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Nutrient Allocation, Immune Activation, and Life-History Trade-Offs Across the Expanding Field of Insect Immunometabolism

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ABSTRACT

Insect immunity is increasingly described in metabolic terms, yet the common language of energetic "cost" can conceal biologically different processes. Immune activation may consume substrates, redirect anabolic flux, alter endocrine signaling, restrict pathogen access to nutrients, change immune-cell metabolic state, or compete with development and reproduction for shared tissue capacities. These processes need not have equivalent organismal consequences, and their direction can change with tissue, pathogen, nutritional state, developmental history, reproductive condition, and the immune endpoint measured. This critical review evaluates these distinctions across recent mechanistic evidence from *Drosophila*, mosquitoes, honeybees, and other insect systems. Particular attention is given to metabolic requirements of cellular immunity, nutrient-sensitive TOR and insulin signaling, fat-body allocation, nutritional immunity, inflammatory damage control, and reproductive or developmental constraints. The evidence challenges three common shortcuts: that infection-associated metabolic change necessarily represents energetic depletion, that altered immune markers necessarily predict host defense, and that reduced reproductive performance necessarily demonstrates direct competition for calories. Instead, immunometabolic phenotypes frequently reflect conditional reallocations among storage, translation, immune-cell activity, endocrine state, barrier defense, tolerance, and life-history investment. The review therefore develops a proposed conditional interpretation in which metabolic changes are evaluated according to resource state, regulatory pathway, tissue and biological level, immune effector demand, pathogen or microbiota context, life-history state, and measured outcome. This framework is intended as an evidence-bounded organizing model rather than a universal mechanism.

Keywords: Insect immunometabolism, Nutrient allocation, TOR signaling, Fat body, Immune–reproduction trade-offs, Metabolic reprogramming

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Introduction

The growing field of insect immunometabolism has established that immune responses cannot be interpreted independently of metabolic state. Infection and immune activation can alter nutrient mobilization, anabolic activity, endocrine regulation, and energy storage, while metabolic condition can determine whether immune functions are initiated or sustained [1]. Yet "metabolic cost" is often used broadly enough to encompass resource

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consumption, active substrate redistribution, inhibition of growth pathways, pathogen-induced wasting, and tissue damage. These are not mechanistically equivalent phenomena.

Much of the strongest mechanistic evidence comes from *Drosophila melanogaster*, where genetic access has exposed reciprocal links between immune signaling, nutrient sensing, metabolism, and organismal physiology [2]. That experimental depth is valuable but also creates an inferential boundary: mechanisms demonstrated in one species, tissue, developmental stage, or infection route cannot automatically be generalized across insects. Work in hematophagous vectors further broadens immunometabolism by showing that resource partitioning can involve the insect, pathogen, and microbiota simultaneously [3]. Such systems make causal ownership particularly difficult to assign because a metabolic change may reflect host defense, microbial activity, parasite exploitation, or combinations of these processes.

The insect fat body is central to this problem because it combines nutrient storage, endocrine communication, immune protein production, growth regulation, and reproductive support [4]. However, fat-body centrality should not become fat-body reductionism. Muscle, gut epithelium, hemocytes, renal tissues, sensory pathways, germline activity, and microbiota-associated metabolism can all modify immune performance.

Accordingly, this review asks not merely whether immunity is costly, but what form the cost or reallocation takes, where it occurs, which biological output is altered, and under what conditions an apparent trade-off is mechanistically justified. The analysis distinguishes substrate depletion from regulated reprioritization, resistance from tolerance, immune-marker change from host outcome, and observed life-history covariance from demonstrated resource competition. The final synthesis is explicitly proposed as an interpretive model rather than a universally validated mechanism.

Energetic requirements of immunity

Energetic limitation can reveal trade-offs, but the underlying evidence does not support a single "immune energy budget." In *Drosophila*, mitochondrial dysfunction and infection can interact with reproductive performance, demonstrating that energetic capacity can condition immunity–fecundity relationships [5]. The important inference is conditional: an energetic constraint may expose a trade-off without proving that the same constraint governs every immune challenge or every reproductive state.

At the cellular level, immune activation can involve a distinct metabolic program. *Drosophila* macrophages shift toward aerobic glycolysis during antibacterial defense, and experimentally disturbing this reprogramming compromises their immune function [6]. This supports a direct requirement for metabolic remodeling within a defined immune-cell population, but it does not establish equivalent glycolytic dependence in every insect hemocyte lineage.

Immune activation also alters what nutrients are used for. Toll signaling in the *Drosophila* fat body redirects anabolic lipid metabolism away from triacylglycerol storage and toward phospholipid synthesis associated with increased secretory capacity [7]. This finding is incompatible with a simple model in which immune activation merely drains stored energy. Metabolic investment can instead be actively reprioritized toward the cellular infrastructure required for defense.

Systemic allocation may also depend on inter-organ communication. Glutamate metabolism in *Drosophila* modifies energetic redistribution between tissues and changes host susceptibility during infection [8]. The relationship should not be described teleologically as the host "choosing" an optimal allocation; nevertheless, it demonstrates that infection-associated metabolic change can be coordinated across organs rather than confined to an immune tissue.

Nutritional state can also regulate the permissible magnitude of immune-cell investment. During larval development, the adipokine NimrodB5 constrains hemocyte proliferation under nutrient scarcity, and disruption of that restraint increases immune-cell abundance at the expense of energy storage and viability under poor nutritional conditions [9]. Immune capacity is therefore not simply activated or suppressed; it can be scaled to the host's available metabolic reserve.

Finally, metabolically relevant control can arise in tissues not conventionally classified as immune organs. During parasitoid challenge, carbohydrate metabolism and insulin/TOR-related signaling in *Drosophila* muscle influence the lamellocyte-dependent encapsulation response [10]. Together, these studies support a multilevel view in which immune demand can be expressed as cell-specific metabolic reprogramming, anabolic redirection, systemic substrate redistribution, nutrient-sensitive control of cell abundance, or support from nonimmune tissues.

Nutrient-sensing pathways

Nutrient-sensing pathways provide some of the clearest evidence that immunometabolic effects are conditional rather than intrinsically pro- or anti-immune. Acute yeast restriction in adult female *Drosophila* can improve antibacterial defense through changes involving TOR, PP2A, and Myc signaling [11]. Reduced TOR activity in this setting therefore cannot be generalized as a universally beneficial immune state; the result depends on nutrient composition, duration of restriction, sex, and infection context.

Immune signaling can also suppress growth-associated signaling directly. Toll activation in *Drosophila* uncouples phosphatidylinositol-3,4,5-trisphosphate production from Akt activation, reducing insulin-pathway output [12]. This interaction provides a molecular route by which immune activation can alter growth and storage without requiring prior whole-organism energetic depletion.

Conversely, pathways historically labelled "immune" can regulate metabolism under homeostatic conditions. The IMD pathway links gut microbiota-derived signals with enteroendocrine activity and host metabolism in *Drosophila* [13]. Similarly, NF-κB-dependent control of the translational regulator 4E-BP contributes to dietary adaptation in the presence of microbiota [14]. These findings expand immunometabolism beyond acute pathogen defense and show that immune-signaling modules participate in the metabolic interpretation of dietary and microbial environments.

The direction of TOR effects changes across systems. In mosquitoes, rapamycin-mediated TOR inhibition can promote immune activation and reduce parasite transmission while simultaneously imposing survival or reproductive costs [15]. The immune endpoint therefore cannot be treated as equivalent to net organismal benefit. In another mosquito context, increased insulin signaling in the *Anopheles stephensi* fat body enhances antibacterial responses and resistance to *Plasmodium falciparum* [16]. This result directly cautions against treating insulin signaling as intrinsically antagonistic to immunity.

TOR can also support host survival rather than impede defense. During enteric infection in *Drosophila*, TOR signaling is required for lipid metabolic remodeling and protection against infection-associated wasting [17]. This function is closer to metabolic tolerance and maintenance than to direct pathogen elimination, underscoring why pathway effects must be classified by outcome.

Endocrine state creates another layer of conditionality. Exposure to 20-hydroxyecdysone can prime antibacterial and anti-malarial immune responses in *Anopheles gambiae* [18]. However, as discussed below, reproductive ecdysteroid signaling in another mosquito system can have an opposing relationship with specific immune outputs. Nutrient-sensing and endocrine pathways therefore do not possess a context-free immune "sign"; their interpretation requires information about species, tissue, physiological state, timing, pathogen, and measured endpoint.

Cellular and humoral immune demands

Different immune effectors impose different metabolic requirements, and those requirements extend beyond fuel consumption. Infection-associated sugar alcohols in *Drosophila* can function as alarmins that transmit information from local tissues to systemic immunity [19]. Metabolites should therefore not be classified only as substrates: some participate directly in immune communication.

Barrier immunity has its own metabolic architecture. In the intestinal epithelium, inflammatory signaling produces metabolic reprogramming required for DUOX-dependent reactive oxygen species defense [20]. This mechanism differs from the demands of systemic antimicrobial-peptide production or hemocyte proliferation and cautions against treating "immune metabolism" as a single effector program.

Nutritional immunity illustrates an additional distinction. Transferrin 1 restricts iron availability during bacterial infection in *Drosophila*, protecting the host through sequestration of a nutrient required by microbes [21]. This is a resource-allocation process, but it is not equivalent to expenditure of host caloric stores. The critical variable is accessibility of a micronutrient to the pathogen.

Metabolism also contributes to tolerance by limiting self-inflicted damage. Renal clearance of oxidized hemolymph lipids protects *Drosophila* from reactive-oxygen-associated inflammatory injury [22]. Such damage control can improve host condition without necessarily reducing pathogen burden, so resistance and tolerance outcomes must remain separate.

The environmental state preceding infection can modify cellular immune competence. Odor cues associated with parasitoid risk alter *Drosophila* hemocyte-related immunity through metabolically mediated sensory pathways [23]. Likewise, sterile injury can generate macrophage-derived reactive oxygen species that prime JAK/STAT

and Toll signaling [24]. These findings show that immune–metabolic activation can precede infection or occur without infection, making "pathogen-induced metabolism" too narrow a category.

Outcome discordance further complicates interpretation. Integrated transcriptomic and lipidomic analysis indicates that ergosterol contributes to survival during bacterial challenge, yet changes in survival are not necessarily accompanied by corresponding changes in antimicrobial-peptide output or bacterial burden [25]. Thus, host-defense phenotypes cannot be inferred reliably from one canonical immune readout.

Finally, the principal professional immune tissues themselves cannot be treated as interchangeable. Hemocytes and fat-body cells show strikingly different transcriptional responses to systemic infection in *Drosophila* [26]. Tissue identity therefore determines which metabolic and immune processes are represented by a measured molecular response.

Because these distinctions are difficult to retain when cellular defense, humoral defense, nutritional withholding, signaling, and damage control are described consecutively, the following matrix separates the relevant inference states without assigning them a common score.

Table 1. Distinguishing metabolic demand, resource withholding, signaling, and damage control across insect immune-effector states

Metabolic activation and withholding			
Immune-effector dimension	**Immune-cell metabolic activation**	**Barrier-effector metabolic support**	**Nutrient withholding**
Observable basis	Increased dependence on glycolytic or other metabolic programs	Metabolic remodeling coupled to ROS-generating machinery	Reduced pathogen-accessible iron or analogous limiting resources
Functional interpretation	Metabolism can be required within the responding immune cell itself	Effector production can require a tissue-specific metabolic state	Host defense can depend on restricting access rather than consuming more energy
Biological context	Activated hemocytes/macrophage-like cells	Intestinal epithelial defense	Systemic host–pathogen competition for micronutrients
Uncertainty	Cell lineage and infection type may alter the metabolic program	Barrier results should not be transferred automatically to systemic immunity	Micronutrient sequestration is not equivalent to caloric expenditure
Experiment	Resolve flux and function at cell-type resolution	Pair metabolic perturbation with defined barrier-effector assays	Measure host and pathogen nutrient pools separately
Standing	Evidence-supported distinction	Evidence-supported distinction	Evidence-supported distinction

Signaling, control, and priming			
Immune-effector dimension	**Metabolite-as-signal state**	**Damage-control state**	**Pre-activation or sterile-priming state**
Observable basis	Metabolites change signaling activity rather than serving only as fuel	Removal or detoxification of damaging metabolic products	Altered immune competence before infection or without pathogen exposure
Functional interpretation	Metabolic intermediates may carry immune information	Metabolic activity may support tolerance rather than pathogen clearance	Immune–metabolic state can be anticipatory or sterile
Biological context	Local-to-systemic immune communication	Inflammation-associated oxidative stress	Ecological cues or noninfectious tissue injury
Uncertainty	Signaling functions are metabolite- and context-specific	Improved survival does not establish increased resistance	Laboratory priming does not establish adaptive field benefit
Experiment	Distinguish signaling concentration from bulk energetic contribution	Measure tissue injury and pathogen burden independently	Test persistence, ecological relevance, and fitness consequences

Standing	Evidence-supported distinction	Evidence-supported distinction	Evidence-supported distinction

Discordant outcomes		
Immune-effector dimension	**Outcome-discordant defense state**	**Tissue-divergent response state**
Observable basis	Survival changes without parallel changes in canonical immune markers or pathogen load	Distinct infection-responsive molecular programs
Functional interpretation	Different defense endpoints can diverge	Biological level constrains interpretation of "systemic" immunometabolism
Biological context	Infection with multiple readouts	Hemocytes versus fat body or other tissues
Uncertainty	Single-marker studies may misclassify immune performance	Transcript abundance alone does not establish metabolic function
Experiment	Use resistance, tolerance, and survival endpoints together	Combine tissue-resolved expression with functional metabolic measurements
Standing	Proposed interpretive classification	Proposed interpretive classification

Reproductive and developmental trade-offs

Evidence for immunity–reproduction trade-offs is strongest when the mechanism connecting the competing functions is identified. Germline manipulation in *Drosophila* reveals an antagonistic relationship between germline proliferation and immune transcription [27]. This supports reproductive-state dependence of immune regulation but does not, by itself, demonstrate direct competition for calories or amino acids.

Mating provides a related but distinct phenomenon. A single mating can cause a persistent reduction in antibacterial defense in female *Drosophila* [28]. The organismal trade-off is observable, yet the causal route remains unresolved unless an allocation mechanism is measured independently. Postmating endocrine changes, tissue remodeling, reproductive provisioning, and direct resource competition are plausible but not interchangeable explanations.

Developmental history can alter later immune performance even before reproduction becomes relevant. In honeybee workers, the developmental environment modifies the response to viral infection in adulthood [29]. Such carry-over effects demonstrate temporal dependence but should not automatically be characterized as adaptive developmental programming; later immune performance may reflect accumulated physiological condition, nutritional history, or developmental constraint.

A more specific mechanism emerges when immunity and reproduction demand the same biosynthetic tissue. In mated female *Drosophila*, simultaneous reproductive and immune demands reveal limits in fat-body protein-production capacity [30]. This identifies a polyfunctional-tissue constraint: competition can occur over translational and secretory capacity rather than merely over a homogeneous pool of metabolic energy.

Endocrine context can further reverse the apparent direction of immunometabolic regulation. In blood-fed *Aedes aegypti*, ecdysone signaling contributes to a reproduction–immunity trade-off through suppression of an amyloid-associated immune mechanism [31]. This result should not be collapsed with 20-hydroxyecdysone-mediated immune priming in *Anopheles* because the species, reproductive state, timing, and immune mechanisms differ.

Developmental microbial exposure introduces another trajectory. Mosquito–bacteria interactions during larval development can produce metabolic alterations with measurable carry-over effects on adult phenotypes [32]. The existence of a carry-over effect does not establish that it is beneficial, nor that adult immune variation reflects an allocation decision made during larval development.

The evidence therefore resolves "trade-off" into several mechanistically distinct states: energetic-capacity limitation, germline-linked transcriptional opposition, postmating suppression without a resolved allocation mechanism, shared fat-body translational constraint, endocrine switching, and developmental carry-over. Their differences are condensed below because a single reproduction-versus-immunity axis would obscure the mechanism and level at which each trade-off is expressed.

Table 2. Mechanistic forms of reproductive and developmental constraint in insect immunometabolism

Capacity constraints		
Energetic-capacity constraint		*Evidence-supported distinction*
Life-history setting	Infection under compromised energetic state	
Immune and reproductive performance covary with metabolic capacity		Resource limitation can expose a trade-off
Observed basis		**Mechanistic consequence**
Energetic impairment may have pleiotropic effects	**ALTERNATIVE**	Manipulate resource availability independently of mitochondrial function
Regulatory and endocrine opposition		
Germline-linked immune opposition		*Evidence-supported distinction*
Life-history setting	Adult reproductive state	
Germline status changes immune transcription		Reproductive state can modify immune regulation
Observed basis		**Mechanistic consequence**
Transcriptional opposition does not prove nutrient competition	**ALTERNATIVE**	Pair germline manipulation with flux and functional-defense assays
Persistent postmating defense reduction		*Evidence-supported distinction*
Life-history setting	Mated female insect	
Lower subsequent antibacterial defense		Mating state can impose lasting immune consequences
Observed basis		**Mechanistic consequence**
Causal metabolic route remains unresolved	**ALTERNATIVE**	Separate endocrine, provisioning, and energetic mechanisms experimentally
Shared fat-body production bottleneck		*Evidence-supported distinction*
Life-history setting	Simultaneous reproduction and infection	
Competing demand for protein synthesis/secretory capacity		A polyfunctional tissue can generate mechanistic conflict
Observed basis		**Mechanistic consequence**
Demonstrated mechanism is species- and state-specific	**ALTERNATIVE**	Quantify translational capacity and tissue demand jointly
Reproductive endocrine switching		*Evidence-supported distinction*
Life-history setting	Blood-fed female mosquito	
Hormonal signaling favors reproduction while suppressing a defined immune process		Endocrine context can alter the direction of immune regulation
Observed basis		**Mechanistic consequence**
Hormonal effects differ across species, timing, and effector pathway	**ALTERNATIVE**	Compare matched hormonal states and immune endpoints across taxa
Developmental carry-over		
Developmental carry-over		*Evidence-supported distinction*
Life-history setting	Larval environmental or microbial history	
Adult immune/metabolic phenotype differs after developmental exposure		Early-life conditions can shape later response capacity
Observed basis		**Mechanistic consequence**
Carry-over is not synonymous with adaptation or increased fitness	**ALTERNATIVE**	Follow metabolic state, immunity, and fitness across stages
Unresolved phenotype-level trade-off		
Mechanistically unresolved trade-off		*Proposed interpretive category*
Life-history setting	Any observed inverse reproduction–immunity relationship without direct allocation evidence	
Negative covariance between life-history outputs		Indicates conflict at the phenotype level only
Observed basis		**Mechanistic consequence**
Resource competition, endocrine regulation, damage,	**ALTERNATIVE**	Require a measured mediator before assigning mechanism

and tissue constraints remain alternatives	

These distinctions also determine what can legitimately be combined into a mechanistic model. **Figure 1** therefore maps reproductive and developmental effects as conditional routes into immune and life-history outcomes rather than as one universal resource-allocation arrow.

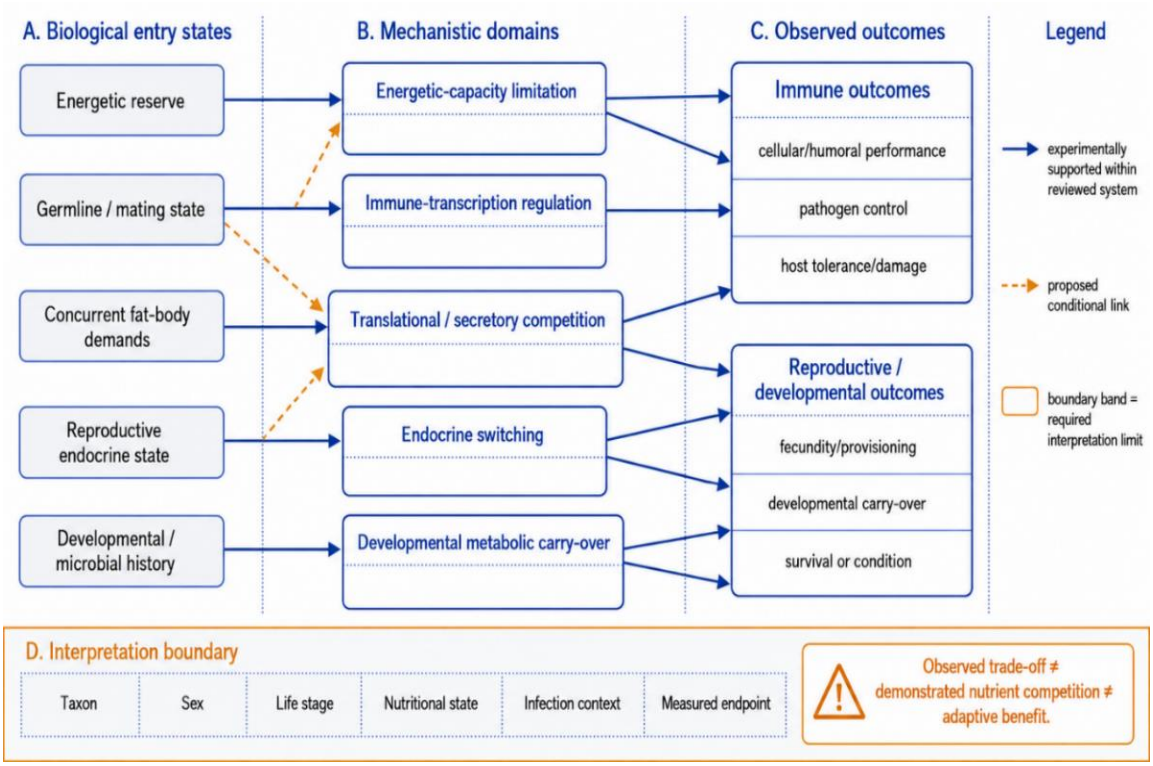


Figure 1. When insect reproduction–immunity trade-offs share a resource mechanism—and when they do not

Metabolic reprogramming during infection

Infection-associated metabolic remodeling is often interpreted as host allocation toward immunity, but causal ownership cannot be assumed. During dengue virus infection of *Aedes aegypti*, extensive midgut lipid remodeling coincides with viral replication [33]. Such covariance establishes that infection and lipid metabolism are coupled, but it does not by itself distinguish host defense from virus-directed exploitation of host membranes or from secondary consequences of cellular stress.

Immune priming provides a related inference problem. Transcriptomic analysis of *Anopheles albimanus* after exposure to *Plasmodium berghei* identifies coordinated regulation of metabolic, immune, and cell-cycle pathways [34]. These data demonstrate molecular reorganization of the primed state, but transcriptional differences are not equivalent to measured substrate flux. Consequently, pathway enrichment should be treated as evidence for altered regulatory state rather than direct measurement of energetic allocation.

Sex can further alter metabolic responses to infection. Zika virus infection in *Drosophila* produces sex-dependent metabolic changes, with interactions between host antiviral capacity and virus-associated metabolic phenotypes [35]. This result argues against treating one sex as a default physiological reference and cautions against transferring metabolic signatures from a surrogate host directly to mosquito–virus systems.

Null relationships are especially informative. Chronic depletion of vertebrate-derived lipids in *Aedes aegypti* cells alters lipid metabolism and suppresses several innate-immune features without increasing dengue infectivity per cell [36]. Thus, an apparently immunosuppressed molecular state need not produce a parallel change in pathogen outcome. Immune expression, pathogen replication, host survival, and tissue damage should therefore be measured as distinct response classes.

Microbiota add another source of metabolic agency. Tryptophan catabolism by the gut microbiota of anopheline mosquitoes can protect the intestinal barrier and reduce parasite susceptibility [37]. Here, the relevant metabolism is neither exclusively host-derived nor reducible to expenditure of stored energy. Conversely, metabolic

disturbance itself can activate immunity-like signaling without infection: disruption of lipolysis in adult *Drosophila* induces a sterile immune-like pathway associated with stem-cell death [38]. Taken together, these studies show why infection-associated metabolic change must first be assigned to a biological level and causal candidate before it is labelled immune allocation.

Context dependence and experimental contradictions

The expanding vector literature reinforces this need for conditional interpretation because host metabolism is strongly modified by microbiota composition, microbial metabolites, diet, and pathogen identity [39]. Apparent contradictions in immunometabolism therefore often reflect differences in experimental state rather than mutually exclusive biological rules.

TOR signaling illustrates this problem. Acute nutrient restriction can associate reduced TOR activity with improved antibacterial defense, whereas pharmacological TOR inhibition in mosquitoes can improve anti-parasite immunity at life-history cost. In enterically infected *Drosophila*, however, TOR activity supports lipid homeostasis and survival. These observations concern different taxa, tissues, perturbations, pathogens, and endpoints; they cannot be adjudicated by assigning TOR a universal immune polarity.

Insulin signaling is similarly conditional. Toll activation can suppress downstream insulin-pathway output in *Drosophila*, yet increased fat-body insulin signaling in *Anopheles stephensi* can enhance antibacterial and anti-*Plasmodium* responses. The relevant question is therefore not whether insulin signaling is "good" or "bad" for immunity, but which tissue, nutritional state, pathogen, and immune function are being examined.

Endocrine evidence reaches the same conclusion. 20-hydroxyecdysone can prime immunity in *Anopheles gambiae*, whereas reproductive ecdysone signaling in blood-fed *Aedes aegypti* can suppress a defined immune mechanism. Species, reproductive state, hormone timing, and effector identity provide plausible boundaries between these findings and should be reported before invoking contradiction.

Experimental endpoints create another source of disagreement. Increased survival without lower pathogen burden may indicate tolerance or reduced immunopathology rather than stronger resistance. Conversely, altered immune-gene expression without altered infectivity may represent molecular responsiveness with little consequence for the measured pathogen. Molecular, cellular, pathogen, tissue-damage, survival, and reproductive outcomes should therefore not substitute for one another.

Finally, laboratory transfer remains a major limitation. Most mechanistic evidence comes from genetically tractable laboratory systems, controlled diets, experimentally defined infections, or cell culture. Such designs identify mechanisms efficiently but rarely establish how often the same mechanism determines fitness under fluctuating nutrition, mixed infections, natural microbiota, environmental stress, or field resource limitation. **Table 3** therefore maps where apparently conflicting results can be reconciled by context and where genuine coverage gaps remain.

Table 3. Context boundaries that separate apparent immunometabolic contradictions from unresolved evidence gaps

What appears inconsistent		Why context matters			Resolution path	
Contradiction	**Evidential pattern**	**Interpretive consequence**	**Analytical context**	**Priority test**	**Residual uncertainty**	**Standing**
Pathway and endocrine polarity						
Pathway-polarity reversal	The same pathway is associated with different immune outcomes under different experimental states	Pathway activity has no defensible context-free immune sign	TOR or insulin signaling across different tissues, diets, pathogens, and taxa	Factorial comparisons using matched immune endpoints	Relative contributions of tissue, nutrient state, perturbation method, and pathogen remain incompletely separated	Evidence-supported heterogeneity
Endocrine-state reversal	Hormonal signaling can prime one immune state yet suppress another	Endocrine effects must be interpreted relative to physiological state and timing	Ecdysteroid signaling before infection versus during reproductive activation	Matched-stage endocrine perturbation across taxa	Cross-species comparability and dose dependence remain uncertain	Evidence-supported heterogeneity
Tissue and endpoint divergence						

Tissue-level divergence	Molecular and metabolic responses differ among tissues during immune challenge	"Systemic immunometabolism" can conceal distinct local programs	Hemocytes, fat body, gut, muscle, and renal tissues	Tissue-resolved flux plus functional perturbation	Functional importance of transcriptomic divergence is often unresolved	Coverage gap
Outcome discordance	One outcome changes while another remains unchanged or changes oppositely	Resistance, tolerance, and life-history performance require separate adjudication	Immune markers, pathogen burden, host damage, survival, and reproduction	Multi-endpoint longitudinal experiments	Relative value of each endpoint varies with infection system	Proposed interpretive requirement
Causal ownership and field transfer						
Causal-ownership ambiguity	Metabolic change accompanies infection but may arise from host, pathogen, microbiota, or shared processes	Association cannot be assigned automatically to host immune allocation	Viral infection or microbiota-associated metabolic remodeling	Isotope tracing and agent-specific metabolic perturbation	Direction and biological agent controlling flux are often unresolved	Coverage gap
Laboratory-to-field transfer	Mechanisms are demonstrated under simplified environmental conditions	Mechanistic validity does not establish ecological prevalence or fitness consequence	Controlled diets, defined infections, transgenic models, and cell culture	Field-linked experiments preserving mechanistic measurements	Natural nutritional variation, coinfection, microbiota, and environmental stress are underrepresented	Proposed validation priority

Critical integrative model

The evidence reviewed here supports a proposed conditional allocation model rather than a unified energetic-cost model. Its starting premise is that an immune-associated metabolic change should first be classified by process: substrate consumption, regulated redistribution, nutrient withholding, immune-cell metabolic specialization, shared-tissue production constraint, damage-control metabolism, or pathogen/microbiota-associated remodeling. These categories describe different biological events and should not be collapsed into a single measure of "cost."

A second axis concerns regulatory state. TOR, insulin, NF-κB-associated signaling, and ecdysteroid pathways affect immunity differently depending on nutritional condition, tissue, developmental or reproductive state, and infection type. The model therefore treats pathway activity as conditional information rather than as an invariant directional predictor. This is essential for reconciling otherwise opposing experimental observations without dismissing them as inconsistency.

A third axis separates biological levels. Hemocyte metabolism, fat-body translation, intestinal barrier defense, muscle carbohydrate regulation, renal damage control, endocrine signaling, and microbiota-derived metabolism can all influence immune outcomes, but they do so through different mechanisms. Evidence at one level should be transferred to another only when an explicit functional bridge has been demonstrated.

The fourth axis distinguishes outcome classes. Resistance concerns pathogen limitation; tolerance concerns maintenance of host condition despite infection; immune activation concerns molecular or cellular response; and life-history effects concern reproduction, development, survival, or later performance. A change in one class cannot substitute automatically for another. This distinction is especially important when survival improves without lower pathogen burden or when immune markers change without altered infectivity.

Finally, the model places taxon, sex, life stage, nutritional state, microbiota, infection route, pathogen identity, and experimental setting around these mechanisms as boundary conditions rather than nuisance variables. The resulting synthesis does not predict a universal optimum or claim that observed trade-offs are adaptive. Instead, it provides a proposed inference sequence: identify the metabolic process, locate the biological level, define the regulatory and life-history state, specify the immune outcome, and only then evaluate whether the evidence supports resource competition, metabolic support of defense, tolerance, or another explanation.

This interpretation also identifies validation priorities. Future studies would be most informative when they combine direct metabolic measurements with tissue-resolved perturbation, pathogen burden, host damage, immune function, and life-history outcomes in the same experimental design. Cross-species comparisons should

match physiological state and infection context rather than compare nominally identical pathways under biologically different conditions. Field-linked experiments are particularly necessary to determine whether mechanisms demonstrated under controlled nutrition retain explanatory value when resource quality, microbiota, temperature, coinfection, and reproductive state vary simultaneously.

Conclusion

Insect immunometabolism is better understood as a family of conditional allocation and regulatory processes than as a single energetic cost of immunity. Recent work demonstrates immune-cell metabolic specialization, tissue-specific substrate redirection, nutrient-sensitive control of hematopoiesis, micronutrient withholding, damage-control metabolism, endocrine switching, reproductive constraints, developmental carry-over, and pathogen- or microbiota-associated metabolic remodeling. These processes may converge on similar phenotypes while arising through different mechanisms.

The proposed conditional allocation model therefore treats metabolic process, biological level, regulatory state, life-history condition, infection context, and measured outcome as necessary components of interpretation. Its principal value is restrictive as much as integrative: it prevents metabolic change from being equated automatically with resource depletion, immune-marker change with host protection, reproductive reduction with direct nutrient competition, or laboratory mechanism with insect-wide ecological generality. Progress in the field will depend less on assigning universal direction to familiar pathways than on determining when, where, and for which biological outcome each immunometabolic mechanism operates.

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