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Review

Transient adult microbiota, gut homeostasis and longevity: Novel insights from the *Drosophila* model

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ABSTRACT

In the last decade, *Drosophila* has emerged as a useful model to study host–microbiota interactions, creating an active research field with prolific publications. In the last 2 years, several studies contributed to a better understanding of the dynamic nature of microbiota composition and its impact on gut immunity and intestinal tissue homeostasis. These studies depicted the mechanisms by which microbiota regulates gut homeostasis to modulate host fitness and lifespan. Moreover, the latest findings demonstrating that the gut is a physiologically and histologically compartmentalized organ brought fresh perspectives to study the region-specific nature of the interactions between the commensal microbes and the intestinal tissue, and consequences of these interactions on overall host biology.

1. Introduction

Animals establish mutually beneficial interactions with microorganisms. This is particularly true for commensal bacterial communities that colonize the intestinal tract of most animal species [1]. However, despite the recent boom in the research in the gut microbiota, the mechanisms shaping these interactions remain to be better understood. A major obstacle in these studies is the complexity of the bacterial communities involved in mammalian host–microbiota interactions. Thus, the use of simpler animal models helps to unravel the evolutionarily conserved mechanisms underlying the impact of intestinal bacterial on their host's physiology. In this light, *Drosophila melanogaster*, the classic model organism whose role has been instrumental in laying the foundation of our knowledge of innate immunity [2], has become a powerful model to dissect the mechanisms behind the mutualistic host–microbe interactions. Thanks to the genetic tractability of both *Drosophila* and its cultivable and simple microbiota, this association model offers a great opportunity to reveal the molecular mechanisms underlying host–microbiota interactions. Several recent reviews have detailed how microbiota shapes *Drosophila* biology [3–5], but in the past two years our knowledge has significantly advanced. Here we provide a focused update of this prolific field with emphasis on three topics: (1) the adult microbiota composition and its transient and variable nature, (2) the impact of gut microbiota on gut immunity and intestinal tissue homeostasis which translates into host fitness and lifespan modulation and (3), the potential to exploit the recently discovered *Drosophila* gut compartmentalization model to study how microbiota regulates intestinal physiology.

2. *Drosophila* gut microbiota composition, establishment and maintenance

Numerous studies have now focused on the composition of the gut microbiota of the animal model *D. melanogaster*, and all revealed a rather simple composition [4–6]. The community is represented by only two phyla, *Firmicutes* and *Proteobacter* and is dominated by two major families, *Lactobacillaceae* and *Acetobacteraceae* and two minor families, *Enterococceae* and *Enterobacteriaceae* (Fig. 1). In most studies, the following species were identified either as dominant or sub-dominant members of the community: *Lactobacillus plantarum*, *Lactobacillus brevis*, *Acetobacter pomorum* and *Enteroccocus faecalis*. While the nutritional environment seems to be a major factor that directly impacts *Drosophila* gut microbiota, the microbial load and composition are also altered in different stages of the life cycle and during ageing [7–9]. Although the

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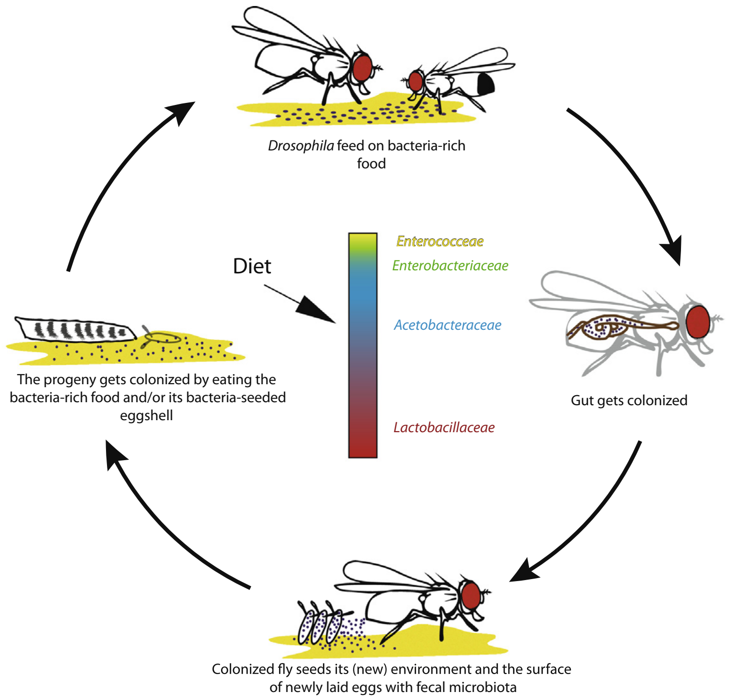

Fig. 1. The establishment and the maintenance of *Drosophila* microbiota depends on the constant intake of microbes from the diet. The gut of newly emerging flies contains very low number of microbes. Constant ingestion of bacteria-rich food allows the microbial colonization of the digestive tract and the maintenance of an intestinal microbiota. The parents' fecal microbiota is transmitted to other flies and to the progenies through the deposition of feces on the substratum on which they thrive. Female also ensure optimal transmission of their own microbiota by seeding the embryonic eggshell of their progenies, which is eaten by the hatching larvae and subsequently smeared onto the food substratum. The dominant bacterial families associated to *Drosophila* adults are color-coded according to their representative proportions. The type of diet the flies encounter can significantly alter the depicted proportions. Adult *Drosophila* drawings are modified from [50].

physiological consequences of these changes remain elusive, recent reports have increased our understanding on the crosstalk between diet, the *Drosophila* gut and its microbiota.

Lately, in order to dissect the impact of substrate and host species, Staubach et al. (2013) analyzed the gut microbiota sampled from flies gathered from different geographical locations and laboratory sources [10]. Consistent with what has been described before, the major bacterial families found in the intestines of all their *Drosophila* samples comprised of *Acetobacteraceae* (55%), *Lactobacillaceae* (31%), *Leuconostocaceae* (4%), *Enterobacteriaceae* (3%) and *Enterococceae* (2%). Remarkably, the bacterial communities in lab-raised flies lack both richness and diversity. The microbiota of wild-caught flies were dominated by *Gluconobacter ssp.*, and that of laboratory-raised flies were dominated by species of the *Acetobacter* or *Lactobacillus* genus. The major findings of this study highlight the previous observation that diet is one of the major factors influencing microbiota composition. Flies fed on strawberries, apples and peaches contain similar bacterial communities regardless where they come from. However, flies fed on oranges and compost harbor relatively distinct communities, and this may be due to the fact that particular ingredients of the food, such as citric acid and/or essential oil, can lower food pH and kill certain species of bacteria. Moreover, the authors observed that bacterial communities differ between *D. melanogaster* and *Drosophila simulans* only in the wild but not in the lab, suggesting that the effect of host species on microbial communities is subtle and/or need natural environmental conditions to manifest.

However, a recent study by Wong et al. challenged the idea of the existence of a "core" fly microbiota, defined as a community of bacterial species that would co-exist in all individuals of a given *Drosophila* species [11]. The authors scored the co-occurrence of bacterial species in individual flies and the congruence between host species and microbiota composition. First, they used species-specific PCR tests to detect the presence of five common *Drosophila* associated bacterial species: *Lactobacillus fructovirans*, *L. plantarum*, *L. brevis*, *Acetobacter tropicalis* and *A. pomorum* in fly individuals gathered from 21 strains spanning 10 *Drosophila* species. Strikingly they did not find a single bacterial species that was present in every individual tested. Although *L. fructivorans* was detected in at least one individual of every strain and *L. plantarum* as well as *A. pomorum* were detected in all but one strain, no bacterial species was "core" to every fly strain. In addition, they analyzed the presence of the same five species in a laboratory strain of *D. melanogaster* over 21 months and observed that *L. brevis* and *L. plantarum* sometimes presented in all of the flies tested, and other times in none of the flies [11]. These data clearly indicate that adult *Drosophila* microbiota composition is highly variable at the species level; it remains to be tested whether this variability also exists at larval stages and later in adult life. In addition, Wong and colleagues investigated the impact of host species variation on microbiota composition. As in Staubach et al. (2013), they found that differences in host species have little impact on the composition of gut microbiota and that no bacterial species was universally present in all *Drosophila* species analyzed [11]. In summary, both studies furthered our understanding in that the gut microbiota composition of adult *Drosophila* is shaped by host diet and nutritional environment and is therefore highly variable (Fig. 1).

The tight link between diet and microbiota composition strongly suggests a role of the flies' feeding habits in shaping their gut microbiota. Two recent studies from the Lemaitre and the Handelsman laboratories demonstrated that the establishment and maintenance of adult *D. melanogaster* microbiota depends on the constant ingestion of bacteria (Fig. 1) [12,13]. Newly emerged adult flies harbor a very low amount of bacteria. However, these young flies establish the microbiota within the first 24 h of their adult life by ingesting bacteria from the

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