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Proteostasis, Redox Control, Autophagy, and Reproduction Form an Integrated Cellular Stress Network Regulating Insect Life Histories

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ABSTRACT

Insect life histories depend on molecular systems that maintain macromolecular integrity while allowing growth, reproduction, stress resistance, and developmental transitions to remain responsive to changing conditions. Proteostasis, redox regulation, autophagy, and reproductive endocrinology are usually investigated as partially separate fields, obscuring how their local interactions may constrain or redirect organismal states. Here, evidence from experimentally tractable insect systems is synthesized into a proposed molecular systems model in which stress responses are organized around conditional coupling rather than a single master pathway. Proteasomal and chaperone functions can alter steroidogenesis, vitellogenesis, receptor trafficking, and fertility; redox state can act both as damage and information, with non-monotonic and pathway-specific effects; autophagy and mitophagy can support nutrient gating, organelle quality control, quiescence, and tissue remodeling; and juvenile hormone, ecdysteroid, insulin-like peptide, and microRNA pathways distribute reproductive control across tissues and stages. The model therefore treats molecular maintenance, endocrine output, and life-history allocation as interacting but non-equivalent levels. It predicts that perturbing one node can produce compensation, delayed costs, or state-specific reversals rather than a fixed directional outcome. The model is intended as an evidence-bounded framework for designing factorial and longitudinal tests, not as a validated universal pathway.

Keywords: Proteostasis, Redox signaling, Autophagy, Juvenile hormone, Ecdysteroid signaling, Insect reproduction

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Introduction

Insects repeatedly face conditions that threaten protein folding, organelle function, redox balance, and energy availability while simultaneously demanding growth, metamorphosis, dispersal, or reproduction. These demands are often interpreted through the language of "stress resistance" versus "reproduction," yet that framing can hide the molecular routes through which one process constrains another. In *Tribolium castaneum* females exposed to deltamethrin, oxidative and energetic stress activates AMPK–CncC signaling together with detoxification while juvenile-hormone-related and reproductive outputs decline, providing direct evidence that stress-defense signaling can intersect endocrine allocation rather than merely accompany it [1]. This experimentally demonstrated route, however, cannot be assumed to represent a universal insect trade-off.

The same caution applies to redox–autophagy interactions. In *Drosophila melanogaster*, catalase-dependent redox regulation of Atg4a enhanced autophagy and extended female lifespan, whereas males did not show the same

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longevity response and starvation sensitivity introduced an additional cost [2]. The defensible inference is therefore not that stronger autophagy is generically beneficial, but that redox-sensitive control of cellular turnover can alter organismal state in a sex- and context-dependent manner.

Reproduction itself creates proteostatic demands. In *Locusta migratoria*, juvenile hormone regulates two Grp78 chaperones required for fat-body homeostasis, vitellogenin production, and oocyte maturation [3]. In blood-fed *Aedes aegypti*, unfolded-protein-response components likewise modulate autophagy and egg production [4]. Molecular maintenance is consequently not simply a background defense system upstream of reproduction; it can be embedded in the cellular machinery required to produce reproductive output.

This article develops a proposed molecular systems model that retains these local mechanisms as distinct evidence units while asking how they may interact across biological levels. The central problem is not whether proteostasis, redox control, autophagy, and reproductive signaling communicate—they demonstrably can—but how those relationships can be organized without converting evidence from different taxa, tissues, sexes, stages, and experimental settings into a falsely unified pathway. The model therefore separates directly demonstrated molecular relationships from cross-study synthesis and treats organismal life-history consequences as a higher inference level requiring independent evidence.

Proteostasis

Proteostasis in this model includes proteasomal degradation, molecular chaperoning, and regulation of protein stability, but it is not reduced to a generic repair function. Its life-history significance depends on which proteins, tissues, and developmental states are affected. In female *Bactrocera dorsalis*, depletion of proteasome β3 subunit PSMB3 reduces ovarian ecdysteroidogenesis and reproductive performance, while 20-hydroxyecdysone supplementation rescues key ovarian defects [5]. This provides a mechanistic bridge from proteasomal function to reproductive endocrine output, but the evidence remains specific to one proteasome component, sex, species, and maturation context.

Proteostasis can also be metabolically gated. In the *Drosophila* male germline, citrate-derived acetyl-CoA supports NatB-dependent N-terminal acetylation of proteins needed during late spermatogenesis, protecting selected targets from dUBR1-mediated degradation [6]. Importantly, the same requirement was not demonstrated in the female germline or gonadal soma. The result supports a cell-state- and sex-specific coupling between metabolism and proteome stability rather than a general rule that greater protein stabilization necessarily improves reproduction.

Secretory reproductive tissues provide another route through which proteostasis enters life-history regulation. In *A. aegypti*, depletion of the endoplasmic-reticulum chaperone BiP causes vitellogenin aggregation and reduces ovarian development, fecundity, and fertility [7]. The reproductive interpretation must remain separate from BiP's additional involvement in dengue-virus replication: multifunctionality does not establish a common causal mechanism between infection biology and reproductive protein handling.

Environmental perturbation further shows why proteostasis should be treated dynamically. Heat exposure in *Monochamus alternatus* depresses reproductive traits in both sexes, followed by substantial recovery during subsequent weeks; HSP20-associated protein interactions identify plausible reproduction-related partners, but do not by themselves demonstrate that HSP20 causes recovery [8]. Transient reproductive loss may therefore reflect reversible disruption rather than irreversible failure, and association between a chaperone and recovering tissues is weaker evidence than functional rescue.

Chaperone activity can also regulate signaling competence without determining signaling output. Cytoplasmic Hsp70 proteins in lepidopteran larvae promote ecdysone-receptor transport into the nucleus, yet juvenile hormone and heat can increase EcR nuclear localization while inhibiting expected ecdysone-responsive transcription [9]. Nuclear localization is consequently not equivalent to pathway activation. Proteostasis may regulate access to a signaling state while transcriptional consequences remain contingent on stimulus identity and cellular context.

Redox signaling

Redox control occupies a different logical position from proteostasis because reactive oxygen species can represent both molecular damage and regulated information. Treating lower ROS as intrinsically beneficial would erase biologically important nonlinearity. In the *Drosophila* testis, elevated ROS compromises germline stem-cell maintenance, whereas experimentally reducing ROS beyond the normal state produces expansion of germline-

stem-cell-like cells and altered differentiation [10]. The relevant variable is therefore redox homeostasis rather than antioxidant maximization.

ROS can also participate directly in developmental signaling. In *Helicoverpa armigera* pupae destined for diapause, ROS-dependent AKT signaling lowers GSK3β activity and contributes to suppression of the Smad1/EcR/HR3 endocrine cascade [11]. In this setting, ROS participates in developmental-state regulation rather than functioning solely as a marker of oxidative injury. The proposed systems model must consequently distinguish damaging oxidative load from redox-dependent signaling even when both occur in related physiological contexts.

A second boundary concerns pathway plurality. Royal jelly reduces endogenous oxidative stress in *Drosophila* through increased oxidoreductase activity without requiring Keap1/Nrf2 signaling [12]. This directly argues against treating CncC/Nrf2 as an obligatory antioxidant master switch. Parallel redox-control routes must remain possible, with their importance conditional on tissue, environmental input, and stressor.

Redox state is additionally linked to mitochondrial differentiation programs. In *Drosophila* testis cyst stem-cell lineages, E2f/Dp/Rbf-dependent regulation of mitochondrial activity contributes to differentiation, whereas restoring mitochondrial biogenesis does not restore cell-cycle exit [13]. Metabolic differentiation and proliferative state are therefore experimentally separable. A cellular maintenance state cannot consequently be represented as a single scalar axis: metabolic or redox correction may normalize one cellular dimension while another remains altered.

Autophagy

Autophagy extends the network from macromolecular quality control to regulated turnover of cytoplasmic material and organelles. Yet autophagic processes differ in substrates, tissues, triggers, and temporal roles. After genotoxic stress in *Drosophila* female germline stem cells, Pink1/Parkin-dependent mitophagy is required for entry into reversible cell-cycle arrest, while mitochondrial biogenesis and fusion contribute to recovery [14]. Mitophagy here participates in a reversible state transition rather than acting simply as constitutive cellular cleaning. This mechanism cannot be generalized to unstressed tissues or organismal fertility without further evidence.

Autophagy-related proteins may also participate in processes that cannot be attributed exclusively to canonical autophagic flux. In *Rhodnius prolixus*, silencing *RpATG6* disrupts yolk accumulation, yolk-organelle biogenesis, and egg viability, whereas general blood digestion and longevity are not equivalently impaired [15]. Because ATG6 participates in endocytic as well as autophagic machinery, the phenotype is more defensibly interpreted as failure of ATG6-dependent trafficking than as proof that bulk autophagy alone controls fertility. Pathway annotation therefore cannot substitute for resolving the cellular operation actually perturbed.

Endocrine signaling can nevertheless reach autophagy through defined molecular mechanisms. During *H. armigera* metamorphosis, 20-hydroxyecdysone activates FOXO-dependent recruitment of KAT8 to the *Atg8* promoter, increasing H4K16 acetylation and autophagic activity in the midgut [16]. This establishes a steroid-to-chromatin-to-autophagy route, but its larval midgut context does not establish the same pathway in adult reproductive tissue.

Timing provides a further constraint. In *Drosophila* larvae, starvation induces autophagy in the prothoracic gland early in the third instar, restricting cholesterol availability for ecdysone production and delaying developmental progression; this nutritional checkpoint is temporally gated and is not reproduced identically later in the instar [17]. Autophagy can therefore function as an endocrine nutritional gate whose physiological consequence changes with developmental state. Assigning autophagy one fixed beneficial, detrimental, reproductive, or survival-promoting direction would erase precisely the conditionality that the evidence reveals.

Reproductive signaling

Reproductive signaling is the network domain in which energetic, proteostatic, redox, and autophagic states can be translated into tissue-specific reproductive decisions. It should not be represented as a single juvenile-hormone or ecdysteroid axis. In *A. aegypti*, insulin-like peptides and ovary ecdysteroidogenic hormone have overlapping but distinct actions on nutrient storage, intracellular signaling, and egg formation across tissues of the gonotrophic cycle [18]. Reproductive control is therefore distributed, with endocrine inputs converging on partially separable physiological processes.

Ecdysone-receptor signaling is similarly context dependent. In the panoistic ovary of *Blattella germanica*, EcR depletion alters ovarian function and germarial proliferation, while effects on steroidogenic genes indicate that receptor activity can differ according to tissue and hormone source [19]. A fixed-sign "20E promotes reproduction" edge would therefore be misleading. The same receptor can participate in different cellular programs according to developmental and anatomical context.

Juvenile hormone also acts through several regulatory layers. In the red imported fire ant *Solenopsis invicta*, JH-associated induction of miR-1175-3p alters Br-C, vitellogenin expression, ovarian activation, and egg production [20]. Because these observations arise from queens and workers in a eusocial species, the miRNA route demonstrates regulatory flexibility rather than a general template for solitary insects. In *L. migratoria*, two stage-biased microRNAs exert opposing control over juvenile hormone acid methyltransferase during metamorphosis and adult reproduction [21]. JH biosynthesis can therefore be temporally reconfigured rather than governed by one static upstream regulator.

Nutritional state provides another entry route. In adult male *Agrotis ipsilon*, dietary sugar and sodium influence sexual maturation through interactions between insulin signaling and juvenile-hormone biosynthesis [22]. This establishes a diet–IIS–JH bridge in a specific male lepidopteran context; it does not establish identical nutrient dependencies in females or other orders. Endocrine control is also not exclusively transcriptional. In female *L. migratoria*, JH remodels zonula-adherens architecture at tricellular junctions of the follicular epithelium, facilitating paracellular transport of yolk proteins into developing oocytes [23]. Reproductive hormones can therefore regulate physical tissue transport as well as gene expression.

These findings produce an apparent evidence conflict that prose alone resolves poorly: the same nominal endocrine pathway can appear activating, permissive, inhibitory, stage-specific, or structurally enabling depending on tissue and measured endpoint. **Table 1** distinguishes those signaling states without treating them as contradictory estimates of one common reproductive effect.

Table 1. Reproductive endocrine signals resolve into distinct tissue-level control modes rather than one common reproductive output

Discriminating check	Biological context with observed basis	Interpretation for the s within its limit
	Distributed peptide control	
	Evidence-supported	
Perturb peptide inputs singly and jointly while resolving tissue-specific outputs	Blood-fed female mosquito gonotrophic cycle ILPs and OEH produce overlapping but tissue-distinct effects	Reproduction is coordinated across several endocrine inputs rather than one dominant signal Tissue and feeding-state dependence
	Context-dependent steroid-receptor output	
	Evidence-supported	
Separate receptor localization, transcription, proliferation, and steroidogenesis	Panoistic cockroach ovary EcR depletion changes ovarian cellular and steroidogenic responses	Receptor identity does not fix direction of reproductive output Ovary type, developmental stage, and hormone source
	JH–miRNA reproductive routing	
	Evidence-supported	
Test whether homologous miRNA routing occurs outside eusocial taxa	Eusocial ant queens and workers JH-linked miR-1175-3p changes Br-C, Vg, ovarian activation, and egg production	JH can be translated through post-transcriptional regulators Caste and social-system specificity
	Stage-opposed JH biosynthetic control	
	Evidence-supported	
Use longitudinal rather than single-stage perturbation	Locust metamorphosis versus adult reproduction Distinct miRNAs oppositely regulate Jhamt and JH across stages	The same endocrine node can reverse regulatory direction through developmental time Species and stage specificity
	Nutrient-gated male maturation	
	Evidence-supported	

Test diet × IIS × JH interactions across sexes	Adult male moth Diet-dependent IIS changes accompany JH biosynthesis and sexual maturation	Nutritional state can enter reproductive control through endocrine coupling Sex and diet composition
Endocrine control of tissue permeability		
Evidence-supported		
Measure epithelial transport with molecular endocrine outputs	Adult female locust follicular epithelium JH-dependent junction remodeling facilitates yolk-protein passage	Reproductive hormones can regulate tissue transport architecture as well as transcription Demonstrated in one orthopteran ovary
Conditional reproductive-output layer		
Proposed synthesis		
Test whether changing context redirects the same upstream perturbation	Cross-study synthesis Divergent endocrine effects depend on tissue, stage, sex, and measured endpoint	Reproductive signaling is interpreted as a context-dependent mapping from endocrine input to tissue output No single experiment validates this cross-taxon mapping

The same distinction requires a visual architecture that keeps reproductive signaling in parallel tissue- and stage-dependent lanes while showing only those upstream cross-links that have mechanistic support. **Figure 1** therefore separates demonstrated within-system relationships from the article's proposed cross-context interpretation.

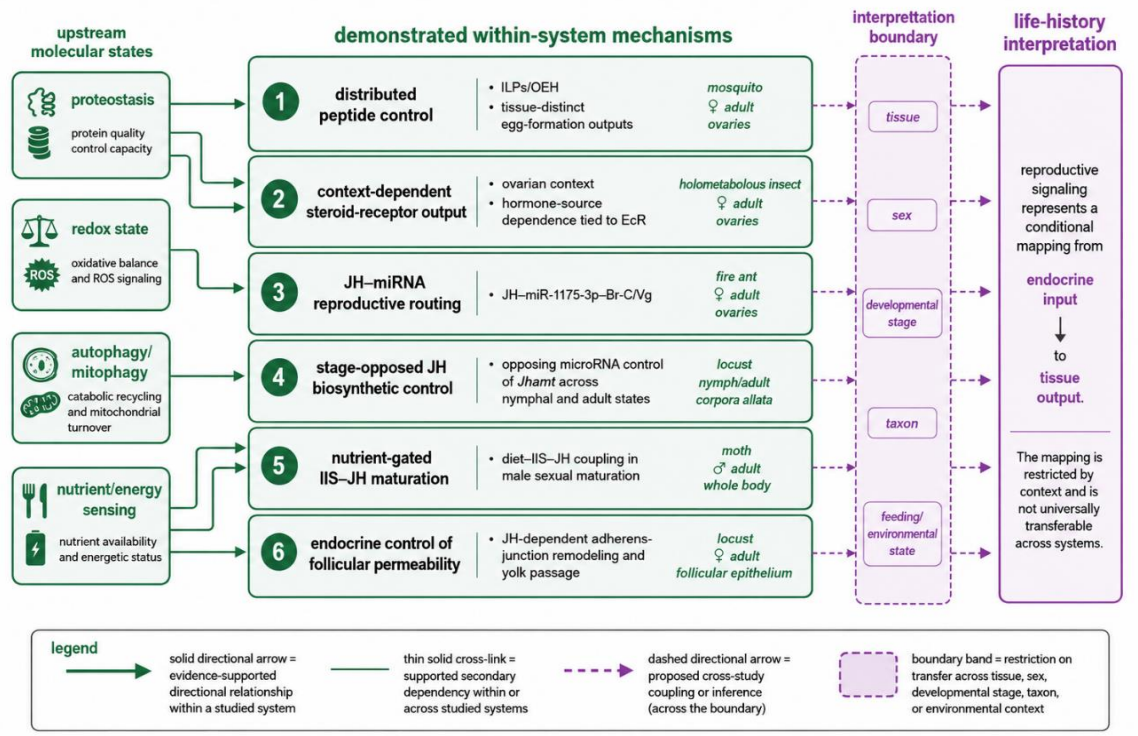


Figure 1. Reproductive signaling changes meaning across tissue, stage, and molecular-entry route

Shared energy and signaling nodes

Shared nodes need not be global controllers. In *Nilaparvata lugens*, PEX14 depletion compromises development, female survival, ovarian development, vitellogenin-related output, and fecundity while disturbing fatty-acid homeostasis [24]. This identifies peroxisomal metabolism as a point at which maintenance and reproduction can become jointly constrained, but does not establish PEX14 as a universal allocation switch or prove that energetic shortage causes every reproductive deficit.

Juvenile hormone is another shared node because its reproductive actions interact with nutrient sensing and ecdysteroid signaling across insect models [25]. Yet cross-taxon variation prevents a fixed-sign interpretation. A

shared endocrine node is therefore better represented as a conditional coupler whose downstream meaning depends on tissue, stage, and physiological state.

Environmental inputs can also bypass apparently central pathways. In *Drosophila*, microbial conditions alter germline stem-cell proliferation and egg maturation through ecdysone and partly juvenile hormone signaling, whereas insulin signaling was not required in the tested context [26]. This result supports alternative routing, not the general dispensability of IIS.

The proposed model therefore distinguishes shared nodes from shared outcomes. AMPK, metabolic substrate availability, IIS, juvenile hormone, ecdysteroids, and organelle quality can couple physiological domains, but perturbing them need not redistribute one common energetic pool. Cross-domain integration is inferred only where the relevant molecular, tissue, or organismal outputs are measured.

Energy should also not be treated as a directly measured common currency unless flux has been quantified. Metabolic support of proteome stability in the male germline demonstrates that substrate availability can alter protein fate [6], whereas mosquito egg formation distributes insulin-like and ovarian endocrine effects across tissues [18] and male moth maturation couples dietary state to IIS and JH [22]. These are mechanistically informative bridges, but they measure different currencies and endpoints. The proposed model therefore keeps energetic state, endocrine signaling, and reproductive output as linked but non-equivalent variables.

Stress-induced life-history reallocation

Stress-induced reallocation is most defensible when reproduction and survival are measured separately. In *Drosophila suzukii*, reproductive performance fails at some thermal exposures below those causing mortality, with both limits depending on exposure duration [27]. Lethal tolerance is therefore an inadequate proxy for reproductive tolerance, although the molecular cause of their separation remains unresolved.

Reduced reproduction can also coincide with preservation rather than damage. During reproductive diapause in female *Drosophila*, germline stem-cell activity is suppressed while later function and reproductive capacity can be retained [28]. This reversible state cannot make all stress-induced reproductive suppression protective or adaptive.

Tissue remodeling provides a third pattern. In female *Gryllus lineaticeps*, Beclin-mediated autophagy contributes to dorsal longitudinal flight-muscle histolysis, yet delaying this process did not produce a corresponding short-term change in oogenesis [29]. Somatic degradation therefore cannot be assumed to transfer resources directly to eggs.

This article accordingly reserves stress-induced life-history reallocation for cases in which at least two organismal or tissue outputs are distinguished and their relative deployment changes. Reproductive suppression, reversible preservation, remodeling, and damage remain separate states unless resource or regulatory transfer is demonstrated.

A practical inference threshold follows. Simultaneous reduction of reproduction and elevation of a stress-response marker demonstrates divergence, not necessarily transfer. Stronger evidence for reallocation would couple directional changes in at least two functions with a mechanistic bridge, temporal precedence, and preferably direct tracing of substrates or regulatory dependence. Where those criteria are absent, the narrower terms suppression, preservation, damage, or remodeling are retained. **Table 2** compares these states without assigning an unsupported hierarchy.

Table 2. Stress responses separate into damage, preservation, remodeling, and reallocation states across life-history stages

Biological with observed basis	Stress-response state with evidential standing	Interpretation, boundary or competing explanation, and discriminating check
Adult D. suzukii under heat **Reproduction fails below some lethal exposures; duration matters**	Reproduction-limited thermal state Evidence-supported	Survival and reproductive viability have separable stress boundaries Molecular cause unresolved Match reproductive and survival endpoints across intensity–duration treatments
Adult female Drosophila diapause	Reversible germline-preservation state Evidence-supported	Reduced current reproduction can coexist with preserved future capacity Specialized diapause state

Germline activity is suppressed while later function can persist		Measure suppression, recovery, and subsequent fertility longitudinally
Adult female cricket **Beclin-dependent flight-muscle degradation without matched short-term oogenesis change**	Selective somatic-remodeling state Evidence-supported	Autophagy can remodel tissue without demonstrated immediate reproductive transfer Muscle identity and observation window Trace released substrates and delayed reproductive outcomes
Adult beetle under xenobiotic stress **Defense signaling rises while reproductive output falls**	Stress-defense/reproduction divergence Evidence-supported	Defense and reproduction can diverge Resource transfer not directly measured Combine pathway perturbation with resource-flux measures
Larval endocrine tissue under nutrient restriction **Autophagy limits steroid precursor availability early but not identically later**	Temporally gated endocrine delay Evidence-supported	Life-history effects can depend on developmental timing Tissue-specific checkpoint Repeat perturbation across developmental windows
Cross-study synthesis **Multiple outputs change but mechanism varies**	Conditional reallocation state Proposed synthesis	Reallocation requires demonstrated redistribution or coordinated reprioritization Cross-taxon integration remains inferential Use multi-endpoint, longitudinal, mechanistically linked tests

Because these states diverge through time, **Figure 2** treats stress response as trajectories through a state field rather than a defense-to-reproduction pathway.

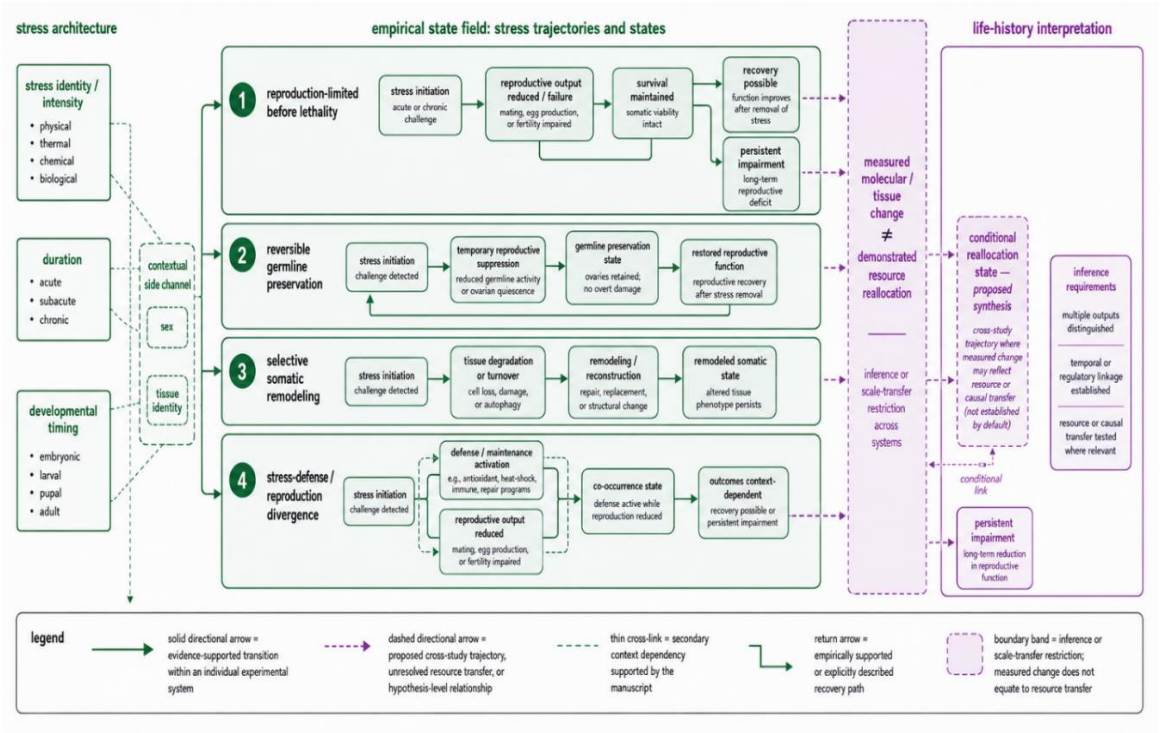


Figure 2. Stress trajectories diverge when maintenance, reproductive suppression, remodeling, and recovery unfold on different timescales

Integrated cellular network

Integration is defensible only if different forms of integration remain separate. Chaperone-dependent vitellogenin handling and proteasome-dependent steroidogenesis show that proteostasis can influence reproduction, but across

different species and tissues [3, 5, 7]. They support a systems-level category of proteostasis-dependent reproductive function, not one conserved route.

Redox evidence likewise resists a fixed directional edge. Germline maintenance can be disturbed by both excessive and abnormally reduced ROS; ROS can participate in diapause signaling; and antioxidant protection can occur without Keap1/Nrf2 [10, 11, 12]. Redox state is therefore represented as a conditional signaling environment rather than a monotonic damage axis.

Autophagic processes occupy similarly distinct positions. Mitophagy can support reversible germline quiescence, endocrine-tissue autophagy can gate nutrient-dependent steroid production, and Beclin-dependent autophagy can drive selective flight-muscle histolysis [14, 17, 29]. These findings justify an autophagy domain without making quiescence, endocrine delay, and tissue catabolism interchangeable.

The proposed network has three inferential levels: local mechanism, conditional coupling, and life-history interpretation. Movement between them requires additional evidence. Null effects, pathway bypass, recovery, and reversals are therefore informative network states rather than noise. The model maps conditional dependencies; it does not claim that all components operate simultaneously in any insect.

At the network level, conditional coupling is represented as a gate rather than a permanent edge. A gate can open when a particular tissue, developmental window, sex, nutritional state, or stress regime permits one domain to alter another. It can close when the same molecular node becomes dispensable, when parallel pathways compensate, or when a downstream tissue is no longer responsive. This architecture accommodates both local causality and cross-study heterogeneity without forcing contradictory results into an average direction. It also makes uncertainty biologically explicit: unknown coupling is different from demonstrated absence of coupling, and both differ from an experimentally supported inhibitory or permissive relationship.

Perturbation predictions

The model predicts where simple one-node/one-output expectations may fail. First, redox, autophagy, or endocrine perturbations may reverse or decouple across stages and tissues. Demonstrated context dependence means experiments should preserve developmental state instead of averaging it away.

Second, molecular rescue should not automatically count as life-history rescue. Normalizing a hormone, mitochondrial program, or protein-handling step may correct one endpoint while another remains altered. Validation should pair a proximal molecular measure with a downstream tissue or reproductive endpoint and include recovery time. Heat-stress recovery illustrates how sampling time can change whether impairment appears transient or persistent [8].

Third, duration should be treated as a mechanistic variable. Thermal reproductive limits vary with duration [27], nutritional autophagy is developmentally gated [17], and prolonged reproductive suppression during diapause can remain reversible [28]. Factorial tests should cross perturbation intensity, duration, and recovery interval while retaining sex, stage, and tissue identity.

Validation should therefore be perturbational and longitudinal rather than purely correlational. A useful test would perturb one candidate node while measuring proteostasis, redox state, autophagic or mitophagic activity, endocrine output, and at least one organismal life-history endpoint at matched times. Reciprocal perturbations would then ask whether restoring a downstream node rescues only the proximal defect or also the life-history phenotype. Such designs can distinguish mediation from parallel response, compensation from recovery, and temporary suppression from persistent reproductive cost without presuming that any one molecular marker represents the state of the whole network.

Finally, cross-taxon transfer requires replication of the relevant node, direction, and organismal consequence rather than homolog presence alone. A mechanism established in one ovary, fat body, germline, endocrine tissue, or flight muscle becomes a hypothesis when transferred to another lineage. Conditional edges should be removable or redirectable when comparative evidence contradicts them.

Conclusion

Proteostasis, redox regulation, autophagy, metabolic sensing, and reproductive signaling are experimentally connected in insects, but their relationships are distributed across tissues, sexes, developmental stages, species, and environments. They are therefore better represented as a conditional cellular stress network than as a universal cascade. The proposed model separates local mechanism, cross-domain coupling, and life-history interpretation

so that maintenance, reproductive suppression, recovery, developmental delay, and tissue remodeling remain analytically distinct.

A pathway response is not equivalent to a reproductive consequence, reproductive suppression is not automatically resource reallocation, and survival does not demonstrate preserved reproductive capacity. Strong validation requires matched molecular and organismal endpoints, explicit temporal designs, recovery measurements, and comparative replication. The model's value lies in organizing such tests while retaining uncertainty and context dependence rather than assigning fixed directions to stress responses.

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