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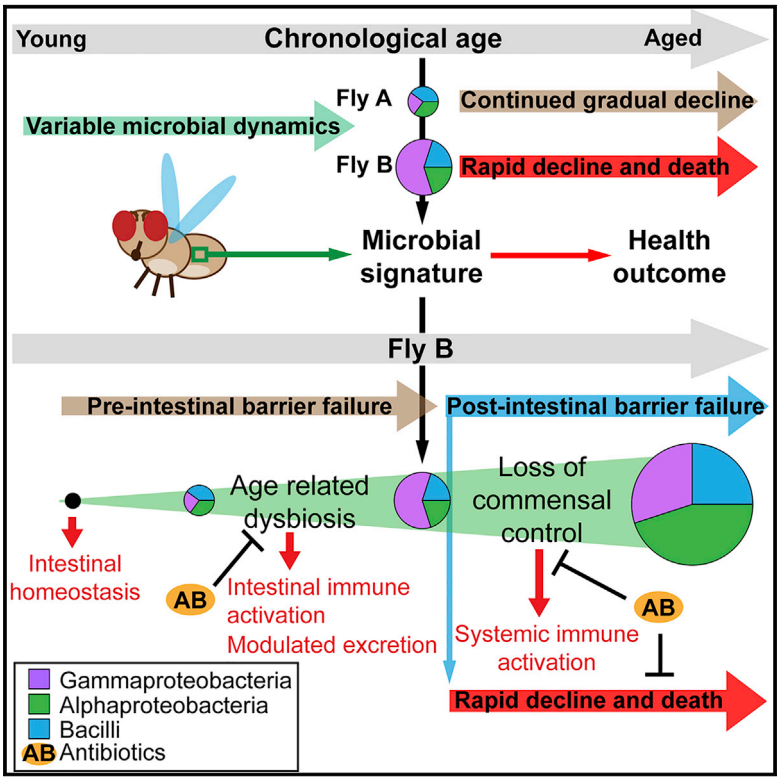
Distinct Shifts in Microbiota Composition during *Drosophila* Aging Impair Intestinal Function and Drive Mortality

Graphical Abstract



Highlights

- Age-related dysbiosis in *Drosophila* is characterized by Gammaproteobacteria expansion
- Dysbiosis predicts age-onset intestinal barrier dysfunction and rapid health decline
- Age-related dysbiosis drives changes in excretory function
- Loss of commensal control following intestinal barrier dysfunction drives mortality

Authors

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In Brief

The relationship between microbiota dynamics and age-related changes in organismal health are poorly understood. Using *Drosophila*, Clark et al. show that dysbiosis of the intestinal microbiota precedes and predicts age-related intestinal barrier dysfunction. Age-related alterations in the microbiota contribute to intestinal immune activation, modulate excretory function, and ultimately lead to mortality.

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Distinct Shifts in Microbiota Composition during *Drosophila* Aging Impair Intestinal Function and Drive Mortality

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SUMMARY

Alterations in the composition of the intestinal microbiota have been correlated with aging and measures of frailty in the elderly. However, the relationships between microbial dynamics, age-related changes in intestinal physiology, and organismal health remain poorly understood. Here, we show that dysbiosis of the intestinal microbiota, characterized by an expansion of the Gammaproteobacteria, is tightly linked to age-onset intestinal barrier dysfunction in *Drosophila*. Indeed, alterations in the microbiota precede and predict the onset of intestinal barrier dysfunction in aged flies. Changes in microbial composition occurring prior to intestinal barrier dysfunction contribute to changes in excretory function and immune gene activation in the aging intestine. In addition, we show that a distinct shift in microbiota composition follows intestinal barrier dysfunction, leading to systemic immune activation and organismal death. Our results indicate that alterations in microbiota dynamics could contribute to and also predict varying rates of health decline during aging in mammals.

INTRODUCTION

The composition of the intestinal microbiota co-develops with the host from birth and is subject to a complex interplay involving genetics, diet, and lifestyle (Nicholson et al., 2012). Dysbiosis of the microbiota has been implicated in a growing number of human disorders, including inflammatory bowel disease, obesity, cardiovascular disease, and neurological disorders (Blumberg and Powrie, 2012; Carding et al., 2015; Khan et al., 2014). Aging is a major risk factor for many of these disorders, and recent studies have found that the microbiota of older people is different than that of younger adults (Claesson et al., 2011) and that microbiota composition in the elderly correlates with measures of frailty, comorbidity, and inflammation (Claesson et al., 2012). However, fundamental questions remain regarding the relationships between age-related changes in microbiota composition and the pathophysiology of aging.

The fruit fly *Drosophila melanogaster* is an excellent model to study the interplay between microbial dynamics, intestinal aging, and organismal health. In aged flies, excessive proliferation of intestinal stem cells and the accumulation of mis-differentiated cells in the intestinal epithelium result in intestinal dysplasia (Biteau et al., 2008; Choi et al., 2008; Park et al., 2009), which limits organismal lifespan (Biteau et al., 2010; Hur et al., 2013; Rera et al., 2011; Wang et al., 2014). Previous studies have reported increased microbial loads in aged *Drosophila* populations (Broderick et al., 2014; Buchon et al., 2009; Guo et al., 2014; Ren et al., 2007) and that flies maintained axenically throughout life display reduced levels of dysplasia and other cellular markers of intestinal aging (Broderick et al., 2014; Buchon et al., 2009; Guo et al., 2014). These findings clearly demonstrate that the presence of gut-associated microbes contributes to cellular changes in the aging intestine. However, the nature of age-related alterations in microbiota composition and how microbiota composition relates to changes in intestinal function and fly health, during aging, remains largely unexplored.

A major challenge in determining how age-related changes in microbiota composition relate to the health of the host relates to the sampling of "aged" individuals. In a population of chronologically age-matched animals, there exists large variation in physiological health and remaining lifespan (Kirkwood et al., 2005). Hence, it can prove difficult to interpret data describing microbiota composition in a population of aged animals and/or in individual animals without knowledge of health status. Recently, we reported that loss of intestinal barrier function accompanies aging across a range of *Drosophila* genotypes and, critically, is a harbinger of organismal death (Rera et al., 2012). In the present work, we show that, regardless of chronological age, loss of intestinal barrier