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Metabolic-Immune Crosstalk as a Driver of Aging and Longevity: An Insight into *Drosophila Melanogaster*

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Abstract

Background: Aging is a complex biological process regulated by interconnected metabolic and immune pathways. Increasing evidence suggests that dysregulation of metabolic–immune crosstalk is a major driver of age-associated functional decline and reduced lifespan. *Drosophila melanogaster* has emerged as a powerful model system to dissect these interactions due to its conserved metabolic signaling networks and well-characterized innate immune system.

Objective: In this context, the study focuses on pathways such as insulin/insulin-like growth factor signaling (IIS), target of rapamycin (TOR), and AMP-activated protein kinase (AMPK) closely interact with innate immune pathways, including Toll, IMD, and JAK/STAT, to influence lifespan and health span.

Methods: This review is based on secondary data obtained from peer-reviewed literature accessed through databases including PubMed, ScienceDirect, Google Scholar, ResearchGate, and HINARI. Relevant studies evaluating *Drosophila Melanogaster***,** metabolic-immune crosstalk, aging and longevity were critically evaluated

Results: Age-related metabolic imbalance can lead to chronic immune activation, contributing to inflammaging, tissue dysfunction, and reduced longevity. Conversely, immune signaling can reshape metabolic homeostasis by altering nutrient allocation, mitochondrial function, and stress responses. This review highlights current advances in understanding how metabolic and immune pathways integrate to regulate aging in *Drosophila melanogaster*, emphasizing tissue-specific effects, environmental modulators such as diet and microbiota, and evolutionary trade-offs between immunity and longevity.

Conclusions: Elucidating these conserved immune-metabolic mechanisms provides critical insights into the biology of aging and may inform strategies to promote healthy aging across species.

Keywords: Aging; Immunometabolism; Innate immunity; Longevity; Insulin signaling; TOR pathway; *Drosophila melanogaster*

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INTRODUCTION

1.1 Aging as a systemic, multi-pathway process

Aging is a multifactorial biological process characterized by the progressive decline of physiological integrity, resulting in impaired function and increased vulnerability to disease and death. Rather than arising from a single causal mechanism, aging reflects the cumulative effects of molecular damage, altered cellular signaling, and systemic dysregulation across tissues (Giansanti *et al*., 2025; Trajkovic *et al.,* 2022). The hallmarks of aging framework highlights conserved biological processes—including deregulated nutrient sensing, mitochondrial dysfunction, loss of proteostasis, and chronic inflammation—that collectively drive age-associated functional decline (Atsoniou *et al.,* 2024; López-Otín *et al*., 2013). Among these hallmarks, energetic decline and immune dysregulation are central features that strongly influence organismal health span and lifespan (Kennedy *et al*., 2014; Johnson and Cagan, 2010). Age-associated impairment of metabolic homeostasis leads to reduced cellular energy availability and compromised stress responses, affecting tissue maintenance and repair (Johnson *et al.,* 2013; Wan *et al*., 1998). Concurrently, aging is accompanied by profound alterations in immune function, including diminished pathogen resistance and chronic activation of innate immune pathways, a phenomenon commonly referred to as immunosenescence (Thomas, 2022; Aw *et al.,* 2007). These immune changes contribute to a persistent low-grade inflammatory state that accelerates tissue deterioration and metabolic imbalance with age (Thomas *et al.*, 2017; Franceschi *et al*., 2018).

1.2 Immunometabolism: a conserved aging paradigm

The concept of immunometabolism has emerged to describe the reciprocal regulation between metabolic pathways and immune function. Metabolic signaling networks not only supply the energetic and biosynthetic demands of immune responses but also actively shape immune cell fate, activation, and resolution (Schuurs-Hoeijmakers *et al*., 2012; Mathis & Shoelson, 2011). Conversely, immune signaling can profoundly influence systemic metabolism by redirecting nutrient allocation, altering mitochondrial function, and modulating stress-response pathways (Olson *et al.,* 2018; Hotamisligil, 2017). A critical outcome of disrupted immunometabolic regulation during aging is inflammaging, defined as chronic, sterile inflammation driven by metabolic stress, accumulated cellular damage, and persistent innate immune activation (Su, 2029; Franceschi & Campisi, 2014). Inflammaging is now recognized as an evolutionarily conserved process that contributes to metabolic dysfunction, tissue degeneration, and reduced longevity across diverse organisms (Naz and Saddique, 2021; Ferrucci & Fabbri, 2018). These observations position metabolic–immune crosstalk as a fundamental and conserved determinant of the aging process.

1.3 Why *Drosophila melanogaster*?

Drosophila melanogaster is a premier model organism for aging research due to its short lifespan, well-annotated genome, and unparalleled genetic tractability (Parvy *et al*., 2018; Sonoshita and Cagan, 2017). Many of the molecular pathways that regulate metabolism and longevity in *Drosophila*, including insulin/insulin-like growth factor signaling (IIS), target of rapamycin (TOR), and AMP-activated protein kinase (AMPK), are highly conserved in mammals (Piper and Partridge, 2018; Partridge *et al.,* 2011; Huang and Muthuswamy, 2010). Manipulation of these pathways in flies robustly alters lifespan and stress resistance, underscoring their central role in aging regulation (Victor *et al*., 2025; Frappaolo et al., 2022). In addition, *Drosophila* possesses a sophisticated innate immune system comprising the Toll, immune deficiency (Imd), and JAK/STAT pathways, which coordinate antimicrobial defense and inflammatory signaling (Frappaolo and Giansanti, 2023; Buchon *et al.,* 2014). The fat body—a multifunctional organ analogous to mammalian liver and adipose tissue—serves as a critical hub integrating metabolic sensing and immune responses at the organismal level (Khan and Rusan, 2024; Arrese & Soulages, 2010). Importantly, age-associated immune activation and metabolic dysfunction in *Drosophila* mirror key aspects of mammalian aging, alteration of senescence and highlighting the translational relevance of this model (Olson et al., 2018; Kounatidis & Ligoxygakis, 2012).

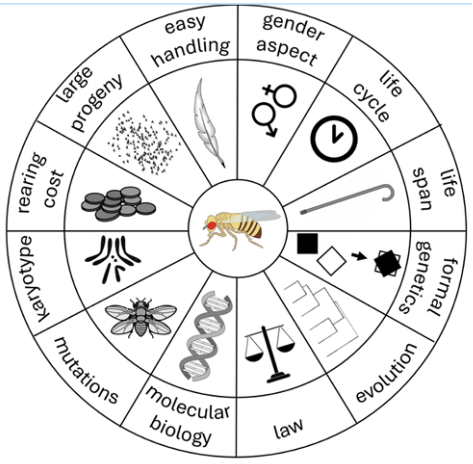

Figure 1: The priorities of using *Drosophila melanogaster* as a scientific research model (Giansanti *et al*., 2025)

1.4 Scope and aims of the manuscript

Despite substantial progress in aging biology, the mechanisms by which metabolic and immune pathways integrate to shape lifespan remain incompletely understood. In particular, how age-dependent metabolic changes influence immune activation, how chronic immune signaling disrupts metabolic homeostasis, and how these interactions vary across tissues are unresolved questions. This manuscript aims to critically examine current evidence supporting metabolic–immune crosstalk as a driver of aging and longevity in *Drosophila melanogaster*. By synthesizing findings from genetic, physiological, and environmental studies, this work proposes a conceptual framework in which immunometabolic balance determines the trajectory of aging. Elucidating these conserved interactions in *Drosophila* provides insight into fundamental aging mechanisms and may inform strategies to promote healthy aging across species.

2.0 Metabolic Regulation of Aging in *Drosophila melanogaster*

2.1 Insulin/IGF signaling (IIS) and longevity

The insulin/insulin-like growth factor signaling (IIS) pathway is one of the most extensively studied regulators of aging and lifespan in *Drosophila melanogaster*. This pathway is activated by a family of insulin-like peptides (dILPs), primarily produced by insulin-producing cells in the brain, which respond to nutrient availability and regulate systemic growth, metabolism, and reproduction (Dombernowsky *et al*., 2015; Grönke *et al*., 2010). Genetic reduction of IIS, through mutations in the insulin receptor (*InR*) or downstream effectors such as phosphoinositide 3-kinase (PI3K), consistently extends lifespan while enhancing resistance to oxidative and metabolic stress (Ying *et al*., 2022; Clancy *et al*., 2001; Tatar *et al*., 2001). dILPs exert context-dependent effects on longevity, with individual peptides contributing differently to lifespan regulation, stress resistance, and fecundity (Minnik *et al*., 2022; Grönke *et al*., 2010). Reduced IIS leads to activation of the FOXO transcription factor, which promotes the expression of genes involved in stress resistance, autophagy, and metabolic adaptation, thereby supporting long-term survival (Sung *et al*., 2021; Hwangbo *et al*., 2004). However, IIS reduction is also associated with decreased growth and reproductive output, highlighting an evolutionary trade-off between somatic maintenance and reproductive investment (Raskov *et al*., 2020; Flatt, 2011). These trade-offs underscore the role of IIS as a central node coordinating energy allocation between growth, reproduction, and longevity.

2.2 TOR signaling and nutrient sensing

The target of rapamycin (TOR) pathway functions as a critical nutrient-sensing system that integrates amino acid availability, cellular energy status, and growth signals to regulate metabolism and aging. In *Drosophila*, TOR signaling operates through two

distinct complexes, TORC1 and TORC2, which differentially regulate protein synthesis, lipid metabolism, autophagy, and cytoskeletal organization (Saxton & Sabatini, 2017; Itatani *et al*., 2016). TORC1, in particular, has been strongly implicated in lifespan control, with genetic or pharmacological inhibition leading to robust lifespan extension (Sonoshita *et al.,* 2015; Kapahi *et al*., 2004). Suppression of TORC1 activity enhances longevity by promoting autophagy and reducing anabolic processes that contribute to cellular damage over time (Villegas, 2019; Bjedov *et al*., 2010). These effects are closely linked to dietary restriction (DR), a well-established intervention that extends lifespan across species, including *Drosophila* (Casali and Batlle, 2019; Mair *et al*., 2005). DR phenotypes in flies often mimic TOR inhibition, suggesting that reduced nutrient signaling through TOR is a key mediator of DR-induced longevity (Katewa & Kapahi, 2017; Bemgi et al., 2016). However, TOR signaling also influences immune competence and stress tolerance, indicating that lifespan extension via TOR modulation involves complex physiological trade-offs rather than simple growth suppression.

2.3 Mitochondrial metabolism and redox homeostasis

Mitochondrial function is central to metabolic homeostasis and plays a pivotal role in aging through its influence on energy production, redox balance, and cellular signaling. In *Drosophila*, age-associated mitochondrial dysfunction manifests as reduced oxidative phosphorylation efficiency, altered mitochondrial dynamics, and increased susceptibility to metabolic stress (Smolarz *et al.,* 2025; Cho *et al*., 2011). Reactive oxygen species (ROS), long considered purely damaging by-products of metabolism, are now recognized as important signaling molecules that regulate stress responses and longevity in a dose-dependent manner (Ristow & Schmeisser, 2014; Kottgen *et al*., 2005; Lusk *et al.,* 1993). Moderate increases in mitochondrial ROS can activate adaptive stress responses that promote longevity, a phenomenon termed mitohormesis, whereas excessive ROS accumulation leads to oxidative damage and cellular dysfunction (Levine and Cagan, 2016; Scialò *et al*., 2016). Mitochondrial dynamics, including the balance between fusion and fission, are also critical determinants of lifespan in *Drosophila*. Disruption of these processes impairs mitochondrial quality control and accelerates aging phenotypes, while enhanced mitochondrial turnover through mitophagy supports metabolic resilience and longevity (Twig *et al.,* 2008; Rana *et al.,* 2017; Das and Cagan, 2017). Together, these findings position mitochondrial metabolism and redox regulation as key modulators of aging downstream of nutrient-sensing pathways.

3.0 Innate Immune Pathways and Aging

3.1 *Drosophila* innate immunity overview

Unlike vertebrates, *Drosophila melanogaster* relies exclusively on an innate immune system to defend against microbial infection. This system is composed of conserved signaling pathways that detect pathogens and coordinate antimicrobial and inflammatory responses. The Toll and immune deficiency (IMD) pathways are the primary regulators of humoral immunity, controlling the transcription of antimicrobial peptides (AMPs) in response to Gram-positive and Gram-negative bacteria, respectively (Shergalis *et al.,* 2018; Lemaitre & Hoffmann, 2007). Activation of these pathways culminates in the nuclear translocation of NF-κB family transcription factors, which drive robust AMP expression in immune-responsive tissues such as the fat body and gut (GAD, 2021; Ferrandon *et al.,* 2007). In addition to Toll and IMD signaling, the JAK/STAT pathway plays a critical role in immune regulation, tissue repair, and stress responses. This pathway is activated by cytokine-like ligands of the unpaired family and contributes to epithelial homeostasis and regenerative responses following infection or injury (Stahl and Tomchik, 2024; Buchon *et al.,* 2009). Collectively, these innate immune pathways provide effective protection against pathogens while maintaining tissue integrity. However, their activity must be tightly regulated, as excessive or prolonged immune activation can disrupt homeostasis and compromise organismal fitness.

3.2 Immune activation across the lifespan

Immune function in *Drosophila* undergoes pronounced changes with age. While young flies mount efficient and transient immune responses to infection, aging is associated with persistent activation of innate immune signaling**,** even in the

absence of overt pathogens (Feigin *et al.,* 2020; Landis *et al.,* 2004). This age-associated immune hyperactivation is characterized by elevated basal expression of AMPs and inflammatory mediators, reflecting a breakdown in immune regulatory mechanisms (Parenti *et al.,* 2020; Pletcher *et al*., 2002). Paradoxically, despite heightened immune signaling, aged flies exhibit a decline in pathogen resistance, resulting in increased susceptibility to bacterial and fungal infections (O'kane, 2011; Zerofsky *et al.*, 2005). This functional deterioration suggests that chronic immune activation does not confer improved defense but instead reflects immune system exhaustion or misregulation. Disrupted feedback control, impaired signaling resolution, and cumulative tissue damage are thought to contribute to this decline in immune competence (Badinloo *et al*., 2018; McGurk *et al.,* 2015). These findings parallel features of immunosenescence observed in vertebrates, underscoring the conserved nature of age-related immune dysfunction.

3.3 Inflammaging in *Drosophila*

The term *inflammaging* describes the chronic, low-grade activation of immune pathways that emerges during aging and contributes to tissue degeneration and reduced lifespan. In *Drosophila*, inflammaging is marked by sustained expression of AMPs and prolonged activation of NF-κB signaling in multiple tissues (Nitta and Sugie, 2022; Kounatidis *et al*., 2017). While AMPs are essential for host defense, their chronic overproduction has been shown to exert cytotoxic effects, disrupt epithelial integrity, and negatively impact lifespan (Cao *et al.*, 2013; Campbell and Tutner, 2010). Importantly, inflammaging in *Drosophila* exhibits strong tissue specificity. The gut plays a particularly prominent role, as age-associated dysregulation of immune signaling compromises epithelial homeostasis and barrier function, leading to systemic inflammation and mortality (Ugur *et al*., 2016; Rera *et al*., 2012). Similarly, excessive immune activation in the fat body alters metabolic regulation and accelerates physiological decline (Kounatidis & Ligoxygakis, 2012; Inagaki *et al.,* 2010). These observations indicate that age-related immune dysregulation is not uniform across the organism but instead reflects context-dependent interactions between immune signaling, tissue function, and metabolic state.

4.0 Metabolic–Immune Crosstalk in Aging

4.1 insulin/insulin-like growth factor signaling – immune pathway interactions

The insulin/insulin-like growth factor signaling (IIS) pathway plays a central role in coordinating metabolic state with immune function in *Drosophila melanogaster*. Insulin signaling has been shown to modulate innate immune responses by influencing the transcriptional output of immune pathways, particularly the production of antimicrobial peptides (AMPs). Reduced IIS activity leads to enhanced expression of several AMPs, suggesting that insulin signaling normally acts to restrain immune activation under nutrient-rich conditions (Becker *et al*., 2010; McGuire *et al.,* 2005). This regulatory relationship highlights the sensitivity of immune output to systemic metabolic cues. A key mediator of IIS–immune crosstalk is the FOXO transcription factor, which becomes activated under conditions of reduced insulin signaling. FOXO directly regulates genes involved in stress resistance, metabolism, and immunity, positioning it as a molecular integrator of metabolic and immune signals (Simon and Dickinson, 2010; Becker *et al*., 2010; Dionne *et al*., 2006). In the context of aging, sustained FOXO activation has been associated with enhanced stress tolerance and lifespan extension but can also promote immune hyperactivation when dysregulated (Bolus *et al*., 2020; Slack *et al*., 2011). These findings underscore the dual role of IIS–FOXO signaling in balancing immune defense and tissue maintenance across the lifespan.

4.2 TOR signaling and immune competence

The target of rapamycin (TOR) pathway links nutrient availability to immune competence by regulating cellular growth, autophagy, and protein synthesis. In *Drosophila*, nutrient-rich conditions activate TOR signaling, which favors anabolic metabolism but can suppress immune responsiveness by limiting investment in defense mechanisms (Ma *et al.,* 2022; Varma *et al*., 2014). Conversely, reduced TOR activity enhances immune readiness, partly through increased autophagic flux and improved cellular stress management (Shweta *et al.,* 2024; Martin *et al*., 2017). TOR inhibition has been shown to extend lifespan while simultaneously modulating immune

function. Pharmacological or genetic suppression of TOR signaling improves survival following infection in aged flies, suggesting that reduced nutrient signaling preserves immune competence during aging (Martin *et al*., 2017; Gatto and Broadie, 2011; Bjedov *et al*., 2010;). However, excessive TOR inhibition can impair immune cell proliferation and tissue repair, indicating that optimal immune outcomes depend on finely tuned TOR activity rather than complete pathway suppression. These findings illustrate how nutrient sensing through TOR shapes immune output and longevity through context-dependent mechanisms.

4.3 Lipid and carbohydrate metabolism in immune aging

Lipid and carbohydrate metabolism are fundamental to immune function, as immune responses impose substantial energetic demands on the organism. In *Drosophila*, the fat body serves as a central immunometabolic organ, integrating nutrient storage, metabolic signaling, and systemic immune responses (Arrese & Soulages, 2010). During infection, the fat body reallocates energy reserves toward immune effector production, including AMPs, at the expense of growth and reproduction (Chambers *et al*., 2012). Aging disrupts this metabolic flexibility, leading to inefficient energy allocation during immune challenge. Altered lipid metabolism in aged flies has been linked to chronic immune activation and reduced stress tolerance, suggesting that metabolic inflexibility exacerbates inflammaging (Woodcock *et al*., 2015). Similarly, dysregulation of carbohydrate metabolism affects immune cell function and survival during prolonged immune responses (Davoodi *et al*., 2019). Together, these findings indicate that age-related impairments in energy allocation compromise immune effectiveness and contribute to the decline in organismal homeostasis with age.

5.0 Tissue-Specific Immunometabolism

5.1 Fat body

The fat body of *Drosophila melanogaster* functions as a central organ integrating metabolism, immunity, and endocrine signaling, analogous to the combined roles of the mammalian liver and adipose tissue. It serves as the primary site for nutrient storage, metabolic regulation, and systemic immune responses, producing the majority of antimicrobial peptides (AMPs) following infection (Rajan & Perrimon, 2013). Through its ability to sense nutrient availability and immune stimuli, the fat body coordinates organism-wide energy allocation during stress conditions. Immunometabolic regulation within the fat body is tightly controlled, as immune activation imposes substantial energetic costs. Upon infection, metabolic pathways are reprogrammed to prioritize immune effector synthesis, often at the expense of growth and reproduction (DiAngelo *et al*., 2009). Aging disrupts this balance, leading to sustained immune activation and altered metabolic output, which contribute to systemic inflammation and reduced lifespan (Koyama *et al*., 2020). These findings indicate that age-dependent dysregulation of fat body immunometabolism is a major driver of inflammaging and metabolic decline in *Drosophila*.

5.2 Gut

The intestinal epithelium represents a critical interface between the host, its diet, and the microbiota, making it a key tissue for immunometabolic regulation during aging. In *Drosophila*, the gut relies on tightly regulated innate immune signaling to maintain microbial homeostasis while preserving epithelial integrity (Lee *et al*., 2013). Metabolic activity in intestinal cells influences immune signaling outputs, linking nutrient absorption directly to immune function. Aging is associated with pronounced changes in gut immunometabolism, including microbial dysbiosis, impaired barrier function, and chronic immune activation (Clark *et al*., 2015). Disruption of epithelial integrity allows microbial products to translocate systemically, triggering inflammatory responses that accelerate organismal decline and mortality (Guo *et al*., 2014). Importantly, age-related alterations in gut metabolism impair regenerative capacity and immune resolution, establishing a feedback loop between metabolic stress and immune dysregulation (Regan *et al*., 2016). These observations highlight the gut as a critical driver of systemic inflammaging through tissue-specific immunometabolic interactions.

5.3 Brain and neuroimmune aging

Although traditionally considered immunologically privileged, the *Drosophila* brain is increasingly

recognized as a site of active immune and metabolic signaling. Neurons and glial cells engage innate immune pathways to maintain neural homeostasis and respond to stress or injury (Doherty *et al*., 2009). Metabolic signaling within the nervous system influences immune gene expression, linking energy status to neuroimmune regulation. During aging, dysregulation of metabolic signaling in neural tissues contributes to chronic activation of innate immune pathways, leading to neuroinflammation and functional decline (Petersen *et al*., 2012). Glial cells, in particular, play a central role in mediating age-associated neuroimmune responses by integrating metabolic cues with inflammatory signaling (Kremer *et al.,* 2017). Persistent neuroimmune activation has been shown to negatively affect lifespan and promote neurodegenerative phenotypes in *Drosophila*, underscoring the importance of balanced immunometabolic signaling in the aging brain (Cao *et al*., 2019). Together, these findings demonstrate that tissue-specific immunometabolic regulation within the nervous system is a key determinant of healthy aging.

6.0 Environmental and Genetic Modulators

6.1 Diet and dietary restriction

Diet is a powerful environmental determinant of lifespan and immune function in *Drosophila melanogaster*. Beyond caloric intake alone, the balance between dietary protein and carbohydrate has emerged as a critical regulator of metabolic health, immune performance, and longevity. Nutritional geometry studies demonstrate that low protein-to-carbohydrate ratios promote lifespan extension, whereas high protein diets accelerate aging despite increased reproductive output (Lee *et al*., 2008). These dietary effects are mediated through conserved nutrient-sensing pathways and influence systemic immune activity. Dietary restriction (DR) modulates immune aging by attenuating chronic immune activation and preserving immune responsiveness during aging. Flies maintained on DR display reduced basal expression of antimicrobial peptides (AMPs) and improved survival following infection, indicating enhanced immune efficiency rather than immune suppression (Fanson *et al*., 2009). Importantly, DR improves metabolic flexibility and stress resistance, which indirectly supports immune homeostasis and delays the onset of inflammaging (Nakagawa *et al*., 2012). These findings highlight diet composition as a key modulator of immunometabolic aging.

6.2 Microbiota composition

The gut microbiota is a dynamic environmental factor that profoundly influences host metabolism, immunity, and lifespan in *Drosophila*. Age-associated shifts in microbial composition, commonly referred to as dysbiosis**,** are linked to increased immune activation, metabolic imbalance, and reduced longevity (Broderick & Lemaitre, 2012). Expansion of pathobionts during aging stimulates chronic activation of innate immune pathways, contributing to systemic inflammation and tissue dysfunction. Microbiota-driven immune activation also feeds back on host metabolism by altering nutrient absorption, lipid storage, and insulin signaling (Shin *et al.,* 2011). Disruption of immune regulation exacerbates dysbiosis, creating immune–metabolic feedback loops that accelerate aging (Fast *et al*., 2018). Experimental manipulation of microbial load or composition has been shown to extend lifespan and reduce immune hyper activation, underscoring the causal role of microbiota-mediated immunometabolic interactions in aging (Obata *et al.,* 2018).

6.3 Genetic interventions

Genetic manipulation has been instrumental in identifying conserved regulators of aging and immunometabolism in *Drosophila*. Numerous longevity mutants, including those affecting nutrient sensing, stress response, and immune signaling pathways, exhibit extended lifespan accompanied by altered immune profiles (Tower, 2015). These models reveal that lifespan extension often coincides with reduced chronic immune activation and improved stress tolerance. Comparative studies of immune-deficient and immune-hyperactive models further demonstrate the importance of immune balance in aging. Flies with reduced innate immune signaling frequently display increased lifespan under sterile conditions, suggesting that excessive immune activation imposes physiological costs (Libert *et al*., 2006). Conversely, constitutive activation of immune pathways accelerates aging and shortens lifespan, even in the absence of infection (Lemaitre *et al*., 1995). Together, these genetic studies support the

concept that optimal longevity depends on finely tuned immune activity rather than maximal immune defense, reinforcing the role of genetic modulation in shaping immunometabolic aging trajectories.

7.0 Implications for Immune metabolic ageing for Longevity and Health span

7.1 Trade-offs between immunity and lifespan

A central implication of immunometabolic aging research is the recognition of fundamental trade-offs between immune investment and lifespan**.** While effective immune responses are essential for survival in pathogen-rich environments, immune activation is energetically costly and can divert resources away from somatic maintenance and repair (Sheldon & Verhulst, 1996). In *Drosophila melanogaster*, experimental activation of innate immune pathways often results in reduced lifespan, even in the absence of infection, highlighting the physiological cost of sustained immune signaling (Leclerc *et al.,* 2006). These trade-offs align with life-history theory, which predicts that organisms must allocate finite resources between growth, reproduction, and survival. In this framework, excessive immune activation during aging can accelerate physiological decline by increasing metabolic demand, promoting tissue damage, and impairing regenerative capacity (Schmid-Hempel, 2005). Conversely, reduced immune investment can extend lifespan under low-pathogen conditions but may compromise survival when infections occur. Thus, longevity is optimized not by maximal immune defense, but by balanced immune activity that minimizes collateral damage while maintaining sufficient protection.

7.2 Adaptive vs maladaptive immune activation

Immune activation during aging exists on a continuum ranging from adaptive to maladaptive. Acute, transient immune responses are generally beneficial, enabling efficient pathogen clearance and tissue repair. However, chronic or dysregulated immune activation becomes maladaptive, contributing to inflammaging, metabolic dysfunction, and tissue degeneration (Fulop *et al.,* 2018). In *Drosophila*, age-associated increases in basal immune signaling reflect a loss of regulatory control rather than enhanced immune protection. Adaptive immune activation is often tightly coupled to metabolic state, allowing immune responses to be mounted only when sufficient energetic resources are available. In contrast, maladaptive immune activation during aging is frequently uncoupled from metabolic need, resulting in persistent inflammatory signaling that undermines healthspan (Fabian *et al*., 2021). Importantly, interventions that suppress chronic immune activation without abolishing acute immune responses have been shown to improve lifespan and functional outcomes, supporting the notion **t**hat immune quality, rather than immune intensity**,** determines aging trajectories.

7.3 Evolutionary perspectives on immunometabolic aging

From an evolutionary perspective, immunometabolic aging reflects the declining force of natural selection with age. Immune and metabolic traits that enhance early-life survival and reproductive success may be favored, even if they incur detrimental effects later in life—a concept known as antagonistic pleiotropy (Williams, 1957). In *Drosophila*, strong immune responsiveness and high metabolic activity early in life can promote fitness under competitive or pathogen-rich conditions, while predisposing individuals to accelerated aging. Furthermore, immune systems evolved primarily to combat acute infections rather than to maintain long-term inflammatory balance. As a result, mechanisms that effectively resolve immune responses early in life may become inefficient with age, leading to chronic immune activation and metabolic disruption (Medzhitov, 2008). Comparative studies across taxa suggest that immunometabolic aging is a conserved outcome of evolutionary trade-offs between early-life fitness and late-life maintenance (Nussey *et al.,* 2013). Understanding these evolutionary constraints provides critical insight into why aging-associated immune dysregulation persists and highlights the importance of targeting immunometabolic balance to promote healthy longevity rather than attempting to eliminate immune activity altogether.

8.0 Translational Relevance

8.1 Conservation of immunometabolic pathways

Many immunometabolic interactions identified in *Drosophila melanogaster* are highly conserved across evolution, providing a robust model for understanding mammalian aging. Key nutrient-

sensing pathways, including insulin/IGF signaling (IIS), target of rapamycin (TOR), and AMP-activated protein kinase (AMPK), regulate both metabolism and immune function in flies and mammals (López-Otín *et al.,* 2013). Similarly, NF-κB-mediated innate immune signaling, FOXO transcription factors, and autophagy pathways demonstrate conserved roles in maintaining homeostasis under metabolic and inflammatory stress (Miller *et al*., 2011). This evolutionary conservation allows *Drosophila* studies to inform mechanisms underlying human immunometabolic aging and systemic inflammaging.

8.2 Insights for mammalian and human aging

Findings from *Drosophila* provide mechanistic insights into the interplay between metabolism and immunity in mammalian aging. Chronic low-grade inflammation, or "inflammaging," observed in aged flies mirrors systemic inflammation in elderly humans, linking persistent immune activation with metabolic dysfunction and tissue decline (Frappaolo et al., 2025; Franceschi et al., 2018). Nutrient-sensing modulation in flies, such as dietary restriction or TOR inhibition, yields lifespan extension and improved immune homeostasis—interventions that similarly enhance healthspan in murine models (Kapahi *et al.,* 2010). These parallels underscore the relevance of *Drosophila* as a preclinical platform to explore therapeutic strategies targeting immunometabolic pathways.

8.3 Therapeutic implications

The elucidation of immunometabolic crosstalk in flies highlights multiple potential intervention points for promoting healthy aging. Pharmacological modulation of nutrient-sensing pathways, such as rapamycin-mediated TOR inhibition or AMPK activators, may reduce chronic inflammation while preserving immune competence (Johnson *et al.,* 2013). Likewise, dietary interventions, including macronutrient balancing and caloric restriction mimetics, can mitigate age-related immune dysfunction and metabolic decline. Beyond pharmacology, manipulation of the gut microbiota represents an emerging strategy, as microbiome composition influences both systemic immunity and metabolic regulation (Kundu *et al.,* 2017). Collectively, these translational insights suggest that targeting immunometabolic pathways can enhance healthspan and reduce age-associated disease risk in humans, providing a framework for precision interventions in aging populations.

9.0 Limitations and Knowledge Gaps

9.1 Context-dependent effects

Although *Drosophila melanogaster* has been instrumental in elucidating immunometabolic interactions, the effects of metabolic and immune interventions are often highly context-dependent**.** For example, dietary restriction or TOR inhibition can extend lifespan in one genetic background or environmental condition but may be neutral or even detrimental in another (Zirin *et al*., 2024; Yamaguchi and Yoshida, 2018; Hales *et al.,* 2015; Mair *et al*., 2005). Similarly, immune activation may enhance pathogen resistance under acute infection but accelerate tissue damage and mortality in sterile conditions (Rubin, 2023; Perveen, 2018; Kaufman, 2017; Ravindran, 2014; Leclerc *et al.*, 2006). These context-specific outcomes highlight the need to consider environmental, dietary, and genetic variables when interpreting experimental results and translating findings to other species.

9.2 Sex-specific responses

Sexual dimorphism in metabolism, immunity, and lifespan is well-documented in *Drosophila*, yet remains incompletely characterized in the context of immunometabolic aging. Males and females differ in nutrient allocation strategies, hormone signaling, and immune gene expression, which can lead to divergent outcomes following metabolic or immune perturbations (Camus *et al.*, 2012). For instance, females may prioritize reproduction over somatic maintenance under certain dietary regimes, whereas males may display heightened sensitivity to immune activation (Regan *et al*., 2016). Accounting for sex-specific responses is essential to accurately model aging trajectories and avoid overgeneralization.

9.3 Need for longitudinal and tissue-resolved studies

Much of the current understanding of immunometabolic aging in *Drosophila* relies on cross-sectional measurements, often focused on whole-body readouts. However, aging is a dynamic

and tissue-specific process, and the interactions between metabolism and immunity may vary across tissues and over time (Koyama *et al*., 2020). Longitudinal studies that monitor immune and metabolic states throughout the lifespan, combined with tissue-resolved molecular profiling, are required to capture the temporal and spatial complexity of immunometabolic aging. Such approaches would also clarify the causal relationships between metabolic decline, chronic inflammation, and lifespan reduction, providing a more mechanistic understanding to inform interventions.

10.0 Future Directions

10.1 Single-cell immunometabolism

Understanding aging at the level of individual cells is a critical frontier in immunometabolism. Bulk measurements of metabolic and immune markers often obscure cell-type–specific heterogeneity, limiting mechanistic insight. Single-cell RNA sequencing (scRNA-seq) and metabolic profiling in *Drosophila* tissues such as the fat body, gut, and brain can reveal distinct cellular programs that drive age-dependent immune dysfunction (Li *et al*., 2020). By resolving cell-type–specific metabolic states alongside immune gene expression, these approaches can uncover early biomarkers of inflammaging and identify targets for tissue-selective interventions.

10.2 Multi-omics approaches

Integrating genomics, transcriptomics, proteomics, and metabolomics provides a holistic view of immunometabolic aging. Multi-omics studies in *Drosophila* enable identification of network-level interactions between nutrient-sensing pathways, immune effectors, and tissue-specific metabolic profiles (Stanley *et al*., 2017). Longitudinal multi-omics data can delineate causal relationships between metabolic decline, chronic inflammation, and lifespan reduction, providing predictive models for interventions. Additionally, these datasets can help identify conserved molecular signatures that are translatable to mammalian and human aging studies.

10.3 Microbiome–immune–metabolic triad

The gut microbiome represents a dynamic interface linking nutrition, immunity, and host metabolism. Future research should focus on the microbiome–immune–metabolic triad**,** exploring how microbial composition modulates tissue-specific metabolism and immune activation during aging. Recent studies in flies indicate that manipulating microbial communities can improve lifespan, reduce chronic inflammation, and restore metabolic homeostasis (Obata *et al.,* 2018). Combining microbiome profiling with host multi-omics and single-cell analyses promises to reveal mechanistic insights into the bidirectional interactions that govern immunometabolic aging and identify novel therapeutic avenues.

11. 0 Summary

Aging is a compounded physiological process geared by interconnected molecular, metabolic, and immune changes that gradually reduce physiological function and expands vulnerability to pathological senescence. Rather than resulting from a single cause, aging involves several pathways such as mitochondrial abnormality, deregulated nutrient activation, prolong inflammation, and impaired cellular maintenance. Among these, metabolic decline and immune dysregulation are particularly important because they strongly influence life trajectories. The basis of immunity and metabolism expands the close relationship between metabolism and immune function. Metabolic signals provide energy for immune responses, while immune signaling triggers nutrient use, mitochondrial activity, and cortisol stress feedback. Drosophila melanogaster, widely known as fruit fly used as a model organism in aging research due its genetic tractability, short lifespan and strong conservation of aging-related pathways with research specie. Key nutrient-sensing pathways such as insulin/IGF signaling (IIS), TOR, and AMPK regulate metabolism, stress resistance, and lifespan in flies similarly to humans. The fly's innate immune system, including the Toll, IMD, and JAK/STAT pathways, also mirrors many aspects of mammalian immunity. The fat body, comparable to the mammalian liver and adipose tissue, acts as a central hub connecting metabolic and immune regulation.

The manuscript highlights major metabolic pathways involved in aging. Reduced IIS activity activates FOXO, promoting stress resistance and longevity but often reducing growth and reproduction. TOR signaling regulates nutrient sensing, growth, autophagy, and lifespan; inhibition of TOR extends lifespan and mimics the beneficial effects of dietary restriction. Mitochondrial metabolism also plays a key role, as mitochondrial dysfunction and oxidative stress increase with age. Moderate reactive oxygen species (ROS) can trigger protective stress responses, while excessive ROS causes cellular damage and accelerates aging. Innate immune pathways also change significantly during aging. Young flies mount efficient immune responses, but aging leads to chronic activation of immune signaling even without infection. This persistent immune activation results in elevated antimicrobial peptide production, tissue damage, and reduced pathogen resistance, reflecting immune exhaustion or dysregulation. Chronic immune activation, or inflammaging, particularly affects the gut and fat body, where disrupted immune signaling impairs tissue integrity and metabolic homeostasis.

The review emphasizes that metabolism and immunity are deeply interconnected. IIS and FOXO signaling regulate both metabolic adaptation and immune activity, while TOR signaling influences immune competence through autophagy and stress resistance. Lipid peroxidation relates immune responses in substantial energy. Aging reduces metabolic flexibility, impairing energy allocation during immune challenges. Environmental and genetic factors further shape aging trajectories. Low dietary protein to carbohydrate restriction improve metabolic flexibility and reduce chronic inflammation. The gut microbiota also plays a major role as senescence demonstrates genetic signaling often extends lifespan, whereas constitutive immune activation accelerates aging.

The review also discusses the evolutionary trade-offs between immunity and longevity. Strong immune balance are important pathogen defense but having a detrimental long effects. Therefore, healthy aging depends on balanced immune activity rather than maximal immune activation. From an evolutionary perspective, traits that improve early-life survival may contribute to late-life decline, explaining why chronic inflammation persists with age. Quite many pathways identified in flies are evolutionarily conserved in mammals bringing Drosophila a valuable tool for teaching human aging. Knowledge gap still evolve despite its use in science though with variation across sexes. More longitudinal, tissue-specific, and single-cell studies are needed to fully understand how metabolism and immunity interact throughout aging. Future research combining single-cell analysis, micro-flora research may provide deeper insight into immune-metabolic aging and reveal new therapeutic targets for promoting healthy longevity.

CONCLUSION

The threshold of immunity and metabolism signals aids a central role in determining aging levels and longevity in *Drosophila melanogaster*. Research along mitochondrial movement, inborn immune signaling and nutrient-sensing, relates that metabolic–immune crosstalk controls tissue-specific balance, systemic inflammation, and lifespan. brain cells, adipose, and micro-gut enacts as critical prowess where immunity and metabolic interactions determine organismal resilience or reduction, marking the relevance of spatially resolved studies.

Environmental factors such as diet composition and microbiota, as well as genetic manipulations, further modulate these interactions, highlighting the dynamic interplay between intrinsic and extrinsic determinants of aging (Broderick & Lemaitre, 2012; Regan *et al*., 2016). Importantly, the balance between adaptive and maladaptive immune activation shapes lifespan, underscoring the evolutionary and energetic trade-offs inherent in immune investment (Sheldon & Verhulst, 1996; Medzhitov, 2008). Given the conservation of key immunometabolic pathways between flies and mammals, *Drosophila* provides a predictive and experimentally tractable model to uncover mechanisms underlying age-related metabolic and immune dysregulation (López-Otín *et al*., 2013; Miller *et al*., 2011). Advances in single-cell profiling, multi-omics, and microbiome studies promise to further resolve the complex interactions driving aging and identify targetable nodes for

therapeutic intervention. Overall, integrating metabolic and immune perspectives is essential for a comprehensive understanding of aging biology and for developing strategies to promote healthy longevity.

ETHICAL APPROVAL

Ethical approval not required

AUTHORS CONTRIBUTION

Conceptualization: JEO and IOE; data curation: JEO, IOE and MAE; writing original draft preparation: JEO, IOE, PEB, WED, AOA and IP; review and editing: JEO, IOE, MO and OPI; Supervision: JEO and IOE. All authors have read and agreed to the publication of the manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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