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Aging Model Based on Drosophila melanogaster: Mechanisms and Perspectives

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Abstract

Aging is a multifaceted biological process characterized by a gradual decline in physiological functions, ultimately resulting in reduced reproductive capacity and eventual death of the organism. For over a century, Drosophila melanogaster, the common fruit fly, has served as a pivotal model for investigating the underlying mechanisms of aging, owing to its relatively short lifespan, ease of genetic manipulation, and high degree of conservation of molecular pathways with higher organisms. This article delves into the principal aspects of utilizing Drosophila in aging research, encompassing the influence of dietary restrictions, insulin/IGF-1, mTOR, and AMPK signaling pathways, as well as the roles of various tissues—such as the intestine and muscles—in modulating lifespan. Special emphasis is placed on the interplay between metabolic and epigenetic factors that determine the rate of aging and on the potential applications of these findings in the development of anti-aging therapeutic strategies.

Keywords: aging, drosophila melanogaster, dietary restrictions, signaling pathways, metabolism, epigenetics, lifespan

Introduction

For over a century, Drosophila melanogaster has been utilized as a model organism in aging research. One of the earliest recorded quantitative studies involving Drosophila under laboratory conditions was published by Roscoe Hyde in 1913, in which he accurately observed and described how hybrid vigor could account for the apparent increase in lifespan when two inbred strains were crossed (Hyde, 1913). A more systematic approach to Drosophila research, which laid the foundation for many methodologies still in use today, was initiated in 1921 by Raymond Pearl and Sylvia Parker. In their

seminal study (Pearl, R., & Parker, S. L., 1921), they reported the catastrophic failure of an air conditioning system that resulted in the death of their colony of mice intended for aging research. After consulting with Professor Morgan and Dr. Loeb, they opted to use Drosophila as a model for investigating lifespan. Over the following 14 years, Pearl and his collaborators published a series of 13 studies detailing fundamental dietary requirements for Drosophila, as well as the effects of repeated anesthesia (with ether), inbreeding depression, adult population density, and temperature fluctuations at different life stages on adult lifespan.

Simultaneously, research on the impact of temperature on lifespan was also emerging (Loeb, J., & Northrop, J. H., 1916), establishing that a 10°C reduction in temperature approximately doubled the flies' lifespan. These findings contributed to the concept that longevity might be determined by the organism's metabolic rate (Pearl, 1928). The rate of life hypothesis suggests that lifespan is dictated by the accumulation of harmful byproducts of aerobic metabolism, as well as mechanical damage that eventually becomes irreparable (Harman, 1956). Biological organisms counteract such damage through enzymatic repair systems, small molecule scavengers that remove or mend chemical injuries, and the replacement of damaged cells with new ones derived from stem cells. Whether aging is primarily driven by the accumulation of damage or by improper and uncontrolled cell proliferation remains debated (Blagosklonny, 2006), but the imperative to sustain biological systems in working condition—and thereby ensure longevity—is closely tied to the necessity of reproduction.

Physiological Indicators of Aging in Flies

Aging can be broadly characterized as a progressive functional decline over time that leads to decreased fertility and eventual mortality. Survival curves of Drosophila populations provide critical insights into aging progression, as well as the potential impact of non-aging-related mortality factors such as poor genetic backgrounds or environmental conditions (Piper, M. D., & Partridge, L., 2016). A typically healthy, well-maintained, outbred Drosophila population exhibits a median lifespan of approximately 70 days and a maximum lifespan of roughly 90 days at 25°C (Ziehm, M., & Thornton, J. M., 2013).

On a finer physiological scale, numerous markers of functional decline associated with aging can be observed. These include metabolic alterations (decreased basal metabolic rate, reduced protein and lipid synthesis), behavioral changes (diminished feeding, courtship, and increased sleep), reduced stress resistance, impaired reproductive capacity (decreased egg-laying success, sperm production, and competitive sperm success), altered neuronal function (learning and memory deficits), changes in locomotor activity (diminished negative geotaxis, impaired voluntary flight and walking), declining immune function, progressive intestinal dysplasia and barrier dysfunction, as well as compromised cardiac function (Iliadi et al., 2012). Studying these features is crucial for two reasons: first, to understand how longevity-altering interventions affect these health markers over time, and second, to determine whether any of these changes causally contribute to demographic aging in

flies, which could help identify targets for interventions aimed at slowing aging.

Why Use Flies in Aging Research?

Drosophila offers numerous advantages as a model organism for aging research. When combined with other short-lived invertebrates such as the nematode Caenorhabditis elegans and the baker's yeast Saccharomyces cerevisiae, Drosophila becomes an exceptionally powerful tool for investigating various aspects of aging (Kennedy et al., 2017). While yeast provides rapid insights into cellular aging, the complex interactions occurring within and between tissues in multicellular, differentiated organisms—such as those involved in insulin/IGF-1 signaling (IIS)—can be effectively modeled in worms and flies. Typically, nematodes live for about three weeks, whereas fruit flies have an approximate lifespan of three months. By leveraging the unique experimental strengths of these organisms in tandem, researchers can efficiently translate longevity-promoting discoveries to longer-lived vertebrates, such as killifish (lifespan ~6–8 months), mice (~3 years), and rats (~3 years).

Several distinctive characteristics make Drosophila an ideal model for aging studies: low maintenance costs, absence of regulatory restrictions for experimental use, ease of generating large populations, well-defined dietary requirements, readily quantifiable reproductive output, dissectible and genetically modifiable tissues, and a vast array of available genetic tools, including CRISPR reagents for genome editing, as well as constructs for tissue- and time-specific gene overexpression or knockout. Many Drosophila tissues have functional equivalents in mammals, including the heart and kidneys (which are absent in C. elegans), and a significant proportion (77%) of genes associated with age-related diseases in humans are expressed in equivalent fly tissues. Most importantly, their relatively short lifespan allows for repeated rounds of experimentation to refine conditions that maximize longevity.

However, some of these advantages also present limitations. Specifically, the small size of Drosophila melanogaster makes assessing age-related health parameters more challenging. Moreover, the exact cause of death in flies remains uncertain, though recent studies investigating age-related increases in intestinal dysplasia and permeability in females may offer insights (Rera et al., 2013). Perhaps the simplest and most widely used non-invasive assay for aging-related health assessments is the measurement of climbing ability (negative geotaxis), which provides a combined assessment of neuronal and muscular function. Notably, long-lived IIS mutants also retain better health for extended periods according to this metric.

Ensuring Healthy Aging Without Side Effects

A primary goal of biogerontology is to shift the focus from understanding and treating aging-related symptoms to elucidating the underlying molecular mechanisms, with the ultimate aim of using this knowledge to develop therapeutic interventions that prevent or delay the onset of multiple aging-related conditions, thereby reducing morbidity. A key aspect of this work is understanding the trade-offs associated with

anti-aging interventions to maximize health improvements while minimizing adverse effects. As experimental conditions—such as dietary composition—are refined with increasing precision, and as interventions targeting specific tissues and cell types at defined life stages become more sophisticated, accumulating evidence suggests that a broad spectrum of aging-related improvements is achievable (Grandison et al., 2009). In this endeavor, model organisms, including Drosophila, play a central role, as iterative rounds of experimentation under slightly modified conditions have led to crucial discoveries in the field of aging research.

Recently, it has been recognized that the nine hallmarks of aging are widely prevalent across biological systems. Experimental evidence has been accumulating, demonstrating that the emergence of these hallmarks plays a crucial role in driving the progressive functional decline that accompanies aging. These hallmarks encompass genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. A central assumption in the field of biogerontology is that aging results from the intricate interplay of these mechanisms and that various hallmarks are interconnected, with different forms of functional deterioration interacting to propel the aging process. The centriole-based theory of organismal aging emphasizes the accumulation of old centrioles, which has the potential to induce these and other hallmarks of aging.

Studies utilizing Drosophila have significantly contributed to the current understanding of the molecular mechanisms underlying aging, as well as to interventions that may mitigate its effects (Kapahi et al., 2017).

Dietary Interventions and Lifespan Modulation

One of the most pivotal discoveries in aging research is the finding that moderate dietary restriction (DR), commonly referred to as calorie restriction (CR) when not leading to malnutrition, can extend lifespan. The earliest documented case of this phenomenon is often attributed to Clive McCay's work on white rats (McCay et al., 1935). Since then, DR has been successfully employed to prolong lifespan in various model organisms, including yeast (Jiang et al., 2000), nematodes (Klass et al., 1977), fruit flies (Chapman et al., 1996), and primates (Mattison et al., 2012). However, in primates, the benefits of DR appear to be somewhat mitigated by an increase in age-related frailty (Hultström, 2015). Irrespective of its longevity effects, DR in monkeys is believed to extend healthspan—the period of life spent in good health (Mattison et al., 2017). Interestingly, studies in fruit flies indicate that DR rapidly reduces age-specific mortality and seemingly reverses the effects of prior dietary excess—a discovery that suggests DR may confer benefits at any stage of life. As a consequence of these findings, and due to the accessibility of dietary manipulations, DR in various forms has gained popularity among health-conscious individuals who harbor long-term aspirations of achieving additional years of healthy life (Rizza et al., 2014).

Nutritional Balance and Longevity

Recent studies employing model organisms, particularly Drosophila and mice, have begun to elucidate that reductions in specific nutrient intake—rather than a blanket reduction in caloric consumption—mediate the health benefits associated with DR, with dietary protein playing a key role (Miller et al., 2005). Furthermore, adjusting the relative proportions of macronutrients (proteins, lipids, and carbohydrates) in an ad libitum diet has been shown to yield lifespan extension comparable to that observed with broad dietary restriction (Solon-Biet et al., 2014). It remains uncertain whether lifespan extension resulting from altered dietary balance operates through mechanisms similar to or distinct from those of conventional DR/CR, as the precise molecular and physiological pathways underlying these effects have yet to be fully delineated. An additional complexity arises from the fact that, in mice at least, DR typically entails a feeding-fasting cycle, since the animals consume their restricted food allowance immediately upon provision and subsequently fast for the remainder of the 24-hour period (Speakman et al., 2016). Regardless of the mechanisms involved, from a human perspective—where strict adherence to DR is often perceived as impractical—modifying dietary balance appears to be a more feasible approach. Consequently, substantial research efforts have been directed toward the development of diets that alter nutrient composition to mimic fasting-induced benefits and enhance long-term health outcomes (Cheng et al., 2017).

In experiments where the macronutrient balance in the diets of flies and mice was manipulated, the optimal lifespan extension was observed when dietary protein content, as a proportion of total caloric intake, fell below the level required for optimal reproduction (Solon-Biet et al., 2015). This pattern of dietary response has also been documented in ants (Dussutour, A., & Simpson, S. J., 2012), crickets (Harrison et al., 2014), and Queensland fruit flies (Fanson et al., 2009). Given the consistency of this trend, it is of considerable interest to investigate the mechanistic basis by which protein exerts such a profound influence on longevity determination.

Several studies have manipulated individual amino acids in the diets of flies and mice, revealing that selective dilution of essential amino acids can extend lifespan. The most consistent finding pertains to the reduction of methionine, an essential amino acid, which has been shown to prolong lifespan in both flies and mice. However, this effect is accompanied by trade-offs such as reduced egg-laying in flies, decreased growth rate, and increased early mortality in mice. The precise mechanisms underlying these effects remain unclear, but significant attention has been given to methionine's critical roles in translation initiation, its degradation to cysteine via the transsulfuration pathway, and the subsequent roles of its catabolites in protein methylation and cellular detoxification. Each of these functions may act by modulating a key hallmark of aging.

Given the multitude of nutrients involved and their intricate physiological interactions, it is almost certain that additional subtle dietary factors influence lifespan. While this presents exciting opportunities for further

research, it also highlights a major challenge in Drosophila studies: the existence of numerous "standard" Drosophila diets (Piper, M. D., & Partridge, L., 2007), which vary across different laboratories. If even minor variations in nutrient composition—such as the dilution of a single amino acid—can alter lifespan, then it is likely that each study employing a distinct diet composed of natural ingredients will exhibit some degree of lifespan variation. One potential solution to this issue involves the use of holidic diets, which provide chemically defined compositions (Piper et al., 2014).

Nutrient-Sensing Pathways and Lifespan Regulation

The extensive body of research demonstrating that diet influences lifespan inevitably leads to the conclusion that nutrient-sensing pathways and their downstream signaling cascades mediate these effects. Below is an overview of the major nutrient signaling pathways that have been shown to regulate lifespan in Drosophila.

Insulin/IGF-1-Like Signaling (IIS) Pathway

Insulin is typically associated with glucose homeostasis, a function that is at least partially conserved in Drosophila (Graham, P., & Pick, L., 2017). Additionally, it plays a crucial role in growth, reproduction, adult health, and aging (Nässel, D. R., & Broeck, J. V., 2016). The Drosophila genome encodes eight insulin-like peptides (ILPs 1–8), a single insulin receptor, and intracellular components of the canonical PI3K signaling cascade (Puig et al., 2003). Upon activation, this pathway transmits signals leading to the phosphorylation and inactivation of the FOXO transcription factor via nuclear exclusion. Collectively, this system is believed to integrate functions analogous to those of mammalian insulin, IGF-1, and relaxins. Since the initial discovery that IIS mutations extend lifespan in flies, numerous other components of this pathway have been reported to modulate longevity (Proshkina et al., 2015) in a manner that requires FOXO activity (Slack et al., 2011).

As the overarching goal of biogerontology is to identify interventions that promote healthy aging without excessive costs, the extensive family of Drosophila ILP genes presents an attractive target for intervention. While some ILPs exhibit functional redundancy (Grönke et al., 2010), evidence suggests that each peptide elicits distinct physiological effects in response to specific environmental conditions, with unique expression patterns that vary across developmental stages (Brogiolo et al., 2001), tissues (Chintapalli et al., 2007), and nutritional stimuli (Post, S., & Tatar, M., 2016).

The specific overexpression of FOXO within the intestinal and adipose tissues has been demonstrated to be sufficient for extending the lifespan of flies (Hwangbo et al., 2004). Through an analysis of the direct transcriptional outputs of activated FOXO in these tissues, researchers identified five transcription factors that may mediate the resultant lifespan extension (Alic et al., 2014). Among them, the transcriptional repressor belonging to the ETS family, known as AOP, shares a comparable set of

transcriptional targets with FOXO. Activation of AOP in the intestine and adipose tissues, whether directly via overexpression or indirectly through inhibition of RAS/ERK signaling (Slack et al., 2015), has revealed that AOP can also contribute to lifespan extension. Given its pivotal role in cancer biology, RAS/ERK signaling has been a primary target for drug development. One FDA-approved drug designed to attenuate its activity, trametinib, has been shown to extend the lifespan of flies when administered through dietary intake. This discovery is particularly significant, as its mechanism of action could hold relevance for mitigating aging-related decline in higher organisms. It also places trametinib among a select group of FDA-approved pharmaceutical agents that have exhibited demonstrable anti-aging properties (Roth, G. S., & Ingram, D. K., 2016).

Considering that AOP and FOXO function synergistically to extend lifespan when overexpressed in the intestine and adipose tissues, Alic et al. characterized the overlap in their transcriptional outputs to identify alterations that might coordinate their roles in promoting longevity. One such gene, Obp99b, has been identified as a potential humoral factor crucial for inter-tissue signaling. Notably, this gene was found to be strongly upregulated in a model of delayed aging in Drosophila induced by reproductive diapause (Kučerová et al., 2016).

mTOR Signaling

The mechanistic target of rapamycin (mTOR) is an amino acid-sensitive signaling kinase that plays a central role in growth regulation (Saxton, R. A., & Sabatini, D. M., 2017). The genetic suppression of mTOR function was first shown to extend lifespan in nematodes (Vellai et al., 2003), an effect that has been evolutionarily conserved in yeast (Kaeberlein et al., 2005), flies (Kapahi et al., 2004), and mice (Lamming et al., 2012).

mTOR is typically regarded as a principal molecule responsible for sensing amino acids and transmitting growth signals within cells. Therefore, it is not surprising that its activity is intricately linked to longevity in response to dietary macronutrient composition. In flies, both activation of the mTOR suppressor TSC2 and dietary administration of the mTOR inhibitor rapamycin have been observed to counteract the lifespan-shortening effects induced by a protein-rich diet composed primarily of yeast (the sole protein source for flies) or an increased amino acid content in food (Emran et al., 2014). Similar relationships between dietary protein intake, mTOR activity, and lifespan have also been documented in mice.

Rapamycin, a well-known mTOR inhibitor, has been extensively studied for its ability to extend lifespan in yeast (Medvedik et al., 2007), nematodes (Robida-Stubbs et al., 2012), flies, and mice (Miller et al., 2014). A meta-analysis of 29 independent lifespan extension experiments in mice using rapamycin confirmed its robust longevity-promoting effects, though the magnitude of its impact varied depending on sex (with a stronger effect in females than in males) and genetic background (Swindell, 2016).

mTOR inhibition results in a general reduction in protein translation and an upregulation of autophagy, two extensively studied phenomena believed to contribute

to lifespan extension by enhancing proteostasis (Taylor, R. C., & Dillin, A., 2011). This increasingly recognized concept encapsulates the beneficial effects of various longevity interventions across multiple model organisms and has been classified as one of the nine hallmarks of aging. The most frequently examined molecular targets of mTOR phosphorylation are the translational activator kinase S6 and the translational repressor 4EBP. Suppression of S6K has been reported to be sufficient for lifespan extension in both flies and mice (Selman et al., 2009), and its inhibition is required for rapamycin to exert its lifespan-extending effects in flies. 4EBP has also been implicated in the longevity response to rapamycin and dietary restriction (Zid, 2009), though its role appears to be context-dependent (Partridge et al., 2011). Functional autophagy is essential for rapamycin-mediated lifespan extension, and overexpression of autophagy components such as ATG1 (Ulgherait et al., 2014) or ATG8a (Simonsen et al., 2008) has been shown to be sufficient for lifespan extension in flies. Consequently, dietary and pharmacological interventions aimed at enhancing autophagy have emerged as promising strategies for promoting healthy aging.

The polyamine spermidine has been found to increase lifespan in yeast, nematodes, and flies in an autophagy-dependent manner (Eisenberg et al., 2009). Additionally, two compounds, AUTEN-67 and AUTEN-99, identified through small-molecule screening for autophagy enhancers, have also been shown to extend lifespan in flies (Kovács et al., 2017). However, the control flies in these studies exhibited extremely short lifespans and signs of age-independent mortality, indicating the need for further validation. In the case of spermidine, evidence supporting its anti-aging effects has been strengthened by findings demonstrating its evolutionarily conserved benefits, which now include improved healthspan and increased lifespan in mice (Eisenberg et al., 2016). In humans, high spermidine intake has been associated with a reduced risk of cardiovascular diseases. Collectively, these findings reinforce the conclusion that reduced mTOR activity extends lifespan by enhancing proteostasis, particularly through the upregulation of autophagy.

GCN2/ATF4 Pathway

Another critical amino acid sensor involved in adaptation to nutritionally imbalanced diets is the evolutionarily conserved protein kinase GCN2. Its function was first characterized in yeast, where it was shown to be activated by uncharged tRNAs and to phosphorylate and inactivate the translation initiation factor eIF2 (Dever et al., 1992), thereby reducing overall translation. Concurrently, the presence of small upstream open reading frames (uORFs) in the 5' UTRs of certain genes facilitates their selective upregulation (Abastado et al., 1991). The transcription factor GCN4 is the product of one such regulated gene and functions to control the expression of numerous genes involved in amino acid and purine biosynthesis (Hinnebusch, 1988). ATF4 is the ortholog of GCN4 in flies and mammals, and its expression is similarly enhanced through translational control following eIF2alpha phosphorylation by stress-sensitive kinases, including GCN2 (Vattem, K., & Wek, R., 2004).

Recent findings have demonstrated that in flies, GCN2 is necessary for lifespan

extension in response to yeast restriction, where it phosphorylates eIF2alpha and leads to upregulation of 4EBP (Kang et al., 2017). These conditions are associated with global translational suppression, except for a subset of proteins that are selectively upregulated. Future investigations should explore how these upregulated proteins contribute to lifespan extension. A compelling candidate is Sestrin2, which is induced by ATF4 in mammals in response to amino acid stress and acts by suppressing mTOR function (Ye et al., 2015). In flies, Sestrin2 has been implicated in age-associated physiological decline through its role in mTOR feedback inhibition (Lee et al., 2010).

AMPK

AMP-activated protein kinase (AMPK) serves as a fundamental cellular energy sensor, continuously monitoring the intracellular ratio of AMP + ADP to ATP. This kinase plays a pivotal role in orchestrating the balance between energy-consuming and energy-producing processes to maintain cellular homeostasis. In Drosophila, loss-of-function mutations in AMPK lead to a pronounced metabolic imbalance, manifesting as heightened sensitivity to starvation, hyperactivity, excessive food intake (hyperphagia), and abnormal lipid accumulation. These phenotypes collectively suggest that the flies experience a state of mild starvation, likely due to inefficient mobilization and utilization of stored energy reserves (Johnson et al., 2010).

Elevated AMPK expression has been demonstrated to be sufficient for lifespan extension in both nematodes and flies. In Drosophila, targeted upregulation of the AMPK alpha subunit within various tissues—including adipose tissue, muscles, neurons, and the gut—results in a significant increase in longevity. Particularly intriguing is the observation that neuron-specific overexpression of AMPK enhances neuronal autophagy, a process essential for lifespan extension, while concurrently promoting autophagic activity and mitigating age-related barrier dysfunction in the intestinal epithelium. This effect appears to be mediated by a reduction in ilp2 expression, implicating systemic insulin downregulation as a key orchestrator of intertissue autophagic activation. In Caenorhabditis elegans, neuronal AMPK similarly functions as a central regulator of systemic longevity signaling, facilitating longevity-promoting effects in peripheral tissues via AMPK activation (Burkewitz et al., 2015). If autophagy activation serves as the primary mechanism through which AMPK extends lifespan, this may occur via its inhibitory effects on mTOR signaling (Howell et al., 2017) or through its direct phosphorylation and activation of autophagy-related proteins (ATG), as demonstrated in mammalian systems (Kim et al., 2011). Notably, recent findings in nematodes suggest that both AMPK and dietary restriction (DR) play essential roles in preventing age-related declines in RNA splicing fidelity, an effect that has been directly linked to increased lifespan (Heintz et al., 2016).

Metformin, a widely prescribed anti-diabetic drug, exhibits a broad spectrum of molecular effects, including attenuation of insulin/IGF-1/mTOR/AMPK signaling, inhibition of the mitochondrial electron transport chain (ETC), and reduction of reactive oxygen species (ROS) production and associated DNA damage (Barzilai et al., 2016). Given its extensive array of

longevity-associated mechanisms, it is unsurprising that metformin administration has been repeatedly reported to extend healthspan and delay multiple aging-related decline markers in both nematodes (Haes et al., 2014) and rodents (Anisimov et al., 2011). Indeed, there is growing enthusiasm for advancing metformin as a potential anti-aging therapeutic in humans, with large-scale clinical trials currently being planned and funded to assess its effects on cardiovascular disease, cancer, dementia, and overall mortality in a cohort of 3,000 individuals aged 65–79 years (Martin-Montalvo et al., 2013).

Surprisingly, a single report on metformin treatment in Drosophila has failed to demonstrate any lifespan benefits across a range of doses, despite evidence that the drug is effectively absorbed and activates AMPK signaling in these flies (Slack et al., 2012). Potential explanations for this discrepancy include the absence of a metformin-sensitive microbiota in Drosophila—an essential factor for metformin-induced lifespan extension in nematodes—or the possibility that the experimental conditions involved a genetically heterogeneous fly population maintained on an already lifespan-optimized diet, leaving little room for additional longevity benefits conferred by the drug.

Lifespan-Limiting Tissues

Aging is characterized by differential rates of functional decline across various tissues. In invertebrate model organisms, targeting specific organs with protective genetic modifications may extend lifespan via one of two primary mechanisms. First, lifespan extension may occur if the intervention solely improves the function of a specific organ that otherwise represents a primary constraint on longevity; in this scenario, lifespan is extended only until another vital organ becomes the limiting factor. Alternatively, lifespan may be prolonged if the targeted organ exerts a systemic regulatory influence on overall physiological homeostasis, thereby optimizing the function of multiple organ systems. While these two frameworks provide useful conceptual models, the reality is likely far more complex, involving intricate intertissue interactions that dynamically influence the aging process. From a translational perspective, whole-organism functional preservation is more desirable than tissue-specific interventions, as the former is expected to mitigate the intrinsic heterogeneity that characterizes aging across individuals.

The Gut

The repeated observation that genetic modifications targeting the gut can modulate lifespan has propelled this organ into the spotlight as a key focus for aging research. Specifically, suppression of insulin/IGF-1 signaling (IIS) in intestinal and adipose tissues, inhibition of RAS/ERK signaling in the gut and fat body, suppression of mTOR signaling in muscle, gut, and neurons, or activation of AMPK—all of which enhance autophagic activity—have been shown to be sufficient for lifespan extension in Drosophila.

The gut is a crucial homeostatic organ that must balance seemingly contradictory roles: facilitating digestion and nutrient absorption while simultaneously hosting a symbiotic microbiota that aids in these processes, all while functioning as a frontline barrier

against ingested toxins and pathogens (Lemaitre & Miguel-Aliaga, 2013). Additionally, the gut is unique among Drosophila tissues in that it harbors an active reservoir of stem cells, making it a central site for understanding the evolutionarily conserved role of stem cell proliferation in aging. Furthermore, the gut acts as a significant endocrine organ, producing various signaling peptides involved in metabolic regulation. Given these diverse roles, maintaining gut function is likely critical for preserving overall organismal health, while gut dysfunction can have cascading negative effects on systemic physiology. It is plausible that sustaining gut homeostasis over time can directly extend lifespan by enhancing digestive and barrier functions or indirectly by regulating systemic metabolic homeostasis.

Shortly after intestinal stem cells (ISCs) were first identified in Drosophila (Micchelli & Perrimon, 2005), it was discovered that their proliferation rates increase dramatically with age, leading to aberrant differentiation (Biteau, Hochmuth, & Jasper, 2008). This phenomenon contributes to a progressive decline in intestinal barrier integrity (Rera, Clark, & Walker, 2012), raising the possibility that gut dysfunction limits lifespan by increasing susceptibility to systemic infections. Indeed, strong correlations have been established between ISC proliferation rates and organismal lifespan (Biteau et al., 2010), as well as between the onset of intestinal microbial dysbiosis and lifespan (Clark et al., 2015). Interventions that mitigate age-related gut dysplasia or microbial imbalance—such as local modulation of inflammatory signaling (Li, Qi, & Jasper, 2016) or maintenance of innate immune responses at youthful levels (Chen et al., 2014)—have been shown to promote intestinal microbial homeostasis and extend lifespan in flies.

Given its fundamental physiological functions, it is unsurprising that the gut also plays a central role in mediating dietary effects on lifespan. Interestingly, the dynamic regulation of gut size differs between male and female flies, likely due to sex-specific reproductive nutrient demands. Unlike males, female flies exhibit plastic intestinal growth in response to dietary quality and mating status, allowing them to optimize nutrient absorption while managing the energetic costs of maintaining an enlarged gut. However, this plasticity comes at a cost, as females are more susceptible to excessive ISC proliferation at advanced ages (Hudry et al., 2016). Notably, males and females also exhibit differential responses to dietary restriction (DR), with female lifespan increasing more dramatically under DR conditions (Magwere et al., 2004). This may be attributed to stronger protective effects of nutrient limitation against excessive ISC proliferation in females. Supporting this notion, feminization of the male gut enhances their longevity response to DR.

Although the extent to which gut dysfunction limits overall lifespan remains unclear, understanding the molecular signals emanating from the gut—such as Obp99b, which responds to altered FOXO/AOP function—will be essential for future investigations. Regardless, the gut remains a critical organ for elucidating stem cell aging mechanisms and the intricate interplay between microbiota, immunity, and organismal longevity.

Muscles

The progressive decline in muscle mass and function represents a fundamental aspect of physical deterioration that accompanies aging in humans. In Drosophila, muscle tissue constitutes a substantial proportion of body mass and exhibits remarkable structural similarities to mammalian muscle. However, a key distinction lies in the absence of regenerative capacity due to the lack of resident stem cells, thereby rendering Drosophila muscle a model system that captures only certain facets of muscle aging. This unique attribute, however, provides an opportunity to explore how interventions aimed at mitigating age-associated dysfunction in non-replaceable muscle cells may facilitate systemic changes that promote healthy aging (Demontis et al., 2013).

One of the earliest indications that Drosophila muscle plays a crucial role in longevity regulation emerged with the discovery that elevated expression of dFOXO specifically in adult muscle could extend the lifespan of flies (Demontis, F., & Perrimon, N., 2010). This effect was at least partially attributed to enhanced autophagy, which contributes to improved proteostasis during aging. Notably, this muscle-specific intervention exerted protective effects throughout the entire organism (e.g., heightened autophagy) via an unidentified signal, which indirectly reduced food intake and consequently mimicked the benefits associated with dietary restriction (DR). Additionally, another unknown muscle-derived signal has been implicated in lifespan extension in response to mild muscle-specific mitochondrial dysfunction (Owusu-Ansah et al., 2013). While the precise identity of these signals remains elusive, they are believed to exert their effects indirectly by attenuating systemic insulin signaling. Furthermore, muscle tissue is thought to play a pivotal role in coordinating organismal health through the secretion of the myokine myoglianin (Demontis et al., 2014). Experimental evidence indicates that muscle-specific overexpression of myoglianin, or its transcriptional regulator Mnt, correlates with reduced global rRNA levels, enhanced climbing ability with age, and prolonged lifespan. These findings highlight both autocrine and endocrine functions of muscle in preserving physiological function. Future research will be essential in elucidating the precise mechanisms by which these anti-aging signals exert their effects across the organism.

Metabolic Constraints

The aforementioned findings underscore the hierarchical organization of lifespan-regulating mechanisms, wherein environmental factors and nutrient perception operate at a higher level, influencing an extensive network of metabolic and intertissue interactions at a lower level. Given the complexity of these processes, it is not surprising that the majority of discoveries have emerged from investigations at the higher tiers of this hierarchy. However, understanding how the intricate coordination of disparate physiological systems culminates in the emergence of a longevity-promoting phenotype remains a significant challenge.

Hallmarks of aging encompass a diverse array of alterations, ranging from genomic and epigenetic modifications to changes in cellular function and systemic homeostasis.

The extent to which molecular events associated with each hallmark contribute to the overarching physiological decline that ultimately leads to mortality remains unclear, as does the manner in which one hallmark influences the manifestation of another. Nevertheless, unraveling these interconnections is crucial for the future development of therapeutic interventions that effectively decelerate aging while minimizing adverse effects.

To date, the most significant advancements in aging research have been driven by reductionist approaches. However, the interdependence of metabolic and signaling pathways necessitates a broader contextual framework for understanding how aging hallmarks are expressed. This concept is exemplified by multiple studies demonstrating that substrate availability serves as a key determinant in shaping epigenomic maintenance mechanisms that contribute to longevity (Brunet, A., & Rando, T., 2017).

Studies in Drosophila have revealed that longevity is associated with reduced levels of free methionine (Laye et al., 2015) to the extent that it stoichiometrically limits translation and egg deposition (Piper et al., 2017). Concurrently, and potentially contributing to intracellular methionine restriction, methionine catabolism via transsulfuration and related pathways is upregulated, leading to an increased supply of substrates for methylation reactions (Parkhitko et al., 2016), as well as the production of glutathione and H2S (Hine et al., 2015), both of which exhibit protective effects against aging. Given that dietary methionine is likely to be present in limited quantities when flies consume natural food sources, it follows that the establishment of methyl-derived epigenetic marks is highly sensitive to fluctuations in nutritional and metabolic status.

Metabolic constraints imposed by central carbon metabolism, particularly in the form of cytosolic acetyl-CoA availability, have been shown to confer protection against age-associated increases in histone acetylation (Peleg et al., 2016). Acetyl-CoA cannot traverse the mitochondrial membrane directly and must instead be exported as part of the citrate shuttle, which also supplies the cytosol with reducing power in the form of NADPH. Restricting acetyl-CoA levels may exert additional effects on aging-associated pathways beyond epigenetic modifications, such as reducing inhibitory acetylation of the longevity-promoting transcription factor FOXO (Van der Horst, A., & Burgering, B., 2007) and alleviating autophagy repression mediated by acetylation (Mariño et al., 2014). Indeed, a decrease in neuronal cytoplasmic acetyl-CoA in Drosophila has been linked to enhanced autophagy (Eisenberg et al., 2014) and is sufficient to extend lifespan.

Collectively, these findings illustrate how metabolic constraints, which are highly sensitive to the organism's nutritional status, dictate the availability of activated one-carbon and two-carbon units necessary for chromatin maintenance and genome stability, thereby exerting protective effects against aging.

Metabolic pathways are interconnected through the shared utilization of numerous components, with key regulatory control dictated primarily by the relative abundance of ATP/ADP, NAD+/NADH, and NADP+/NADPH pairs (Nielsen, J., 2017).

Consequently, the proper maintenance of these cofactor pairs is essential for sustaining metabolic homeostasis and, by extension, plays a pivotal role in longevity regulation (Bonkowski, M. S., & Sinclair, D. A., 2016). Understanding and manipulating key metabolic control points derived from genome-scale metabolic modeling could, therefore, constitute a crucial future direction for identifying aging interventions, analogous to their widespread adoption in the search for cancer therapeutic targets (Nielsen, J., 2016).

Discussion

The use of Drosophila melanogaster as a model organism has provided unparalleled insights into the molecular and physiological mechanisms underlying aging. This study synthesizes decades of research to elucidate how dietary interventions, nutrient-sensing pathways, and tissue-specific dynamics collectively influence lifespan and healthspan in fruit flies. The findings underscore the fruit fly's utility in aging research while highlighting critical gaps and opportunities for translational applications. Below, we contextualize these discoveries within the broader field of biogerontology, evaluate their implications, and propose future directions.

Key Mechanisms of Lifespan Extension

One of the most robust findings in aging research is the lifespan-extending effect of dietary restriction (DR), a phenomenon conserved across taxa, including yeast, nematodes, flies, and mammals (Piper & Partridge, 2016; Mattison et al., 2012). In Drosophila, DR reduces age-specific mortality and reverses the detrimental effects of nutrient excess, suggesting its benefits are not merely preventative but potentially restorative (Chapman & Partridge, 1996). However, recent studies challenge the notion that caloric restriction alone drives longevity, emphasizing instead the role of macronutrient balance. For instance, reducing dietary protein, particularly methionine, extends lifespan in flies and mice but at the cost of reproductive output (Miller et al., 2005; Solon-Biet et al., 2014). This trade-off underscores the evolutionary tension between survival and reproduction, a cornerstone of life-history theory.

The insulin/IGF-1 signaling (IIS) and mechanistic target of rapamycin (mTOR) pathways emerge as central regulators of these dietary effects. Inhibition of IIS, either through genetic mutations or tissue-specific FOXO activation, enhances stress resistance and longevity by promoting autophagy and metabolic homeostasis (Hwangbo et al., 2004; Alic et al., 2014). Similarly, mTOR suppression via rapamycin or genetic manipulation extends lifespan by reducing protein synthesis and enhancing proteostasis (Kapahi et al., 2004; Lamming et al., 2012). These findings align with the "hallmarks of aging" framework, which posits that aging arises from interconnected processes such as loss of proteostasis and dysregulated nutrient sensing (López-Otín et al., 2013). Notably, the interplay between IIS and mTOR pathways suggests a hierarchical regulatory network where dietary inputs modulate downstream effectors like 4EBP and Sestrin2 to fine-tune longevity (Kang et al., 2017; Lee et al., 2010).

Tissue-Specific Contributions to Aging

Aging is not a uniform process but manifests through the decline of specific tissues, each contributing uniquely to organismal senescence. The gut, for instance, has emerged as a critical lifespan-limiting organ due to its roles in nutrient absorption, barrier integrity, and stem cell dynamics. Age-related intestinal dysplasia, driven by hyperproliferation of intestinal stem cells (ISCs), compromises barrier function and increases susceptibility to systemic inflammation (Biteau et al., 2008; Rera et al., 2012). Interventions that mitigate ISC overactivity, such as modulating inflammatory signaling or maintaining youthful immune responses, enhance gut homeostasis and extend lifespan (Li et al., 2016; Chen et al., 2014). These findings resonate with studies in mammals, where gut dysbiosis and leaky gut syndrome are linked to age-related pathologies (Clark et al., 2015).

Muscle tissue also plays a pivotal role in systemic aging. In Drosophila, muscle-specific overexpression of dFOXO improves proteostasis and indirectly reduces systemic insulin signaling, mimicking the benefits of DR (Demontis & Perrimon, 2010). Furthermore, muscle-derived myokine signals, such as myoglianin, regulate global rRNA levels and locomotor function, highlighting the endocrine influence of muscle on organismal health (Demontis et al., 2014). These observations parallel findings in humans, where sarcopenia (age-related muscle loss) correlates with metabolic dysfunction and reduced longevity (Cruz-Jentoft et al., 2019). However, a key distinction lies in the regenerative capacity of mammalian muscle, which is absent in flies, suggesting that non-cell-autonomous signals may be critical for mitigating age-related decline across species.

Sexual Dimorphism and Methodological Considerations

Sex differences in aging trajectories add another layer of complexity. Female Drosophila exhibit greater lifespan extension under DR than males, likely due to sex-specific nutrient demands and gut plasticity (Magwere et al., 2004; Hudry et al., 2016). Females dynamically adjust intestinal growth in response to mating and diet, but this adaptability predisposes them to age-related ISC dysfunction. Conversely, masculinizing the female gut attenuates DR benefits, implicating hormonal and genetic factors in lifespan regulation. These findings emphasize the need for sex-stratified analyses in aging research, as overlooking sexual dimorphism may obscure mechanistic insights or therapeutic targets.

Methodologically, the variability of "standard" fly diets across laboratories poses a significant challenge. Even minor differences in amino acid composition can confound lifespan outcomes, as demonstrated by the profound effects of methionine restriction (Piper et al., 2014). The adoption of holidic diets—chemically defined formulations—offers a solution by enabling precise control over nutrient intake (Piper et al., 2017). Such standardization is critical for reproducibility and for disentangling the effects of specific nutrients from caloric intake.

Contradictions and Unresolved Questions

Despite progress, several paradoxes remain. For example, metformin extends lifespan in nematodes and mice but fails to do so in Drosophila (Slack et al., 2012; Martin-Montalvo et al., 2013). This discrepancy may stem from differences in microbiota, as metformin's benefits in worms require bacterial interactions absent in axenic flies. Alternatively, the genetically heterogeneous or already optimized diets used in fly studies may leave little room for further improvement. These findings caution against overgeneralizing results across models and underscore the importance of context-dependent mechanisms.

Another unresolved question is the primacy of damage accumulation versus programmed aging. While the "rate of living" theory posits that metabolic byproducts drive aging (Harman, 1956), recent work implicates epigenetic and transcriptional drift as equally critical (Brunet & Rando, 2017). In Drosophila, methionine restriction alters histone acetylation and methylation, linking metabolic inputs to chromatin states (Peleg et al., 2016; Parkhitko et al., 2016). Whether these epigenetic changes are causes or consequences of aging remains debated, necessitating longitudinal studies that track molecular and physiological trajectories in tandem.

Translational Implications and Future Directions

The translational potential of Drosophila research is exemplified by drugs like rapamycin and trametinib, which extend lifespan in flies and mice by targeting conserved pathways (Swindell, 2016; Slack et al., 2015). However, translating these findings to humans requires addressing species-specific differences. For instance, while flies lack adaptive immunity, their innate immune responses share similarities with mammals, offering clues for combating age-related immunosenescence (Iliadi et al., 2012). Similarly, the gut's role as a microbial interface in flies mirrors its function in humans, suggesting that probiotics or anti-inflammatory therapies could promote healthy aging across taxa (Rera et al., 2013).

Future research should prioritize three areas:

1. Intertissue Communication: Identifying the humoral factors (e.g., Obp99b) that mediate cross-talk between gut, muscle, and brain could unveil systemic regulators of aging (Kučerová et al., 2016).
2. Epigenetic- Metabolic Crosstalk: Investigating how nutrient availability shapes chromatin states—and vice versa—will clarify whether epigenetic interventions can decelerate aging (Peleg et al., 2016).
3. Personalized Interventions: Leveraging Drosophila's genetic tractability to model human polymorphisms could enable tailored therapies based on genetic or metabolic profiles (Dobson et al., 2016).

In summary, Drosophila melanogaster remains an indispensable model for dissecting the complexities of aging. Its short lifespan, genetic malleability, and conservation of key pathways provide a

unique platform for rapid discovery. While challenges such as dietary variability and species-specific limitations persist, the integration of systems biology and standardized methodologies promises to bridge the gap between model organisms and human applications. By unraveling the interplay between metabolism, epigenetics, and tissue-specific decline, this work paves the way for interventions that extend not just lifespan, but healthspan—a paramount goal in an aging global population.

Concluding Remarks

Research on the fruit fly Drosophila has played an indispensable role in advancing our current understanding of the molecular underpinnings of aging. In particular, the fly's well-defined dietary requirements, genetically tractable tissue systems, and short lifespan make it an ideal model for developing precise interventions aimed at promoting healthy longevity. While reductionist approaches have been remarkably successful in driving scientific progress thus far, efforts to construct a comprehensive network-based framework that integrates metabolism, signaling pathways, and intertissue communication in longevity regulation are only beginning. To fulfill its promise of delivering tangible benefits for human aging, biogerontology must decipher how diverse metabolic processes are orchestrated to optimize physiological health. This endeavor will benefit from the development of large-scale metabolic models capable of pinpointing key regulatory nodes for targeted interventions. Given its practicality and historical utility, Drosophila remains particularly well-suited for these investigations.

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