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[REVIEW]

Nutritional Adaptation and Microbes: Insights From *Drosophila*Yukako Hattori^{1,2,3*}¹Graduate School of Biostudies, Kyoto University, Kyoto 606-8501, Japan²Center for Living Systems Information Science, Kyoto University, Kyoto 606-8501, Japan³JST FOREST, Tokyo 102-8666, Japan

Life-history traits such as growth, reproduction, and lifespan in animals are shaped by both genetic and environmental factors, with nutrition being one of the most important environmental factors. However, it remains unclear how and to what extent changes in the nutritional environment affect animals and what molecular mechanisms they employ to adapt to these varying conditions. In recent years, the fruit fly *Drosophila melanogaster* and related species have been developed as model systems for studying the effects of nutrition and microbes on animals at the molecular level. This review summarizes recent findings on nutritional adaptation in *Drosophila* species, focusing on nutrition-dependent neuronal developmental mechanisms, carbohydrate-responsive systems that generate differences in adaptabilities among species, and animal-associated microbes that support host growth.

Key words: nutritional adaptation, *Drosophila* species, carbohydrate-responsive systems, yeast and bacteria, molecular mechanisms

INTRODUCTION

In the context of evolution, one key survival strategy among animals is the ability to adapt to their surrounding environment. These adaptations encompass a wide range of environmental factors, with nutritional resources being particularly critical. Nutrition influences numerous life history traits, impacting individual growth, reproduction, and lifespan (Simpson et al., 2015; Leulier et al., 2017; Zhang et al., 2017; Piper and Partridge, 2018). Poor nutritional environments, such as starvation and unbalanced diets, are widely recognized as detrimental to animal health (Godfrey and Barker, 2000; Katona and Katona-Apte, 2008). Even in the absence of extreme conditions, daily fluctuations in nutritional intake, which can be driven by seasonal changes or food availability, require animals to dynamically adapt (Behrman et al., 2015).

Model organisms play a crucial role in unraveling the molecular mechanisms of biological processes, and *Drosophila melanogaster* has been a key model for over a century. Recently, *D. melanogaster* and related species, such as *Drosophila sechellia*, have become increasingly important as model systems for studying adaptive mechanisms to nutritional environments and the role of animal-associated microbes (Markow, 2015; Droujinine and Perrimon, 2016; Miguel-Aliaga et al., 2018; Grenier and Leulier, 2020; Lee et al., 2020; Auer et al., 2021). Research using these flies has provided profound insights into how

nutritional environments affect physiological processes and how animals adapt at both the organismal and molecular levels. This review aims to deepen our understanding of key aspects of nutritional adaptation, focusing on how nutrition impacts neuronal development, carbohydrate-responsive systems that drive species-specific adaptability, and the role of animal-associated microbes in supporting host growth.

***Drosophila melanogaster*: a model for nutritional adaptation**

Drosophila melanogaster is a well-studied model organism in genetics and developmental biology. Recently, it has emerged as a system for analyzing nutritional-adaptive mechanisms, with research directed at quantifying the effects of diet on life history traits such as growth, longevity, and fertility (Lee et al., 2008; Kosakamoto et al., 2023, 2024). *Drosophila melanogaster* possesses functionally similar organs to those of mammals, such as the nervous system, muscle, gut, gonad, and fat body, which is analogous to the liver or adipose tissue (Andersen et al., 2013; Padmanabha and Baker, 2014; Diop and Bodmer, 2015; Droujinine and Perrimon, 2016). In both *D. melanogaster* and mammals, the gut digests food and absorbs nutrients, with waste being excreted afterward (Apidianakis and Rahme, 2011). Key signaling molecules that mediate inter-organ responses to various nutrients are conserved between humans and *D. melanogaster*. *Drosophila* insulin-like peptides (Dilps), homologs of mammalian insulin and insulin-like growth factor (IGF), are secreted from median neurosecretory cells (insulin-producing cells [IPCs]) of the brain into the hemolymph in response to nutritional conditions and act on vari-

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ous cells throughout the body to regulate growth, nutrient storage, and metabolism (Semaniuk et al., 2021). These signaling molecules, secreted from tissues such as the central nervous system, fat body, gut, and muscle, enable the organism to respond to environmental changes (Okamoto et al., 2013; Droujinine and Perrimon, 2016; Imura et al., 2020; Yoshinari et al., 2021; Hoshino et al., 2023). Other studies have focused on the relationship between organogenesis and metabolism; for example, it was reported that proper hemolymph glucose control through trehalose metabolism plays a crucial role in maintaining developmental homeostasis, ensuring that dietary stresses do not lead to significant variations in traits such as wing size (Matsushita and Nishimura, 2020).

Molecular mechanisms of nutrient-dependent neuronal development

The nutritional environment during the growth period significantly impacts developmental processes. In neural development, neurons formed by the division and differentiation of neural stem cells develop dendrites for information input and axons for output, constructing complex and highly regulated neural circuits. The nutrient-dependent regulation of neural stem cell division has been well studied in *D. melanogaster*, mammals, and the African clawed frog (*Xenopus laevis*) (Chell and Brand, 2010; Lanet and Maurange, 2014; Spéder and Brand, 2014; Homem et al., 2015; McKeown et al., 2016; McKeown and Cline, 2019). Nutritional conditions have also been reported to influence dendrite and axon development in differentiating neurons (Shimono et al., 2014; Liu et al., 2017; Rincel et al., 2018). For example, in *D. melanogaster* larvae, serotonin-producing neurons elongate axons that project to the prothoracic gland, and these become longer under high nutritional conditions than under low nutritional conditions, thereby enhancing the biosynthesis of steroid hormones that promote larval development (Shimada-Niwa and Niwa, 2014). However, the molecular mechanisms by which nutritional changes are transmitted to neurons to regulate neurite growth remain largely unknown.

To elucidate such mechanisms, the Class IV dendritic arborization (C4da) neurons of *D. melanogaster* peripheral sensory neurons serve as a useful model. These neurons can be manipulated with well-developed genetic techniques, and

their dendrites develop in a two-dimensional, stereotyped spatial pattern between the epidermis and muscle, making their morphology readily observable (Fig. 1A). C4da neuronal dendrites cover the entire larval body and respond to nociceptive stimuli such as high temperatures, localized pressure, and short-wavelength light, causing larval avoidance behavior (Tracey et al., 2003; Hwang et al., 2007; Xiang et al., 2010; Zhong et al., 2010; Guntur et al., 2015; Terada et al., 2016; Chin and Tracey, 2017). Additionally, C4da neurons sense amino acid levels via amino acid transporters and transmit the information to downstream neurons in the central nervous system, helping larvae overcome nutritional stress and develop into pupae (Jayakumar et al., 2018, 2016).

Cell-autonomous and non-autonomous genetic mechanisms of dendritic morphogenesis in C4da neurons have been studied (Jan and Jan, 2010; Dong et al., 2015; Valnegri et al., 2015). Cell-autonomous mechanisms include transcriptional regulators that orchestrate neuron subtype-specific dendritic morphology (Hattori et al., 2013), as well as

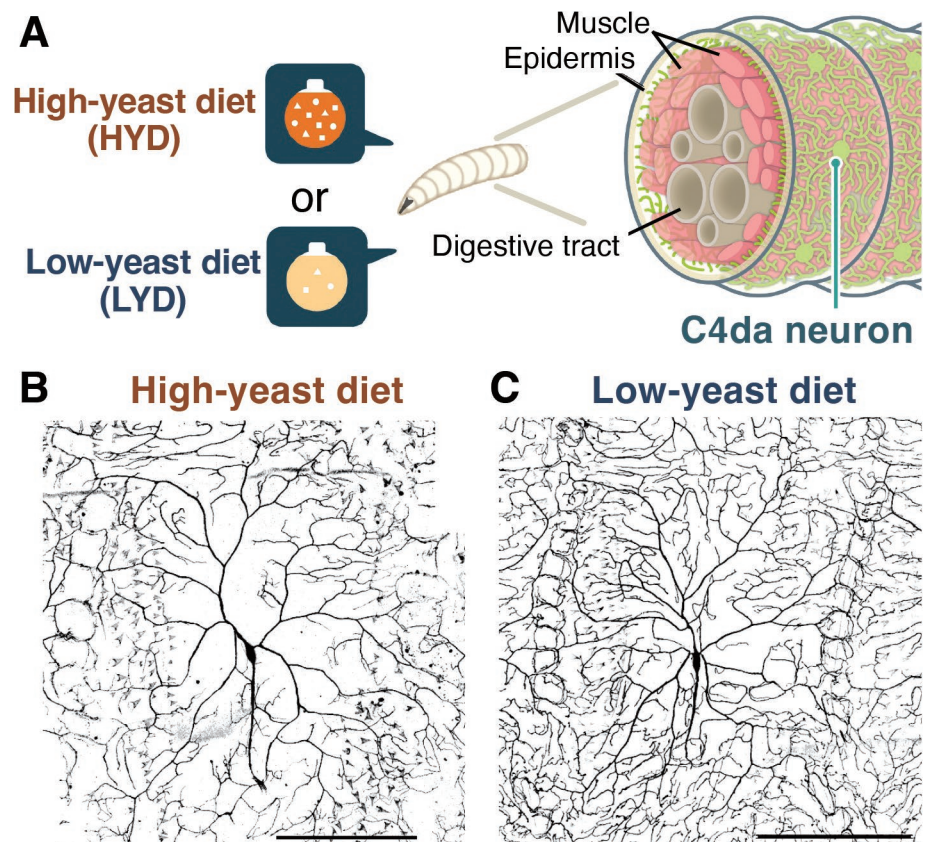


Fig. 1. Nutrition-dependent increase in the number of dendritic terminals in C4da neurons of *D. melanogaster* larvae. **(A)** Experimental scheme (left) and schematic diagram (right) showing a cross-section of the larva, indicating the position of C4da neurons relative to the epidermis, muscles, and digestive tract. C4da neurons extend their dendrites two-dimensionally between the epidermis and muscles. Larvae were fed one of two diets with different amounts of yeast, and the effects on C4da neuron dendritic morphology were compared between these conditions. **(B, C)** Dendritic morphology of C4da neurons in mature larvae fed a high-yeast diet (HYD) **(B)** or a low-yeast diet (LYD) **(C)**. The number of dendritic terminals is significantly increased in LYD compared to HYD. Scale bars: 200 μ m. Illustrations in Figs. 1A, 2, 4, and 5 were originally created by Hiroko Uchida, and some of them have been partially modified for publication, with permission.

the amino acid transporter SLC36/Pathetic and sterol regulatory element-binding protein (SREBP), which is involved in lipid synthesis (Meltzer et al., 2017; Ziegler et al., 2017). Non-autonomous mechanisms involve interactions between the C4da neuron and neighboring tissues, such as the epidermis. For example, epidermal cells secrete ligands such as semaphorin Sema-2b and the TGF- β family member Maverick, which signal to receptors on C4da neurons, directing the two-dimensional and space-filling elongation of dendrites (Meltzer et al., 2016; Hoyer et al., 2018).

In addition to these genetic factors, the dendritic morphology of C4da neurons is influenced by nutritional conditions. In the laboratory, *D. melanogaster* larvae are reared on diets containing heat-sterilized yeast as a main ingredient. Larvae fed a low-yeast diet (LYD) show more dendritic branching in C4da neurons compared to those fed a high-yeast diet (HYD) (Fig. 1B, C; Watanabe et al., 2017; Poe et al., 2020). The dendritic terminal automatic detection software DeTerm (Kanaoka et al., 2019) has been utilized to analyze various nutritional conditions and genotypes, and experiments using this analysis revealed that in response to a combined deficiency of B vitamins, minerals, and cholesterol, one of the Wnt ligands, Wingless (Wg), is secreted from muscle and acts on neurons to promote dendrite branching and elongation (Fig. 2A; Kanaoka et al., 2023). Additionally, analyses of the electrophysiological activity of C4da neurons and larval behavior showed that the responsiveness of C4da neurons to light stimuli is reduced under LYD compared to HYD, with fewer larvae exhibiting escape behavior from light (Fig. 2B; Kanaoka et al., 2023). Studies have shown that animals engage in risky behaviors under low nutritional conditions (Symmonds et al., 2010; Bräcker et al., 2013; Filosa et al., 2016; Padilla et al., 2016). Thus, under low nutritional conditions, larvae may continue food-seeking behavior without escaping from potentially dangerous light stimuli, which could expose them to risks such as desiccation, ultraviolet light, or parasitoid wasps (Fig. 2B). In contrast, a separate study found that larvae under a low-yeast condition exhibit more rapid avoidance behavior and increased responsiveness to thermal stimuli (Poe et al., 2020). Considering that from the second to third instar larval stage, the responsiveness of C4da neurons to light stimuli is reduced while heat

avoidance behavior is enhanced (Jaszczak et al., 2022), these seemingly opposing results may suggest that nutritional conditions influence larval behavior through distinct regulatory mechanisms depending on the type of stimulus.

Carbohydrate-responsive systems that generate differences in adaptabilities among *Drosophila* species

Drosophila species exploit a wide range of natural food sources, including flowers, mushrooms, fruits, cacti, and sap (Markow and O'Grady, 2008; Markow, 2015). *Drosophila*

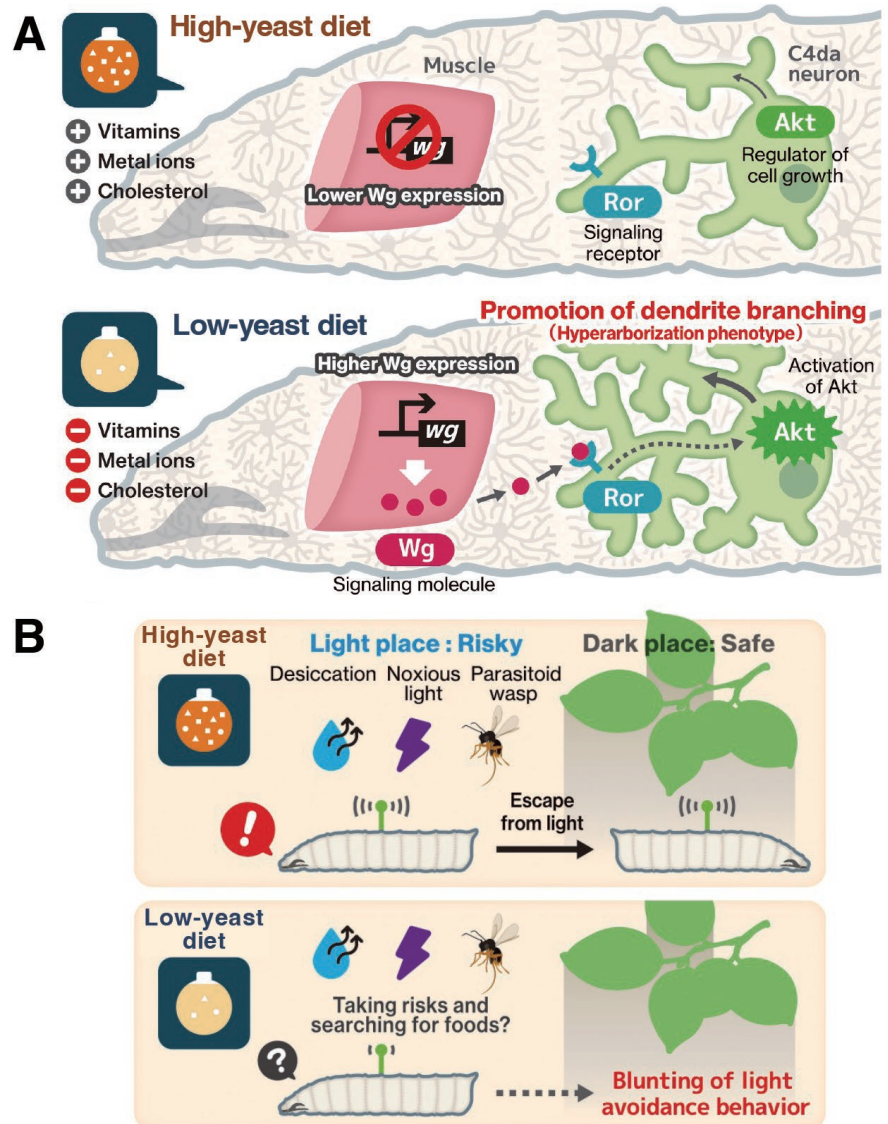


Fig. 2. Inter-organ signaling regulates nutrient-dependent dendrite branching of C4da neurons. **(A)** Compared to larvae reared under HYD conditions (top), larvae reared under LYD conditions (bottom) exhibit increased dendritic branching of C4da neurons due to a combined deficiency in vitamins, metal ions, and cholesterol. In LYD, the expression of the Wnt gene *wg* is higher in the muscles compared to that in HYD. The secreted Wg binds to the receptor Ror on C4da neurons, leading to the activation of the serine/threonine kinase Akt, which promotes dendritic branching. In contrast, in HYD conditions, the expression of *wg* is partially suppressed. **(B)** Larvae under LYD conditions show reduced responsiveness to light stimuli. This may have adaptive significance, as under nutrient-deficient conditions, larvae might be more willing to take risks in search of food, even in environments exposed to desiccation, harmful light, or predators.

melanogaster is a generalist found worldwide, feeding on a wide variety of fruits and vegetables (Fig. 3A; Markow and O'Grady, 2008; Markow, 2015). In contrast, *D. sechellia*, *Drosophila erecta*, and *Drosophila elegans* are specialists, inhabiting restricted areas and feeding only on specific fruits and flowers (Fig. 3A; Rio et al., 1983; Hirai and Kimura, 1997; Markow and O'Grady, 2008; Chandler et al., 2011; Markow, 2015). For example, *D. sechellia* is found only in the Seychelles Islands in the Indian Ocean and feeds exclusively on *Morinda citrifolia* fruit, commonly called "noni" (Fig. 3A). The octanoic acid in *M. citrifolia* is toxic to other *Drosophila* species, acting to repel them (R'Kha et al., 1991; Legal et al., 1992). However, *D. sechellia* has developed a tolerance to this compound and possesses an olfactory and

gustatory system favoring the host plant (Jones, 1998; Matsuo et al., 2007; Huang and Erezylmaz, 2015; Auer et al., 2021; Álvarez-Ocaña et al., 2023; Takagi et al., 2024). Biogeographical and phylogenetic evidence also suggests that *D. sechellia* evolved in isolation after colonization of the Seychelles Islands by its sister species, a generalist, *Drosophila simulans* (Hey and Kliman, 1993; Kliman et al., 2000; Drosophila 12 Genomes Consortium, 2007).

Thus, the mechanisms by which some specialist species favor specific plants or tolerate toxic compounds have been studied. However, much remains unknown about how generalists adapt to a wide variety of nutritional environments. Comparing the nutritional components of food consumed by two generalists (*D. melanogaster* and *D. simulans*)

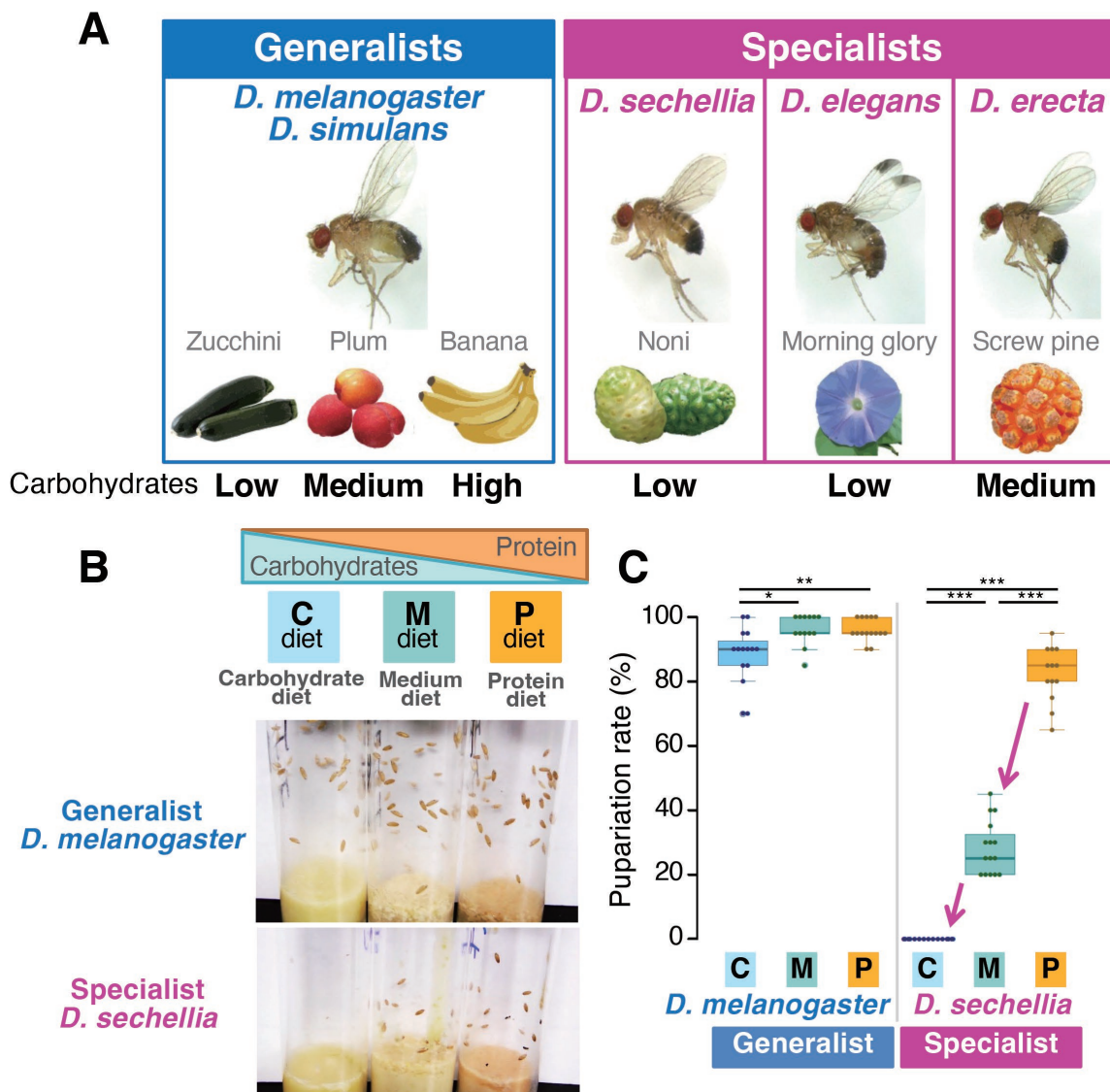


Fig. 3. Comparison of feeding habits and nutritional adaptabilities among *Drosophila* species. **(A)** Feeding habits of generalists and specialists, and the carbohydrate levels of foods. The carbohydrate levels of foods are presented based on the ratio of carbohydrates to proteins. **(B)** Generalist *D. melanogaster* and specialist *D. sechellia* raised on three types of diets with varying nutritional balances (Protein-to-carbohydrate ratios). From left to right: high carbohydrate diet (C diet), medium carbohydrate diet (M diet), and high protein diet (P diet). **(C)** Pupariation rates on C, M, and P diets. Each data point represents the percentage of larvae (out of 20) that developed into pupae. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (Steel-Dwass test, $n = 13-15$). The specialist *D. sechellia* showed a significant decrease in pupariation rate as the carbohydrate content of the diet increased (arrows). Partially modified from Watanabe et al. (2019) and Uemura et al. (2021).

and three specialists (*D. sechellia*, *D. erecta*, and *D. elegans*) in natural environments reveals that generalists can feed on both low- and high-carbohydrate food, while specialist *D. sechellia* and *D. elegans* are adapted to low-carbohydrate diets in nature (Fig. 3A). When larvae are reared in the laboratory on three isocaloric diets with different protein-to-carbohydrate ratios, the generalists can pupariate on any of the diets, whereas the specialist *D. sechellia* and *D. elegans* exhibit significant growth defects when provided high-carbohydrate diets (Fig. 3B, C). This suggests that these specialist species lack the adaptive systems for high-carbohydrate diets present in generalist species. Comparative multi-omics analyses revealed that the generalist *D. melanogaster* regulates the expression of more than 200 different metabolic enzyme genes in various tissues through carbohydrate-responsive systems, including the TGF- β /Activin signaling pathway, maintaining metabolic homeostasis under different feeding conditions (Fig. 4; Chng et al., 2014; Ghosh and O'Connor, 2014; Mattila et al., 2015; Mattila and Hietakangas, 2017; Watanabe et al., 2019). In contrast, such regulation is defective in the specialist *D. sechellia*, leading to increased amounts of metabolites and an inability to grow under high-carbohydrate conditions (Fig. 4; Watanabe et al., 2019). Experiments using hybrids of *D. melanogaster* mutants and *D. sechellia* suggest that the defect in *D. sechellia* appears to be polygenic rather than a result of a single gene dysfunction in the TGF- β /Activin signaling pathway (Watanabe et al., 2019). Another study on hybrids of the generalist *D. simulans* and the specialist *D. sechellia* identified genomic regions in *D. simulans* that confer sugar tolerance (Melvin et al., 2018). Dietary effects on adult lifespan also varied among species, with *D. sechellia* showing shorter lifespans on high-carbohydrate or high-

glucose diets (Watada et al., 2020; Abe et al., 2022). In *D. sechellia*, a high-glucose diet is suggested to impair gut immune function, leading to alterations in the gut microbiota, disruption of the gut epithelial structure, and ultimately a shortened lifespan (Abe et al., 2022).

Drosophila-associated microbes in the laboratory

Recently, *D. melanogaster* has been used as an excellent model system for studying animal-associated microbes. One advantage is that the microbial community (microbiota) is much simpler than that of mammals. While the human gut contains 500–1000 bacterial species, *Drosophila* species, both in laboratory and natural environments, host fewer than 20 species, most of which can be cultured under aerobic conditions, with some forming stable associations with adult flies (Chandler et al., 2011, 2012; Lee and Brey, 2013; Pais et al., 2018; Dodge et al., 2023). Additionally, microbes from the adult microbiota and the environment are present on the surface of eggs, but germ-free (GF) larvae can be obtained simply by dissolving the eggshell with bleach and rinsing with sterile water (Ma et al., 2015; Koyle et al., 2016; Ludington and Ja, 2020). This allows for the testing of the effects of specific microbial species, or combinations thereof, on GF larvae in individual test tubes, enabling the analysis of various microbial conditions. Furthermore, numerous genetic tools are available for *Drosophila* species, facilitating the analysis of host gene functions.

In laboratory conditions, acetic acid bacteria (AAB) and lactic acid bacteria (LAB) have been the primary focus as *Drosophila*-associated microbes (Shin et al., 2011; Storelli et al., 2011; Erkosar et al., 2015; Consuegra et al., 2020; Henriques et al., 2020; Yun and Hyun, 2023; Fujita et al., 2024). When GF larvae are raised under nutrient-poor diets,

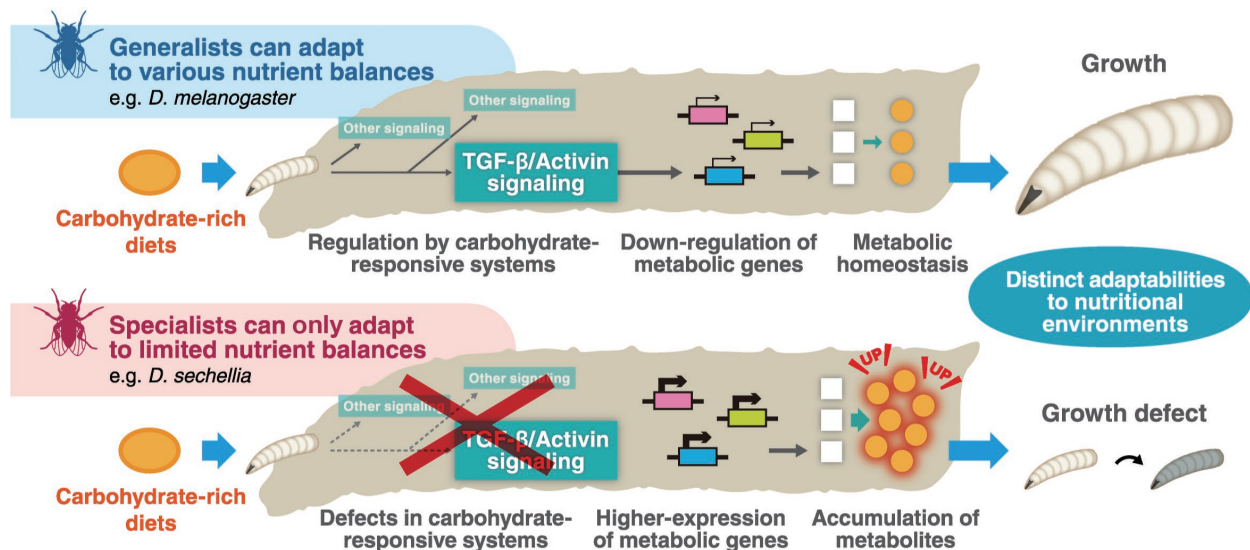


Fig. 4. Differences in carbohydrate-responsive systems between generalist *D. melanogaster* and specialist *D. sechellia*. (Top) In wild-type generalist *D. melanogaster*, the carbohydrate-responsive systems, including the TGF- β /Activin signaling pathway, downregulate the expression of various metabolic enzyme genes systemically, enabling metabolic homeostasis and larval growth under varying dietary conditions. (Bottom) In contrast, specialist *D. sechellia*, similar to the *D. melanogaster* *daw* mutant, lacks this regulation. Under high-carbohydrate conditions, *D. sechellia* shows increased expression of metabolic enzyme genes and elevated levels of numerous metabolites. As a result, its pupariation rate decreases on high-carbohydrate diets. Additionally, since specialist *D. sechellia* exhibits more severe phenotypes compared to the *daw* mutant, it is suggested that *D. sechellia* may have mutations not only in the TGF- β /Activin signaling pathway but also in other carbohydrate-responsive mechanisms.

they exhibit significant growth delays compared to conventionally reared larvae. However, these delays can be prevented by either AAB or LAB (Shin et al., 2011; Storelli et al., 2011). AAB have been shown to supply branched-chain amino acids to adults under nutrient-poor conditions, restoring amino acid preferences in the adults (Kim et al., 2021). Among LAB, a strain of *Lactiplantibacillus plantarum* has been reported to prevent growth delays in *D. melanogaster* larvae (Storelli et al., 2011), and the strain also promotes growth in mice in nutrient-poor conditions (Schwarzer et al., 2016). When administered to mice weaned on a diet low in fat and protein, the *L. plantarum* bacterial cell wall, particularly the peptidoglycan component muramyl dipeptide, is sensed by the innate immune receptor NOD2 in intestinal

epithelial cells, leading to increased production of insulin-like growth factor-1 (IGF-1) and subsequent growth promotion (Schwarzer et al., 2023). The colonization of LAB and AAB in the *D. melanogaster* gut has also been investigated. GF adult flies were fed fluorescently labeled LAB and AAB, allowing analysis of the establishment and stability of the gut microbiota. These bacteria stably colonized the foregut, forming spatially distinct niches and inducing morphological changes in the foregut (Dodge et al., 2023).

Essential microbes for the growth of wild larvae of *Drosophila* species

In laboratory studies of *Drosophila*-associated microbes, research focusing on bacteria other than AAB and LAB, as

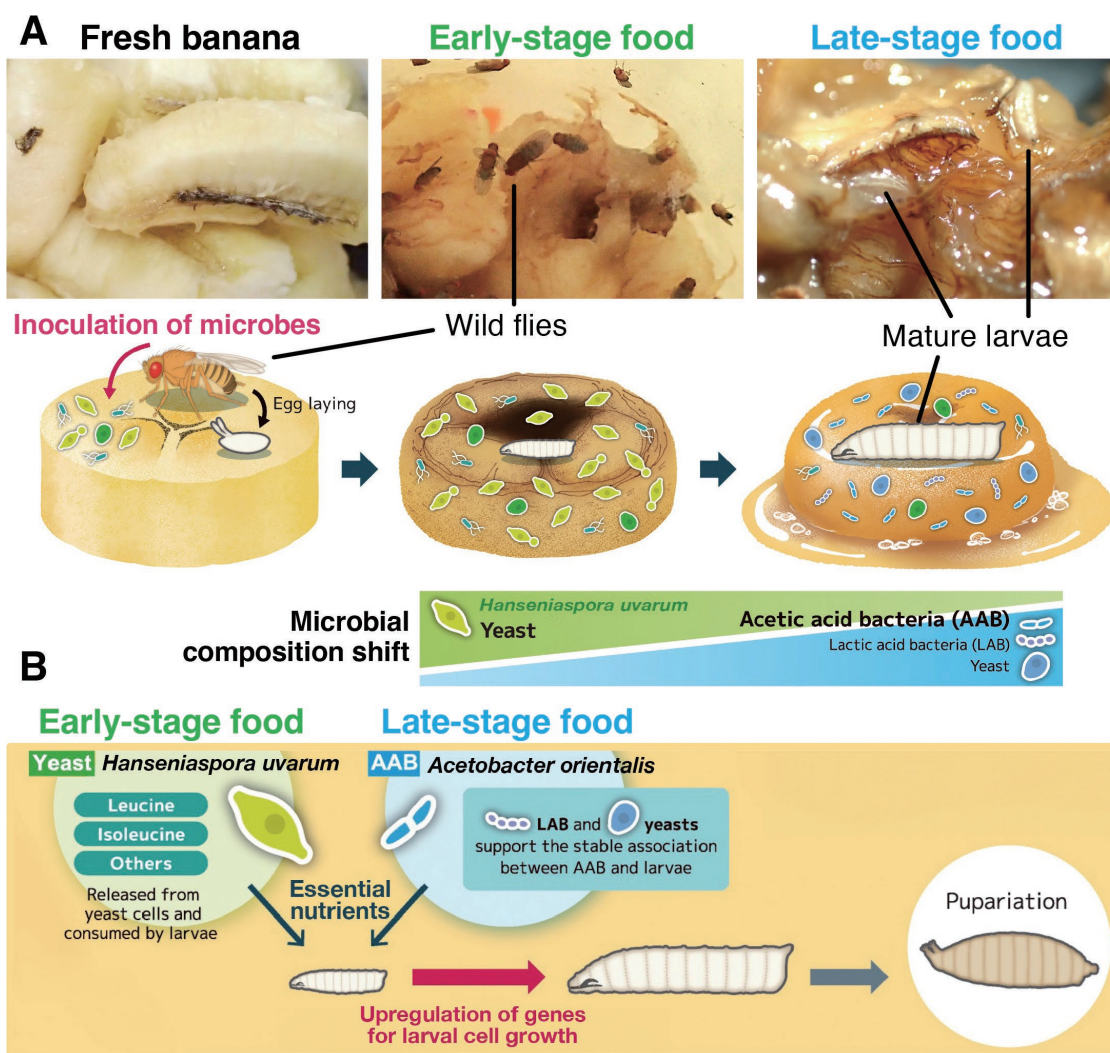


Fig. 5. Yeast and bacteria and their cooperative interactions supporting the growth of wild larvae of *Drosophila* species. **(A)** Fermented fruit consumed by wild *Drosophila* species. Traps with unfermented bananas (left) were set up outdoors in human residential areas, and the early-stage fermented food (middle), which wild *Drosophila* species were feeding on and laying eggs in, was collected. The food, excluding the adult flies, was incubated in the laboratory, and when the larvae matured, the late-stage fermented food (right) was collected. The composition of fungal and bacterial communities dramatically changes with fermentation. **(B)** In early-stage fermented food, the yeast *Hanseniaspora uvarum* releases nutrients such as leucine and isoleucine outside its cells, promoting larval growth. In contrast, the yeast and bacteria dominating the late-stage fermented food alone scarcely promote larval growth. However, when the acetic acid bacteria (AAB) coexist with lactic acid bacteria (LAB) or yeast, larval growth is promoted. The presence of LAB or yeast enables stable coexistence between AAB and larvae, where AAB supply nutrients to the larvae. This nutrient supply increases the expression of various genes supporting cell proliferation in the larvae, thereby promoting larval growth.

well as fungi such as yeast, is limited. One reason for this bias is the composition of laboratory diets, which contain antifungal agents to prevent the growth of mold harmful to flies. Furthermore, the main ingredients of the diet include heat-sterilized budding yeast *Saccharomyces cerevisiae* to provide essential nutrients such as sterols and B vitamins (Broderick and Lemaitre, 2012), although this yeast species rarely coexists with *Drosophila* species in the wild (Hoang et al., 2015). As a result, laboratory-reared flies can grow without forming symbiotic relationships with live yeast or bacteria. The chemically defined (holidic) medium for *D. melanogaster*, which contains the known nutrients from yeast, also supports larval growth, although much less efficiently than yeast-based diets (Piper and Partridge, 2014; Piper et al., 2017). Hence, the relationship between *Drosophila* species and their associated microbes has often been described as facultative, meaning the microbes are not essential for their growth (Martino et al., 2018; Gallo et al., 2022).

In contrast, wild *D. melanogaster* larvae grow by consuming plant-based diets fermented by yeast and bacteria (Fig. 5A; Broderick and Lemaitre, 2012; Watanabe et al., 2019), and microbes play an essential role in larval development. GF larvae cannot grow at all when fed fresh fruits such as bananas or figs; however, adding yeast or bacteria to these fruits allows the larvae to grow (Anagnostou et al., 2010; Pais et al., 2018). However, identifying the specific microbial species crucial for larval growth and fully understanding their growth-promoting mechanisms remains a complex challenge. A recent study analyzed the microbial community in fermented fruits consumed by wild larvae of *Drosophila* species and concluded that the microbial composition changes significantly during fermentation (Mure et al., 2023). In the early stage, the yeast *Hanseniaspora uvarum* dominates and supports larval growth, whereas, in the later stage, AAB coexist with other microbes (yeast and LAB), promoting larval development (Fig. 5A, B). Furthermore, analysis of intracellular and extracellular metabolites of yeast suggests that for yeast to promote larval growth, it is crucial not only to biosynthesize nutrients but also for these nutrients to either leak out or be released from the yeast cells, making them available to larvae (Fig. 5B; Mure et al., 2023). A separate study reported that AAB *Acetobacter thailandicus*, isolated from the gut of wild-caught adult *D. melanogaster*, can stably colonize the adult gut, and suggested that in nature, adults continually inoculate fresh fruits with this beneficial bacterium, thereby enhancing the developmental success of the next generation of larvae (Pais et al., 2018).

CONCLUSION AND FUTURE PROSPECTS

By focusing on the model organism *D. melanogaster*, along with its related species and associated microbes, significant progress has been made in elucidating how animals adapt to their nutritional environment and how interspecies relationships support animal growth. Nutritional environments also have long-term effects, including on the next generation, with epigenetic regulation via histone methylation being involved in this process (Öst et al., 2014; Cavalli and Heard, 2019). It would be interesting to elucidate how chromatin regulation mediated by histone modifications var-

ies among species and how these differences contribute to nutritional adaptability. Additionally, elucidating the molecular mechanisms by which yeast and bacteria function within the host is expected to deepen our understanding of the functions of microbiota. To achieve this, it will be necessary to conduct not only genetic analyses of the host but also comparative genomic analyses among microbial species and functional analyses of microbial genes (Harumoto and Lemaitre, 2018; Koga et al., 2022; Kageyama et al., 2023). Extending these findings beyond *D. melanogaster* to a broader range of animal species will contribute to a comprehensive understanding of how animals adapt to their nutritional environments at the molecular level.

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COMPETING INTERESTS

The author declares no conflicts of interest.

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