positions in different physiological states.

Because such nodes can influence several traits while producing context-dependent or discordant consequences, their interpretation is more informative when trait, process, and organismal consequence are kept separate. **Table 2** maps those distinctions without assigning unsupported scores or universal pathway rankings.

Table 2. Shared fat-body regulatory nodes can generate concordant, divergent, or state-dependent consequences across biological levels

Shared node		State dependence		Adjudication		
Regulatory interface	**Directly measured process**	**Conditioning state**	**Cross-level consequence**	**Interpretive limit**	**Test**	**Standing**
Kinase and insulin-linked regulation						
AMPK–PP2A–IIS interaction	Endocrine and phosphorylation state	Developmental transition and steroid state	Developmental growth regulation	One demonstrated cross-talk route does not establish a universal endocrine hierarchy	Test homologous interactions across developmental states and taxa	Evidence-supported mechanism; broader role proposed
Fat-body IIS	Metabolite profile and immune signaling	Age, infection type, magnitude of pathway activation	Resistance to microbial or parasite challenge	Improved molecular or immune output does not imply improvement in all fitness components	Measure metabolic, immune, and reproductive outcomes together	Evidence-supported multidomain effect

Lipid and inter-organ signaling						
Phospholipid state	Membrane-lipid composition and insulin sensitivity	Chronic diet and adipocyte metabolic state	Brain-directed feeding behavior	Lipid abundance and lipid composition are not equivalent variables	Combine lipidomics with endocrine and behavioral measurements	Evidence-supported inter-organ coupling
AKH-linked signaling	Endocrine activation in different targets	Time of day and tissue receiving the signal	Time-dependent activity output	The same hormone can have different downstream consequences	Use tissue-specific and temporally resolved perturbation	Evidence-supported reciprocal regulation
STING-associated lipid regulation	Lipid stores and lipid-synthetic interactions	Genetic state and environmental challenge	Starvation and oxidative-stress sensitivity	An immune-associated protein need not act through the vertebrate mechanism sharing its name	Test metabolic and immune functions separately	Evidence-supported insect-specific multifunctionality
Conditional systems proposition						
Proposed conditional-node state	Simultaneous change in two or more physiological domains	Nutrition, reproduction, infection, development, sex, age, or environmental stress	Concordant or discordant organismal output	Shared molecular participation does not prove a shared causal bottleneck	Apply factorial perturbations and cross-level measurements	Proposed synthesis

The principal interpretive difficulty is not identifying more cross-talk, but deciding whether apparently concordant or discordant outputs represent a shared mechanism, different measurement levels, or context-dependent use of the same node. **Figure 2** therefore treats shared-node evidence as a discordance-triage problem rather than as a universal signaling network.

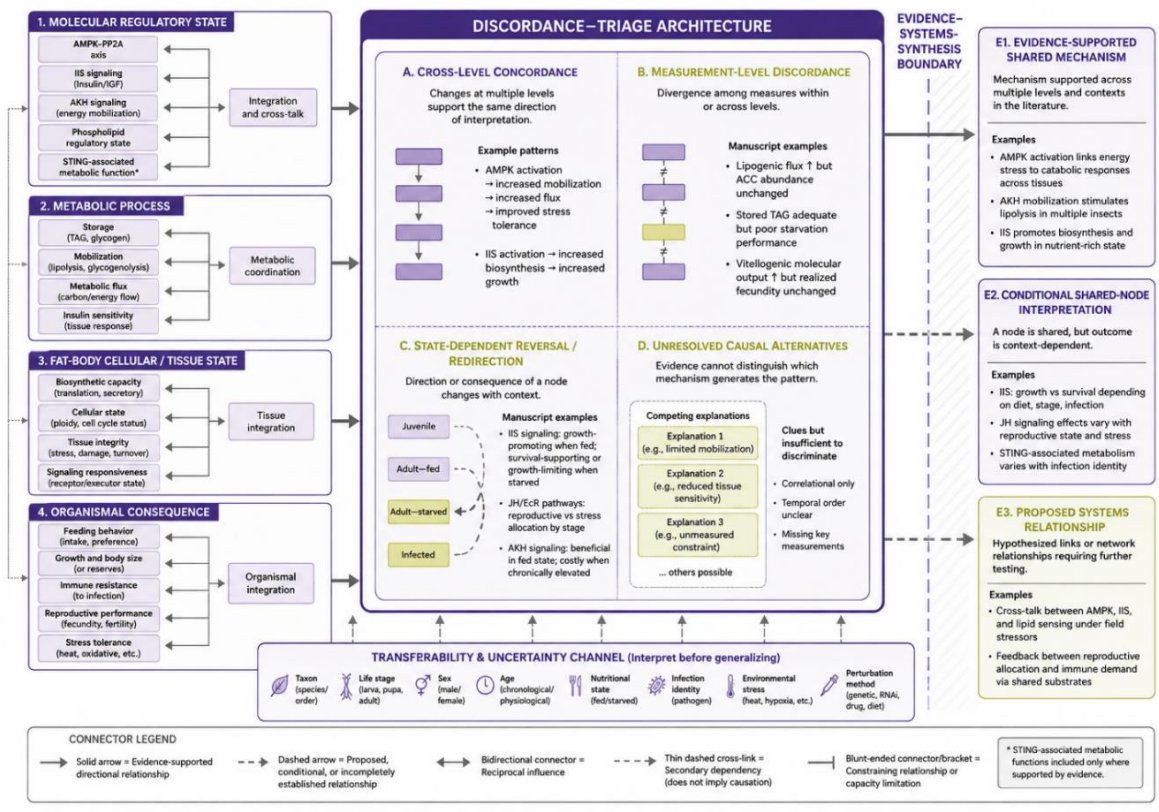


Figure 2. Discordant outputs reveal when a shared regulatory node cannot be interpreted as a fixed physiological switch

Shared regulatory nodes are interpreted through a discordance-triage architecture. Separate evidence lanes enter a central adjudication field that distinguishes cross-domain concordance, measurement-level discordance, context-dependent reversal, and unresolved causal alternatives. Supported relationships are separated from the manuscript's proposed systems interpretation. Solid arrows denote evidence-supported directional relationships; dashed arrows denote proposed or incompletely validated relationships; bidirectional connectors denote reciprocal regulation; and thin cross-links denote secondary dependencies. A boundary band prevents molecular responses, metabolic flux, tissue state, and organismal performance from being treated as interchangeable endpoints. Taxon, developmental stage, sex, age, diet, infection, and environmental state remain explicit transferability constraints. AKH, adipokinetic hormone; AMPK, AMP-activated protein kinase; IIS, insulin/IGF signaling.

Systems model of competing physiological demands

The proposed model treats fat-body regulation as the interaction of five variables: demand, regulatory state, tissue capacity, resource accessibility, and realized output. Demand specifies what the organism is attempting to accomplish—growth, immune defense, reproduction, detoxification, or stress survival. Regulatory state describes the signaling configuration through which that demand is communicated. Tissue capacity describes the molecular and cellular machinery available to execute it. Resource accessibility distinguishes reserves that exist from substrates that can actually be mobilized. Realized output is the phenotype measured at the molecular, tissue, or organismal level.

Competition need not therefore mean simple competition for calories. Simultaneous reproduction and infection can expose translational constraints [3], whereas starvation can produce abundant stored TAG when autophagic mobilization is impaired [11]. A physiological demand may fail because the limiting quantity is protein-synthetic capacity, mobilization, regulatory compatibility, or timing rather than total energy.

The sign of a regulatory effect is similarly conditional. Fat-body IIS can modify metabolism, immunity, and reproductive-associated outputs without changing all of them in the same direction [19]. Reciprocal inter-organ signaling adds another source of conditionality because endocrine output can feed back through neural and fat-body targets rather than following a one-way chain [28].

Accordingly, the model does not predict a universal hierarchy such as survival before reproduction or immunity before growth. It predicts that the dominant constraint should depend on the intersection between current demands and the capacities required to execute them. Evidence and inference must remain separated: as the freezing study demonstrates, a conspicuous fat-body phenotype can be downstream of the primary injury rather than its initiating mechanism [24].

Testable molecular predictions

The model generates predictions that can be falsified without presuming a universal pathway architecture. First, if shared tissue capacity constrains simultaneous functions, factorial combinations of reproductive and immune demand should sometimes produce nonlinear losses of output that are absent when each demand occurs alone [3]. The prediction concerns interaction, not a predetermined direction or effect size.

Second, perturbation of a candidate regulatory node should change in magnitude or sign across nutritional states when compensatory pathways are available. Nutrition-dependent responses to pyruvate-kinase depletion provide one example of this logic [9]. Appropriate tests should therefore cross genetic or molecular perturbations with feeding, starvation, developmental, or reproductive states rather than comparing only one experimental condition.

Third, molecular abundance should sometimes fail to predict physiological allocation. The mismatch between acetyl-CoA-carboxylase abundance and post-blood-meal lipogenic flux illustrates why transcript or protein measurements should be paired with flux or functional assays when allocation is the mechanistic claim [10].

Fourth, endocrine nodes implicated in one physiological trade-off should be tested under combinations of nutrition, reproduction, and infection. The demonstrated juvenile-hormone contribution to post-mating immune suppression provides an empirical starting point [16], but cross-taxon studies should not prespecify identical effects.

Finally, generalization should require replication across genotypes, life stages, sexes, taxa, and challenge identities. Infection-specific cis/trans regulatory divergence in the fat body shows that regulatory architecture itself can change with biological context [18]. A convincing test of the proposed systems model would therefore combine tissue-specific perturbation, metabolic flux, cell-state measurements, endocrine readouts, and organismal performance in explicitly factorial designs.

Conclusion

The insect fat body is best understood neither as a passive depot nor as a single master controller. It is a polyfunctional tissue in which nutrient sensing, immunity, reproduction, stress responses, detoxification, and endocrine communication can converge on partially shared machinery. The evidence also shows why convergence should not be mistaken for uniformity: molecular abundance can diverge from flux, stored reserves from accessible resources, intermediate reproductive markers from realized reproduction, and tissue damage from causal injury.

The proposed systems model therefore separates physiological demand, regulatory state, tissue capacity, resource accessibility, and realized output. Its central claim is conditional rather than universal: shared nodes matter because their consequences depend on which demands coexist and on the biological state in which they are engaged. Testing that proposition will require cross-level, factorial, tissue-specific experiments that preserve taxonomic, developmental, sex, environmental, and temporal boundaries rather than averaging them away.

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