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Microbiomes as modulators of *Drosophila melanogaster* homeostasis and disease

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Abstract

Drosophila melanogaster harbors a simple gut microbial community, or microbiome, that regulates several facets of its physiology. As a result, the host employs multiple mechanisms of maintaining control over its microbiome in an effort to promote overall organismal homeostasis. Perturbations to the balance between microbiome and host can result in states of instability or disease, making maintenance of microbial homeostasis a fundamental physiologic aspect of *D. melanogaster* biology. While the interactions between microbes and their hosts can be direct, particularly in the context of immunity and gut renewal, effects resulting from indirect interactions, such as those between microbiota members, can be equally as important. This review highlights the major ways in which *D. melanogaster* regulates microbial homeostasis, the consequences of disruptions to homeostasis, and the different mechanisms by which the microbiome interacts with its host.

Keywords

Drosophila-microbe interactions; gut immunity; microbe-microbe interactions

Introduction

Drosophila melanogaster is established as a powerhouse model for host-microbe interactions owing to the tractability of both the host and the microbial community. A large array of traditional and multi-omic techniques are available in *D. melanogaster* to aid investigations into physiologic consequences of microbial interactions in the gut. Use of the fly model has identified core aspects of host physiology that are influenced or regulated by the microbiome, increasing our understanding of how the microbiota can tip the balance between states of homeostasis and instability, or disease. In this review, we highlight how an understanding of the interactions of *D. melanogaster* with its microbiome will reveal relationships between homeostasis and disease.

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The microbiome is a malleable organ that modulates host physiology

D. melanogaster typically harbors simple bacterial communities containing species primarily from the *Lactobacillus* and *Acetobacter* genera [1,2]. The nature of the microbial community-including factors shaping the microbiome, its diversity and abundance, its roles in host physiology, and the ecological consideration of these associations- has been extensively reviewed elsewhere [3,4]. Some of the more well- studied contributions of the fly microbiome to physiology include impacts on innate immunity, intestinal homeostasis, reproduction, nutrition, and metabolism (Figure 1) [5–22]. These studies have revealed the fly microbiome to be, in some ways, an additional organ that interacts with other host systems to influence overall biology. Like other organs, the microbiome is a distinct entity that mediates host processes to promote overall organismal homeostasis. What is unique about considering the microbiome as an organ is its fluidity or malleability, as while it can have powerful influences over physiology, it is also subject to being influenced or controlled itself by the host environment and host biology.

Host immunity as a mechanism of microbiome control

As an important component of host physiology, the microbiome contributes to establishment of the basal expression of many physiological functions. In turn, there is feedback of a number of these pathways on the microbiome, and their ability to maintain the microbiome (location, density, diversity) is critical for balancing host responses and functions. The host immune response is an important regulator of the microbiome of eukaryotic organisms and can be considered the most critical way by which a host communicates with its microbiome and vice versa.

The *D. melanogaster* immune repertoire includes a humoral response, characterized by the release of antimicrobial peptides (AMPs) and reactive oxygen and chlorine species, and a cellular response, which involves phagocytic cells and an invertebrate-specific melanization response [23,24]. These immune pathways are induced in response to both beneficial and pathogenic microbes. One of the initial, and most rapidly induced, host responses is the production of reactive oxygen and chlorine species (ROS and RCS, respectively). Lactate derived from Lactobacilli activates the Nox pathway in gut cells to release reactive oxygen species (ROS) as a mechanism to reduce overgrowth of the microbiota [7,25], while pathogenic bacteria stimulate ROS and RCS production via the dual oxidase system (Duox; Figure 2) [26]. These different mechanisms of microbial control via ROS allow the host to mount variable responses to control gut homeostasis, but the distinction between pathogen and microbiota is not absolute. *Lactobacillus brevis*, a common microbiota member, was found to release uracil and stimulate ROS production via Duox, indicating the importance of specific microbial members in immune-mediated regulation of homeostasis [26]. Less is known about the role of RCS, which is also regulated by Duox, in the *D. melanogaster* gut. However, a recent study has shown that RCS can limit colonization by an invader (a human-derived *E. coli* probiotic) to the fly gut [RM Derke *et al.*, https://www.biorxiv.org/content/10.1101/690669v2].

As in the oxidative burst response, the humoral immune response, characterized by the production of AMPs, is similarly stimulated by both pathogens and the microbiota. This is due to the nature of the two regulatory pathways, the immune-deficiency (Imd) and Toll, which are activated by pattern recognition receptors (PRRs) in response to conserved microbial associated molecular patterns (MAMPs). The immune-deficiency (Imd) signaling pathway is primarily induced by recognition of Gram-negative, or- DAP-type, peptidoglycan by peptidoglycan receptor proteins (PGRPs) present either in the membrane or cytosol of gut epithelial cells [27]. Many fly pathogens and microbiome members including *Acetobacter* spp., as well as some Lactobacilli (See Table 1) possess DAP-type peptidoglycan [28,29], whereas activation of the Toll pathway is initiated either by recognition of lysine (Lys)-type peptidoglycan by PGRP-SA or fungal ß-glucans by the misnamed Gram-negative binding proteins (GNBPs; not involved in sensing Gram-negative peptidoglycan) [30]. *D. melanogaster* PGRPs within the Imd signaling cascade known to recognize peptidoglycan derived from the microbiota include PGRP-LC, -LE, -SD, -LB, and -SC (Figure 2) [31,32]. Recently, PGRP-LB was shown to protect the host from deleterious effects caused by the dissemination of peptidoglycan into the hemolymph and other organ systems, demonstrating the delicate balance that exists between the immune system and microbes in the gut (Figure 2) [33].

Interestingly, the majority of commonly reported members of the bacterial microbiome have cell walls containing DAP-type peptidoglycan. In addition, the nature of Toll activation, which involves complex serine protease cascades downstream of PRR binding, is not considered compatible with the normal pH and enzyme profile of the fly gut [31]. For these reasons, the Toll pathway is not regarded as a major immune response pathway responding to and controlling microbial load in the fly gut. At least two common *Lactobacillus* spp. in the fly, *L. brevis* and *L. fructovorans*, contain Lys-type peptidoglycan (Table 1), but interactions between these bacteria and Toll activation have not been extensively examined. Lys-type peptidoglycan-mediated Toll activation was recently shown to be modulated by nephrocytes, which filter hemolymph. Flies lacking nephrocytes experienced constitutive Toll activation due to microbiota-derived peptidoglycan in the hemolymph, identifying a novel contribution of Toll signaling in homeostatic regulation of the microbiome [34]. Additional recent work suggests a role for Toll in activating epithelial renewal in the gut in response to the microbiota, but further studies are necessary to better understand the role of Toll signaling in regulating gut homeostasis [ML Atilano & M Glittenberg *et al.*, https://www.biorxiv.org/content/10.1101/248138v1].

Microbiome and the art of fly homeostatic maintenance

While the host immune response has an important role in negotiating interactions between a host and its microbiome, mechanisms that control or repair damage and maintain homeostasis have emerged as being equally critical for fly health. Perturbations that alter the homeostatic balance between the host and microbiome can lead to states of instability or disease.

ROS and RCS, in addition to regulating microbial load in the gut, damage gut cells that in turn stimulate epithelial renewal via EGFR and JAK-STAT signaling pathways, leading to

gut repair [25,35]. These pathways are induced in response to both microbiota and pathogens, but the level of damage they cause, and thus, the level to which the pathways and renewal program are activated differs [8,12]. One consequence is that the damage inflicted by microbiota can in essence prime the gut environment, thereby contributing to maintenance of homeostasis by allowing a more rapid renewal response to pathogens [7,25,26].

Dysbiosis, a state of disrupted microbiome composition and/or abundance, is associated with many disease states across diverse eukaryotes. In flies, dysbiosis is associated with overactive immune stimulation [36,37], and has been linked to aging- related pathologies, such as increased gut permeability and mortality due to decreased intestinal stem cell turnover [8,9]. Because intestinal stem cell turnover is intimately linked to immune activation in the gut, the effects the microbiome exerts on the immune system has downstream impacts on intestinal integrity [38]. Two mechanisms by which dysbiotic microbiomes synergize with host immunity to cause gut instability are via overaccumulation of lactate and ROS. When increased due to the presence of *L. plantarum*, the microbial byproduct lactate causes gut acidification and epithelial dysplasia, resulting in ROS production and reduced fly lifespan-pathologies that are not observed in flies containing lactate-deficient *L. plantarum* [7]. Additionally confirming *L. plantarum* as a microbe with the potential to promote disease phenotypes, mono-association with *L. plantarum* was shown to result in an overall loss of gut barrier integrity, possibly due to overactivation of damaging ROS in the gut [10]. However, *L. plantarum* has also been associated with a reduction in dysbiosis. In flies deficient in the histone demethylase KDM5, which leads to an overactive Imd response and dysbiosis, *L. plantarum* supplementation was sufficient to restore normal activation of Imd [37], indicating that additional factors may be involved that modulate the impact of gut microbes on host health.

Indirect contributions of the microbiome to homeostasis

The microbiome and microbiome products can directly affect host signaling pathways to both maintain and perturb homeostasis. Equally important are indirect effects of the microbiome, but we currently know far less about their contributions and underlying mechanisms. One such indirect effect is via microbe-microbe interactions, either between microbiota members or between microbiota and pathogens. Certain host responses have been attributed to mixed (but defined) communities that are not seen in hosts mono-colonized with individual members of the mixed community [39]. Recently, Sommer & Newell reported a mutualistic relationship between two *D. melanogaster* gut microbes, *A. fabarum* and *L. brevis*, in which the *Acetobacter sp*. utilized *Lactobacillus* fermentation products for its growth, which in turn impacted host metabolic status [40]. Another recent study showed that a specific consortium of *Lactobacillus* and *Acetobacter* species, when present in the gut, prevented epithelial renewal responses to *Vibrio cholerae* infection, indicating that interactions between microbiota members influenced the pathologic host response to *V. cholerae* infection [13]. Together, these studies demonstrate how species-specific interactions between microbes in the gut can modulate host physiology.

Interactions have also been reported between the microbiome and invading pathogens, either to the host's benefit or peril. *L. plantarum* is protective of flies challenged with *Pseudomonas aeruginosa* or *Serratia marcescens*, but the mechanism behind this protection has not been fully explored [41]. In addition, certain strains of yeast, which are considered part of the *D. melanogaster* microbial community in nature, offer similar protection against the pathogen *Aspergillus flavus* when administered live (but not dead), but again, the underlying mechanisms are not well understood [42]. In contrast, Fast *et al.* identified a mechanism by which the fly microbiome increases *Vibrio cholerae* virulence. This deleterious effect of a single microbiome member was mediated by an as yet uncharacterized interaction between *Acetobacter pasteurianus* and the *V. cholerae* Type 6 Secretion System (T6SS), possibly through the Imd pathway [5]. Interestingly, the pathologies associated with *A. pasteurianus*-T6SS interactions were found to be independent of *V. cholerae*'s effects on host epithelial renewal as seen in [13], reinforcing that microbiome-mediated effects on physiology can be multi-faceted.

It is also possible that observed interactions between the microbiota and pathogens can be attributed to the role of the microbiome as barriers to pathogen colonization. While many members of the *D. melanogaster* microbiome are thought to colonize due to continuous re-inoculation from the food substrate, their presence in the gut may yet block pathogens from establishing themselves. This is suggested by work showing that prior colonization of microbiota members reduced subsequent invasion by strains of the same species (*Lactobacillus plantarum*). An *L. plantarum* strain isolated from wild-caught flies was best at colonizing the gut and less likely to be displaced by *L. plantarum* strains from lab-reared flies or humans [43]. In another study, an *A. thailandicus* isolated from wild flies also colonized more stably than other common microbiome members [44]. Together, these studies highlight that strain-level differences within the microbiome can affect host interactions. Future work investigating the importance of species- and strain-specific microbe-microbe interactions in host physiology will be of great interest to better understand the microbiome as a homeostatic regulatory organ.

Nutritional and metabolic contributions to gut homeostasis

While regulation of immunity and epithelial renewal pathways are perhaps the most well-studied aspects of microbiome-mediated gut homeostasis, the *D. melanogaster* microbiota additionally contributes to host nutrition and metabolic function. Gut bacteria activate insulin signaling, either via the TOR pathway or acetic acid metabolism, to promote larval growth [19,20,45]. Axenic flies are metabolically deficient compared to their conventionally reared counterparts [39,45], suggesting that the host utilizes the microbiome to promote normal metabolism and development. Indeed, both living and dead gut microbes rescue undernutrition phenotypes on protein-poor diets, indicating that the microbiome can be a direct nutritional source [22]. It is likely that microbiome-mediated impacts on nutrition and metabolism have downstream implications for immune function and gut renewal, and vice-versa, but these relationships require more attention in future work.

Conclusions

Investigations into interactions between microbes and *D. melanogaster* have revealed the microbiome to be an important, yet malleable aspect of fly physiology. As such, the host has mechanisms in place to maintain homeostasis of its resident community, some of which depend on direct host-microbe interactions, others of which are dependent on cross-talk between microbiota members themselves. Breakdown of these control mechanisms lead to loss of both host and microbiome homeostasis, resulting in states of instability that can be detrimental to fly health. As the microbiome is such a complex and pervasive entity with regard to physiology, future work exploring additional mechanisms of host microbial maintenance and influences of species-specific, and even strain-specific, interactions within the gut will be of great value in understanding the microbiome as a fundamental system.

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Highlights

- Influences of the microbiome on host physiology can be both direct and indirect
- Hosts possess mechanisms to maintain homeostasis in response to the microbiome
- Perturbations of homeostatic mechanisms can result in disease states in the host

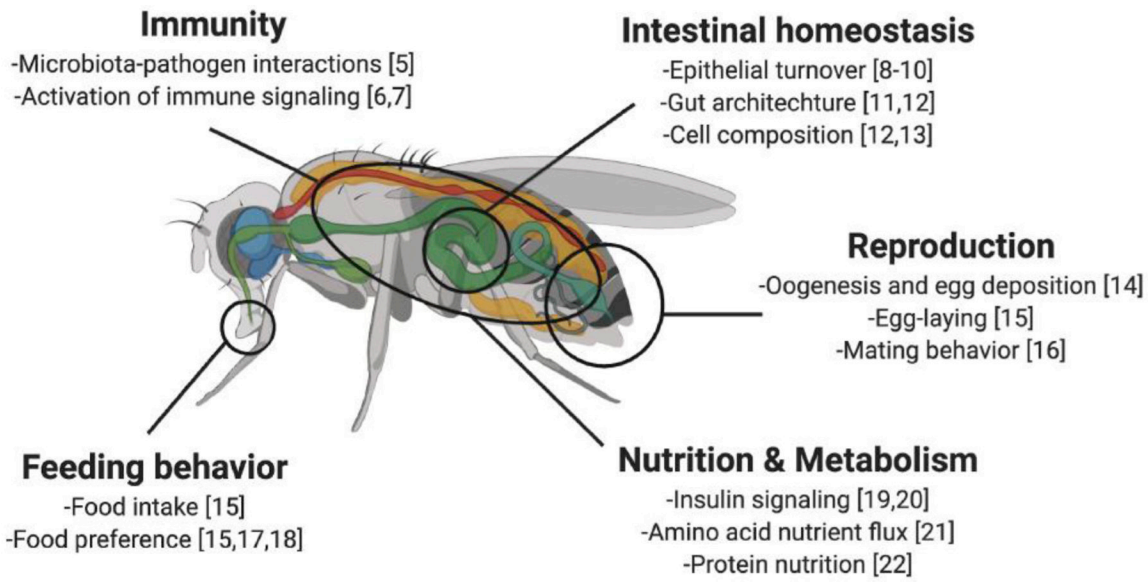

Figure 1.
The *D. melanogaster* microbiome influences nearly all aspects of host physiology.

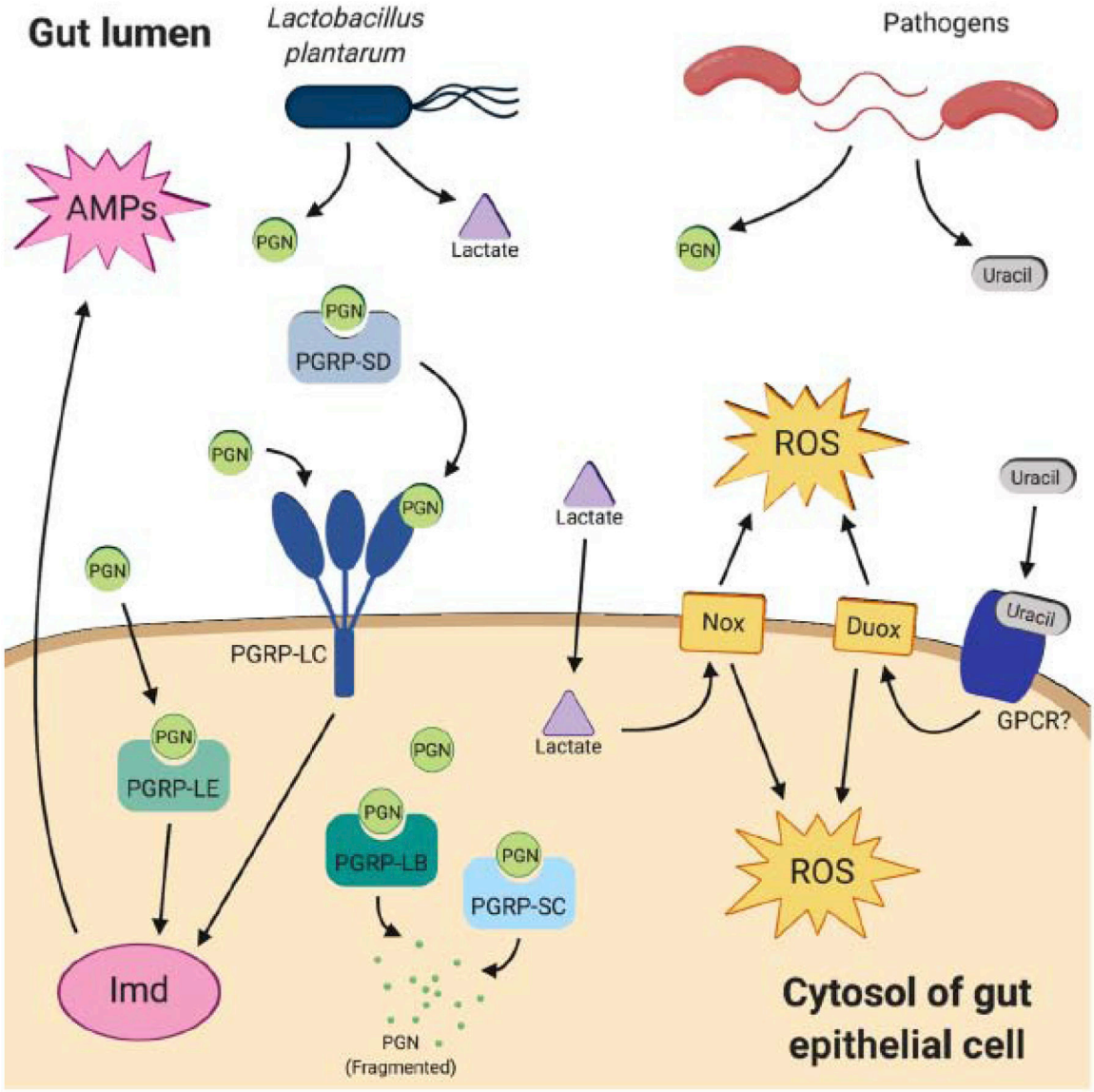

Figure 2.

Gut bacteria modulate Imd activation, leading to control of both microbiome and pathogen load via AMPs and ROS. PGN = peptidoglycan; PGRP = peptidoglycan receptor protein; AMPs = antimicrobial peptides; ROS = reactive oxygen species; GPCR = G-protein coupled receptor

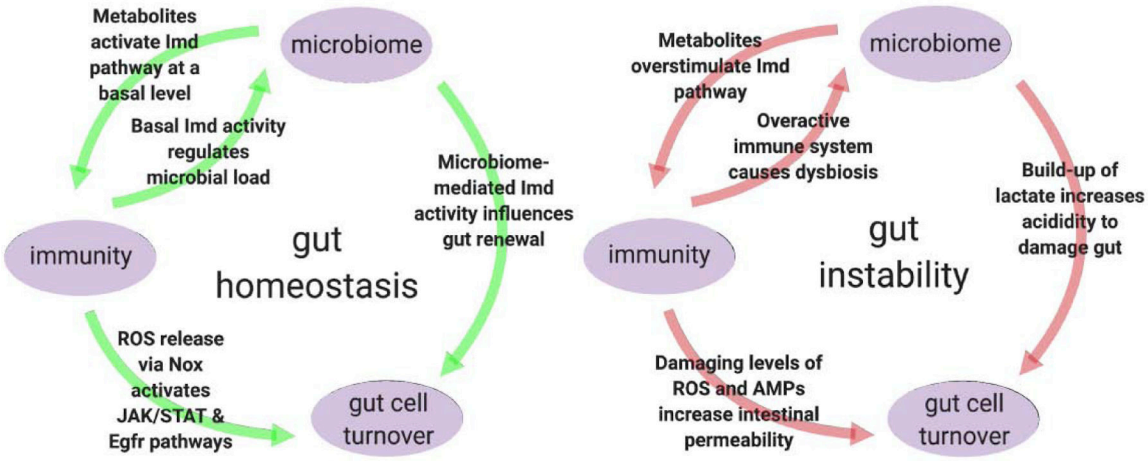

Figure 3.

Gut homeostasis is regulated as a tripartite balance between immune activation, gut repair, and actions of the microbiome.

Table 1.

Gram stain results and peptidoglycan structure of common *D. melanogaster* microbiota members.

Bacterial species	Gram stain	Peptidoglycan type	References
Lactobacillus plantarum	+	DAP	[28]
Lactobacillus brevis	+	Lys	[28]
Lactobacillus fructovorans	+	Lys	[28]
Acetobacter pasteurianus	−	DAP	[29]
Acetobacter pomorum	−	DAP	[29]
Acetobacter tropicalis	−	DAP	[29]
Acetobacter aceti	−	DAP	[29]