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# Gut microbiota, healthy ageing and age-associated intestinal diseases: Drosphila intestine as a good model

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**Abstract:** The simplicity of Drosophila gut microbiome renders the fly intestine as a good model to study the interaction between the host and gut microbiota. Changes in commensal populations, defined as 'dysbiosis' in this review and others, are associated with disorders like autoimmune and allergic diseases, inflamma-tory bowel disease (IBD), obesity and diabetes, cancer and other ageing associated intestinal diseases etc. Deciphering the mechanisms underlying the gut micro-biome and ageing, ageing-associated intestinal diseases is critical. In this review, the fly gut microbiome has been compared with human gut microbiome. Recent work in the role of gut microbiome in ageing, inflammatory diseases of the intestine and cancer has been discussed in both Drosophila and mammals. Preventing intestinal dysbiosis for promoting health-span and lifespan is highly possible in Drosophila and mammals. Using Drosophila intestine as the model to address the questions raised above will provide insights on ageing and ageing-associated intestinal diseases.

**Key words:** Drosophila; gut microbiota; dysbiosis; fly intestine; ageing; lifespan; inflammation.

## Introduction

The gut microbiota is essential for the development and homeostasis of intestine and for the host well-being. The abnormal regulation of gut microbiota have been linked with inflammatory and metabolic disorders , including in-flammatory bowel disease, irritable bowel syndrome and obesity, diabetes, cancer etc (1,2 ). The associated micro-biota in fruit flies is relatively simple compared to human gut microbiota. The Drosophila intestine is emerging as a good model to elucidate the mechanisms underlying the complex interaction between the host and its microflora (3). This makes the fly intestine as an attractive model to study the mammalian ageing, cancer and intestinal di-seases.

## Drosophila Gut Microbiome and Human Gut Micro-biome

There are many factors that shape the community of fruit flies: host and nutritional factors, environmental fac-tors, etc. Notably, the host diet has a greater effect on the bacterial microbiome than host species. The same bac-terial lineages are associated with different host species, diets, and resident locations (1). So due to different lab atmosphere and food recipes, different labs with the same fly strains will have varied intestinal gut bacteria.

Drosophila has a taxonomically restricted bacterial microbiome. According to the previous literature, four bacterial families make up 90% of all gut bacteria which include Enterobacteriales, Rhodospirillales, Lactoba-cillales, Enterococcaceae (21%). Modulation of NFkB through caudal (Intestinal homeobox Gene) in the gut can impact the expression of AMPs, which in turn can alter the commensal population in the intestine. Since caudal acts as the gut-specific repressor of NFkB downstream genes AMPs and inhibition of Caudal in the intestine leads to the over-expression of AMPs. Over-expressions of AMPs in the presence of gut commensals causes apoptosis and results in the alteration of gut commensal community and gut pathology. This was demonstrated by the increase of a high pathogenic bacteria strain and the decrease of a beneficial bacteria strain that exists in normal fly gut (4). In this scenario, examining the bacteria species in terms of their beneficial/detrimental effect and their influence on gut innate immune response will provide value to stu-dy the bacteria community alteration during the ageing process in the intestine. The effect of these bacteria in the fly gut is still under investigation and debatable. Additio-nally, the make-up of bacteria is impacted by the signaling of the host or the genotype. Identifying specific bacteria strains is important to study the fly gut microbiota com-munity and useful for studying the health of the fly gut in general.

The human gastrointestinal (GI) tract harbors a large amount and high concentration of microbes (5). And the ecosystem of human gut microbiome is very complex (6). Similar to the age-related or disease-related microbiome changes in the fly intestine, elderly human individuals have a shift in the relative proportions of the Firmicutes and the Bacteroidetes. The microbiota of the elderly has a higher proportion of Bacteroidetes while the young adults have higher proportions of Firmicutes (Lactobac-cillus included) with anti-inflammatory effect (7). At the phylum level, Actinobacteria, which are believed to be health-promoting bacteria, decrease with ageing in mam-mals. Generally, the elderly, compared to young adults, have reduced gut microbiome biodiversity and compro-

mised stability (7).

Understanding the gut microbiome is important for stu-dying ageing and intestinal diseases and we need a simple model to study gut microflora. The Drosophila intestine is a good model to study gut microbiome given the simpli-city of gut microbiome composition and the easiness of obtaining gut microbiome culture in the flies. Therefore, the study on fly gut microbiota can shed light on studying ageing and intestinal diseases in mammals.

**Dysbiosis and Dysplasia: from Drosophila to mammals**

Dysbiosis refers to the breakdown in the balance between species of "protective" versus "harmful" intes-tinal bacteria. In other words, dysbiosis can refer to in-creased levels of harmful bacteria and reduced levels of the beneficial bacteria. Dysbiosis is associated with se-veral diseases including Crohn's disease, inflammatory bowel disease (8,9), cancer and obesity etc (2).

It is crucial to maintain the homeostasis of intestinal microbiota with age. In the ageing intestine, the boost of gut commensals occur concurrently with dyplasia (2). And this hyperplasia can be abolished by keeping the flies germ-free, suggesting that increased gut bacteria proliferation can produce detrimental effects and leads to over-proliferation of ISCs in the ageing intestine. This is based mainly on the observation that, the deregulation of gut microbiota, and more specially, the boost of gut bac-teria (defined this as " dysbiosis") occurs in the ageing intestine. Dysbiosis leads to an unfavorable condition for the host and/or immune homeostasis that can cause a nu-mber of intestinal disorders (10). More importantly, dys-biosis can cause dysplasia, which was shown not only in my work, but also by others as well (10,11). In addition to the boost of bacteria, dysbiosis can also be manifested as the shift of gut bacteria community. The bacteria com-munity shift that can cause gut pathology in the ageing fly intestine was not examined in the literature (2), the cau-sal relationship between dysbiosis and dysplasia is clear-ly established in many publications. The dysbiosis of the gut microbiota, characterized by the expansion of oppor-tunistic pathogens such as E. coli, can lead to dysplasia in mammals and invertebrates (12). Likewise, dysbiosis of the intestinal microfora, characterized by an expansion of the Gammaproteobacteria, is strongly correlated to intestinal barrier dysfunction with ageing in Drosophila. Changes in microbial composition occurring prior to or following intestinal barrier dysfunction contribute to al-teration of the immune responses in the ageing flies (13). Altogether, alterations in the composition and quantity of microbiota can contribute to and also predict various rates of health decline during ageing in mammals. In this regard, establishing a casual link between dybiosis and dysplasia is critical in studying ageing-associated diseases and intestinal diseases, including inflammatory bowel di-sease, autoimmune diseases, allergic diseases, diabetes, obesity and cancer (13- 15).

Despite the deleterious influence of gut microbiota de-regulation (dysbiosis) on animal health with age, gut mi-crobiota is crucial to produce beneficial effects in young animals. In young guts at basal conditions, the gut is ex-posed to indigenous microorganisms and this is important to induce ISC proliferation for normal self-renewal pro-cess. Specifically, this notion is supported by the recent work, showing a moderate ISC proliferation, gut immune response and bacteria number in young flies (2). Moreo-ver, bacteria-induced oxidative burst and other innate im-mune signaling pathways coordinate to induce intestinal epithelium renewal (11,16).

**Lifespan, ageing and gut microbiota in fruit flies**

The effects of ageing on the microbiota, and the conse-quences of microbiome changes on tissue homeostasis in the ageing intestine remain unclear. Recent studies that have characterized the gut microbiota composition in the elderly have found that the microbiota of older people is different and more diverse than that of younger adults, and that microbiota composition in the elderly correlates si-gnificantly with measures of frailty and co-morbidity (6). It has been proposed that the inflammation associated with dysbiosis promotes the development of various age-re-lated diseases of the host, and that manipulating host/com-mensal interactions might be a viable avenue to promote healthy ageing (7,17).

By comparing the germ-free flies with the conventio-nally reared flies in the ageing process, the effect of gut microbiota on ageing and longevity can be studied res-pectively (2). In flies, bacteria present during a critical period after eclosion have a beneficial effect and can en-hance lifespan. Later in life, bacteria can be deleterious to fruit flies and reduce lifespan. So the studies on gut micro-biome at different periods of flies are critical for ageing research (18).

**Gut Microbiome in inflammation, ageing and other in-testinal diseases**

The gut microbiota is capable of interacting with the host immune system (host mucosal epithelial and im-mune-related cells etc) and affects fundamental biologi-cal processes. For instance, obesity leads to a low-level chronic inflammatory state that is influenced greatly by the gut microbiota. Obese individuals have a decrease in Bacteroidetes accompanied by an increase in Actinobac-terium (6). Notably, around 1% of the US population ex-perience inflammatory diseases of the intestine. Prolonged inflammation and tissue injury, which can be caused by age-related dysbiosis, has also been proposed to potentiate gastrointestinal (GI) cancer (15).

In addition to the role of gut microbiome in obesity and cancer mentioned above, changes in commensal po-pulations ('dysbiosis') are associated with disorders like inflammatory bowel disease (IBD), Crohn's disease, ulce-rative colitis, autoimmune and allergic diseases, diabetes (15). Characterizing the role of fly gut microbiome will be clinically relevant to study ageing and age-associated intestinal diseases.

**Preventing intestinal dysbiosis to promote healthspan and lifespan**

Exogenous bacteria can impact the longevity of Dro-sophila, as shown by previous work analyzing the effects of

done to utilize antibiotic treatment to produce axenic flies. However, antibiotic treatment is an artificial condition that may affect the integrity of the gut epithelium and renders it more permeable to exogenous bacteria from exterior environment. In addition, the presence of bacteria during the first week of adult life was reported to enhance longevity. Conversely, the presence of bacteria later in life can re-duce lifespan. Therefore, the effect of bacteria on longe-vity is not that simple and needs further investigation (19).

It has been demonstrated that regulating host/commensal interactions in the barrier epithelia can limit dysplasia and extend lifespan (2). Previous work has also shown that the gut microbiota can have beneficial and delete-rious consequences on the host. Completely eliminating pathogenic and commensal bacteria does not enhance longevity (4, 19, - ). Preventing intestinal dysbiosis, but not eliminating all the gut bacteria, can help maintain immune homeostasis and tissue homeostasis and thus promoting longevity (2). The composition of bacteria is highly li-kely to shift during ageing in the fruit flies. This notion is supported by recent findings that there are age-related changes in the human commensal population (1, 17). This indicates that interventions to prevent intestinal dysbiosis may be able to also alleviate age-related pathologies and promote health- and lifespan in humans (7, 18).

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