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Role of gut microbiota in aging-related health decline; insights from invertebrate models

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Abstract

Studies in mammals, including humans, have reported age-related changes in microbiota dynamics. A major challenge, however, is to dissect the cause and effect relationships involved. Invertebrate model organisms such as the fruit fly *Drosophila* and the nematode *Caenorhabditis elegans* have been invaluable in studies of the biological mechanisms of aging. Indeed, studies in flies and worms have resulted in the identification of a number of interventions that can slow aging and prolong lifespan. In this review, we discuss recent work using invertebrate models to provide insight into the interplay between microbiota dynamics, intestinal homeostasis during aging and lifespan determination. An emerging theme from these studies is that the microbiota contributes to cellular and physiological changes in the aging intestine and, in some cases, age-related shifts in microbiota dynamics can drive health decline in aged animals.

Keywords

Intestinal barrier; microbiome; dysbiosis; longevity; mortality

Introduction

Providing insight into the biological mechanisms of aging is a pressing challenge with enormous biomedical significance. For many years, studies of the biology of aging were largely descriptive and correlative in nature. However, in the last two decades, pioneering work primarily using invertebrate model organisms has shed light on the molecular and cellular mechanisms of aging [1]. The nematode *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster* have been at the forefront of these efforts. Studies in both flies and worms have identified a number of genetic and pharmacological interventions that ameliorate aging and prolong lifespan [2,3]. The ultimate goal of this work is to identify novel therapeutic approaches to promote healthy aging, i.e. to delay the onset of pathology or disease, in humans [4,5,3].

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Although invertebrate models have been successfully exploited to identify prolongevity interventions, the pathophysiological underpinnings of most of these interventions are not clearly defined.

In recent years, a number of studies have shown that the intestine represents a critical target organ for genetic manipulations that prolong lifespan [6–15]. One interpretation of these findings is that maintaining intestinal homeostasis during aging is an important determinant of health and viability at the organismal level [11,15]. A logical extension of this idea is that alterations in the intestinal microbiota could influence organismal health during aging. In this review, we discuss recent work using invertebrate models to better understand the interplay between age-related changes in the gut microbiota, intestinal homeostasis and longevity.

Modeling the human microbiota: the role of invertebrate model systems

The human gastrointestinal tract houses a complex microbial population, the taxonomic membership of which is greatly impacted by environmental, lifestyle and dietary factors. Healthy adult individuals show significant inter-individual variability in microbiota composition. However, within a healthy individual this population appears to remain relatively stable over time [16,17]. In contrast, the microbiota of individuals with ill health differs significantly from that of healthy individuals. Microbial populations associated with ill health have been described as imbalanced relative to those of healthy controls, and this state of imbalance is referred to as dysbiosis. The inherent variability of healthy microbiota populations makes dysbiosis difficult to define and no consistent marker has yet been identified. However, a reduced overall diversity of taxa characterized by preferential loss of beneficial organisms and increased abundance of pathogens or pathobiont species appears to be an accepted signature of dysbiosis in much of the current literature [18].

Dysbiosis has now been associated with a large number of disease states, many of which are age-related, and has also been linked with frailty in the elderly (Reviewed in [19–21]). This has led to speculation regarding the role of the intestinal microbiota in maintaining host health throughout the life course. Given that the correlations between dysbiosis and ill health have primarily been identified in cross-sectional studies, the cause and effect relationship between microbial dynamics and health status remains uncertain. Longitudinal studies of the onset of type 2 diabetes and inflammatory bowel disease are currently being carried out by the Integrative Human Microbiome Project [22] and these studies should shed light on the temporal relationship between microbial dynamics and disease onset/development. However, experimental models are required to establish causality and to identify the molecular mechanisms that define the microbiota-host health axis.

The mouse is currently the most commonly used model organism in microbiota based studies, largely because, as a mammal, its gastrointestinal tract shares significant similarity with that of humans and because of the availability of a large number of relevant disease models. However, high maintenance costs limit its use in aging studies and particularly in lifespan analysis. The application of the invertebrate model organisms, the fruit fly *D. melanogaster* and the nematode worm *C. elegans*, to the study of host-microbe interactions

during aging is a natural extension of their productive history of use in understanding the molecular mechanisms that modulate longevity. Both the fly and the worm have short lifespans, lasting on average two months and 2–3 weeks respectively, in addition to fast reproduction, an extensive repertoire of molecular and genetic tools and low maintenance costs. This makes them ideal for lifespan analyses that require large population sizes.

The fly and the worm provide model systems of differing complexity. The intestinal tract of the worm consists of a simple tube of enterocyte cells [23] typically associated with a single bacterial species, *E. coli*, in laboratory populations. In contrast, the *Drosophila* intestine is more complex and contains multiple cell types and regional compartmentalization [24,25] associated with a more diverse microbial population. Extensive research into the aging process of both animals has yielded a number of biomarkers of intestinal and organismal aging, several of which can be measured without sacrificing the animal [15,26,27]. This ensures that the aging process, and health status, of individual animals can be followed in longitudinal studies that encompass the entire lifespan. Critically, in both organisms the molecular pathways regulating metabolic and innate immune function are evolutionarily conserved. Therefore, these model organisms are ideally placed to drive the discovery of molecular mechanisms that underlie host-microbe associations, and to study their relevance to lifespan and the pathophysiology of aging.

Age-related changes in Microbiota Dynamics

The human intestinal microbiota is dominated by the bacterial phyla Bacteriodetes, Firmicutes, Actinobacteria and Proteobacteria [28]. Other microorganisms, such as viruses and fungi, are also present but have not been well studied. While there are some species that are believed to be present in the majority of healthy individuals, the high inter-individual variability in microbiota composition has led to debate regarding the existence of common community structures. Despite efforts to group microbiota profiles into enterotypes, the current literature continues to support the view that each microbiota profile may be uniquely situated along a continuous gradient of taxa abundances [16,17,29,30]. In addition to the resident intestinal microbiota, ingestion of food-borne microbes contributes a transient microbial population that has the potential to impact host health (reviewed in [31]).

While in healthy adults the intestinal microbial community appears relatively stable over a period of months, aging results in significant changes to community structure. Reported changes in taxonomic composition with age vary somewhat between studies, but appear to include shifts in the Bacteriodetes:Firmicutes ratio and *Clostridium* groups, and increased carriage of Proteobacteria members, particularly the Gammaproteobacteria [32–34]. Notably, the most significant changes in microbiota composition are correlated with health status rather than with chronological age. Age-related changes have been shown to correlate with diet, residence status and health [35,36], levels of inflammation [34], and measures of frailty [37,38]. While the aged intestinal microbiota often shows the features of dysbiosis detailed above, i.e. reduced diversity and a loss of beneficial taxa, this is complicated by the significant differences in lifestyle, diet and health among the aged population. Importantly, reduced diversity is associated with frailty and reduced cognitive performance, rather than with chronological age [19]. In contrast, the risk of malnutrition in the elderly is associated

with increased microbiota diversity, and particularly the Clostridiales subpopulation. Counter intuitively, this population is also associated with frailty and with long stay residential care [19]. Overall, inter-individual variability is increased when compared to young, healthy controls [31] and this variability challenges attempts to define age-associated signatures of dysbiosis. In the mouse, aging also influences microbiota composition. However, whether these changes correlate with frailty is unclear due to a low sample size [39]

Both *C. elegans* and *Drosophila* are associated with complex bacterial populations in their native habitats. These communities are dominated by species from the phyla Proteobacteria and Firmicutes, with members of Bacteriodetes and Actinobacteria also fairly abundant, albeit at lower levels than found in the human intestinal microbiota [40–45]. Therefore, at this high taxonomic level there is significant overlap in the bacterial taxa associated with the worm, fly, mouse and human. There is little evidence of a core microbiota in either the fly or the worm, and inter-individual variability is high [42,41]. Both invertebrate models feed on microbes present in their environment, so their intestinal microbiota is closely associated with their food substrate. The food source is primarily bacteria for *C. elegans* and yeasts for *Drosophila*. However, in both cases intestinal microbiota composition is not simply determined by the bacterial proportions present in the food substrate but is driven by the host and impacted by developmental stage and genotype [41,46]. Remarkably, there is also strong evidence that the impact of these intestinal microbes is not exclusively nutritional [47,48,40].

In laboratory populations, *C. elegans* are typically maintained on a diet of *E. coli*, historically due to the availability of *E. coli* in research laboratories. This *C. elegans* - *E. coli* association is therefore the simplest host-microbe model system available. Several groups have reported that aged worms show a significant accumulation of *E.coli* in their intestines [49–51]. Laboratory *Drosophila* strains host an intestinal microbiota with a composition that ranges from three to 30 bacterial species and is highly variable depending on laboratory, genotype and diet [52–54]. In addition to bacterial species, fungi and other microbial eukaryotes, as well as Archea and viral taxa add to the complexity of this microbial population [54]. However, only the bacterial component has been extensively studied to date. A number of studies have demonstrated that microbial load in the *Drosophila* intestine increases with age [55,56,54,57,9]. Our recent work has shown that increased microbial loads are also associated with a shift in bacterial composition toward a greater proportion of Proteobacteria species, in particular members of the Gammaproteobacteria (including the genera *Escherichia, Providencia, Haemophilus, Actinobacter, Pseudomonas* and *Vibrio*), and reduced Firmicutes levels [54]. Critically, we have demonstrated that, as in humans, the largest changes in both microbial load and species composition in the *Drosophila* intestinal microbiota are more closely associated with the health status of the animal than they are with chronological age [54]. This suggests that the fundamental principles that underlie intestinal functional decline, and organismal decline, may be highly evolutionarily conserved. A key challenge for the field is the identification of these principles, and how the intestinal microbiota may contribute to this process.

Microbial dynamics and the pathophysiology of aging

Recent studies have demonstrated the importance of maintaining intestinal homeostasis to whole organism health and longevity [11,15]. In order to understand the role of the intestinal microbiota in age-related decline we, therefore, need to identify both the mechanisms underlying microbial contributions to intestinal decline, and the impact of intestinal decline on distal tissues. The aging intestines of both worms and flies show morphological decline. In *C. elegans*, this includes a loss of nuclei, changes to the shape and size of the intestine, and a loss of microvilli [58]. Increased bacterial loads correlate with age-related decline in the worm intestine [58]. In *Drosophila*, a breakdown of regional identities [24,14] and epithelial dysplasia [59–61] are driven by changes in intestinal stem cell proliferation and differentiation (the regulation of intestinal stem cells and dysplasia has been recently reviewed in [62]). Moreover, there is now clear evidence that preventing microbial exposure delays the onset of intestinal dysplasia [55,56,9,63]. These studies suggest that changes in the microbial population during aging drive immune activation in the intestinal epithelium, which in turn drives epithelial dysplasia [63,9]. However, the cause and effect relationships between dysbiosis, dysplasia and age-related immune activation during aging are not clear-cut. While interventions that reduce microbial exposure also reduce age-related immune activation [56,9,57], in *Drosophila* reducing age-related immune activation is itself sufficient to prevent microbial dysbiosis [9]. In addition, interventions that prevent intestinal stem cell proliferation and maintain gut compartmentalization are sufficient to reduce both age-related immune activation and microbial dysbiosis [14,64]. Taken together, these studies demonstrate that the regulation of epithelial regeneration, control of the microbiota, and immune function is tightly networked. Whether age-related decline in the intestine occurs in a stereotyped manner and is always initiated by particular changes in one of these factors, or whether it can be driven by stochastic changes in any of them remain open questions.

One way to address the timing of events that drive intestinal decline is to utilize markers of health status that do not require animal sacrifice, to allow individual animals to be followed during aging. One such marker of age-related intestinal decline is intestinal barrier dysfunction. In the fly, the loss of intestinal barrier function can be assayed by the feeding of a non-absorbable dye, which in healthy animals is retained within the intestine but which in animals with intestinal barrier dysfunction will spread throughout the body cavity, visible through the cuticle [65,12]. We have shown that the loss of barrier function in the fly is a clear indicator of age-related health decline, and is a better predictor of organismal death than chronological age [65]. More recent work has demonstrated that intestinal barrier loss is an evolutionarily conserved biomarker of aging [66–69]. Using this dye-based assay to track flies prior to, and after, intestinal barrier loss we have demonstrated that while the most dramatic changes in microbial load occur following barrier dysfunction, changes in microbial composition are apparent several days prior to the loss of barrier function [54]. Indeed, using fecal sampling we discovered that alterations in the microbiota precede and predict the onset of intestinal barrier dysfunction in aged flies [54]. Flies that are raised axenically, without microbial exposure, also show a significant delay in the onset of intestinal barrier dysfunction [54]. Taken together, these data suggest that changes in the microbial population in the *Drosophila* intestine are an early event, and potentially a driving

factor, in intestinal decline. In fact, a recent study by Thevaranjan, Bowdish and colleagues has demonstrated that the composition of the aged microbiota contributes to increased intestinal permeability in old mice [69], suggesting that the relationship between dysbiosis and intestinal permeability is conserved over large evolutionary distances.

While the studies discussed above have identified a number of biomarkers of age-related intestinal decline, work to characterize the impact of these changes on key intestinal functions such as nutrient uptake and water absorption is in its infancy. Changes in the expression of key metabolic regulators, such as the transcription factor Foxo, which is activated in response to reduced insulin signaling, and digestive enzymes suggest significant changes in nutrient uptake and processing may occur in the aging fly intestine [70,71]. Similarly, we have shown that changes in the pH and water content of the fly's fecal output occur with age, suggestive of declines in epithelial transport and absorption [54]. While we have shown that antibiotic treatment that prevents age-related dysbiosis can ameliorate some of these functional changes [54] more work is needed to establish the contribution of the microbiota to the digestive and absorptive functions of the intestinal epithelium.

In addition to a dramatic expansion in the intestinal microbial population, flies that have lost intestinal barrier function show reduced fat and glycogen stores, reduced mobility and systemic immune activation [65]. Changes in nutrient uptake and energy metabolism in the intestine, and the loss of intestinal barrier function itself may be the causative factors driving whole organism health decline. This suggestion is supported by the ability of interventions that maintain intestinal homeostasis during aging to prolong lifespan (reviewed in [11]). Our recent work has shown that, in the fly, intestinal barrier dysfunction alone does not drive organismal decline. Rather, it is the combination of intestinal barrier dysfunction with expansion of the intestinal microbial population that drives systemic immune activation and mortality [54]. Indeed, antibiotic treatment of flies that have lost intestinal barrier function restores their remaining lifespan to that of age-matched healthy controls [54]. In an interesting parallel, it has been reported that the extent of bacterial accumulation in the intestine is inversely correlated with worm lifespan [50], again supporting a key role for host-microbe interactions in determining health and longevity.

Influence of gut microbiota on host lifespan

The most direct approach to examine the influence of the gut microbiota on host longevity is to examine the impact of axenic culture. There is a two-fold increase in *C. elegans* lifespan under axenic culture ([72]). However, because bacteria are also a food source it is not possible to exclude the possibility that dietary restriction contributes to extended lifespan under axenic conditions. Several studies have examined the impact of axenic culture on *Drosophila* lifespan. However, the results have not always been consistent. In pioneering work, Brummel, Benzer and colleagues reported that the presence of bacteria in the first week of adult life was required for a normal lifespan [73]. In other words, axenic culture was reported to shorten lifespan in male flies. Interestingly, in the same study, it was reported that, late in life, the presence of bacteria can shorten lifespan. More specifically, treating flies with antibiotics from midlife onwards extended lifespan. However, in a comprehensive follow-up study from Ren, Tower and colleagues reported that reducing bacterial load by

axenic culture or antibiotics had no effect on male fly lifespan [57]. Differing nutrient conditions between experiments/labs may represent one potential explanation for these inconsistent reports of the impact of bacterial exposure on fly lifespan. Indeed, the presence of microbes can promote fly longevity under low nutrient conditions [74]. More recently, we have reported that axenic culture prolongs female fly lifespan [54]. Our findings are consistent with a report showing that antibiotic treatment can also extend fly lifespan [64]. In addition, our observation that axenic female flies are long-lived is consistent with reports from different labs showing that axenic flies show a delay in intestinal aging at a cellular level [55,56,9]. We also observed that preventing bacterial growth, via antibiotic feeding, significantly extended the lifespan of aged flies showing intestinal barrier failure [54]. To further assess the impact of the microbiota on lifespan, we fed homogenate from aged flies to young flies. As a result, there was an increase in bacterial load and shift in microbiota composition. Importantly, feeding homogenate from aged flies to young flies significantly decreased lifespan [54]. Taken together, these findings support the notion that the microbiota can contribute to age-onset mortality in *Drosophila*.

Beyond the impact of axenic culture, there have been numerous studies examining the impact of bacteria on worm lifespan. As discussed above, worms fed the standard laboratory *E. coli* strain OP50 have been reported to show an age-related accumulation of bacteria in the gut [49–51]. Moreover, feeding worms dead bacteria or treating with kanamycin can increase *C. elegans* lifespan perhaps by preventing or delaying *E. coli* accumulation in the intestinal lumen [49,75]. Interestingly, worms fed a diet of *E. coli* deficient in coenzyme Q or with defects in ATP synthase live longer than worms fed OP50 [76,77]. Follow up studies revealed that respiratory deficient Q-less *E. coli* do not accumulate in the aging intestinal tract to the same degree as OP50 [51]. Thus, there is a growing body of evidence to suggest that the age-related accumulation of bacteria in the worm intestine contributes to mortality. However, this hypothesis has been challenged by a recent study examining individual worms maintained on *E. coli* OP50 expressing GFP [78]. In this study, it was reported that there is considerable heterogeneity in the accumulation of bacteria in individual worms during aging, with many worms not appearing to accumulate bacteria at all [78]. This finding suggests that bacterial accumulation is not a universal contributor to age-onset mortality in worms. It is, therefore, possible that individual worms die from distinct pathologies. Interestingly, it has been reported that variable pathogenicity from *E. coli* is a major source of lifespan variability in individual worms [79]. In summary, while there may be individual variability involved, there is an emerging understanding that bacterial pathogenicity can contribute to mortality in aged worms.

Identifying mechanisms of microbial impact on host longevity

Beyond studies of age-related bacterial accumulation, work in the *C. elegans – E. coli* system has begun to characterize the molecular mechanisms by which the intestinal microbiota may influence host longevity. The simplicity of this model system has allowed the screening of *E. coli* mutants for their impact on host longevity. Recent studies have identified a number of mutants that increase host lifespan and demonstrated the specific genetic control of microbial regulation of host longevity [78,80]. Inhibition of folate synthesis by *E. coli*, through mutation or pharmacologically, extends worm lifespan in a

growth-independent manner [81,78]. Interestingly, however, supplementation or restriction of *C. elegans* folate levels has no impact on longevity [78]. Altogether, these data demonstrate that the process of folate synthesis in *E. coli*, and not folate levels themselves, limits host lifespan. Whether microbial folate synthesis contributes to age-related decline in mammals remains to be investigated. Nevertheless, this work demonstrates the utility of simple model organisms in the rapid identification and characterization of the molecular mechanisms underlying microbial contributions to functional decline in the aging host. A number of additional studies have demonstrated that diffusible molecules originating in bacteria can impact worm lifespan [82]. *C. elegans* lack the enzyme nitric oxide (NO) synthase and, hence, rely upon bacterially derived NO. Remarkably, it has been demonstrated that bacterially derived NO enhances *C. elegans* lifespan [83]. In addition, small non-coding RNAs (ncRNAs) expressed endogenously by *E. coli* can modulate *C. elegans* longevity [84]. More specifically, feeding worms *E. coli* deficient in the ncRNA DsrA significantly increases lifespan. Therefore, bacterial-derived molecules can both shorten and prolong worm lifespan.

Future studies/Outstanding questions

Genetic studies using flies and worms have resulted in the identification of genes and pathways that modulate aging and lifespan in mammals, including the TOR, AMPK, and autophagy pathways [5,2,85,86,13,87]. Hence, there is growing optimism regarding the ability to develop safe interventions to slow aging and increase healthy lifespan in humans [4,3]. However, even in invertebrate models, the relevance of the microbiota in anti-aging interventions is only beginning to be explored. While bacterial-specific effects associated with worm longevity interventions have been reported [88–90], the pathophysiological mechanisms involved remain unclear. Moving forward, it will be important to determine whether the prolongevity effects of manipulating pathways such as AMPK/autophagy are mediated through improved commensal homeostasis. A better understanding of whether anti-aging interventions are influenced by or dependent upon microbiota composition may be critical in assessing whether these interventions are likely to prove effective in promoting healthy aging in a broad spectrum of aged individuals.

While this work is in its infancy, the apparent similarities in the nature of age-onset dysbiosis and its association with ill health between the invertebrate models and mammals is suggestive. The contribution of dysbiosis to the development of inflammation and the role of inflammation itself have been recognized in the context of both disease and age-related ill health. However, the importance of the reciprocal nature of the relationship between inflammation and dysbiosis is only recently becoming apparent. In line with data from mammalian models of inflammatory bowel disorders [91], studies in *Drosophila* have demonstrated that chronic immune activation can drive dysbiosis [92]. In addition, in *Drosophila* prevention of age-related immune activation is sufficient to prevent dysbiosis [9], and in the mouse anti-TNF treatment can reduce age-related dysbiosis [69]. These findings are consistent with the reduction of dysbiosis following reduction of intestinal inflammation in pediatric Crohn’s disease patients [93]. Together these data suggest a model whereby the development of dysbiosis and increased inflammation feed in to each other resulting in a downward spiral that drives intestinal, and ultimately organismal, decline (figure 1).

Therefore, it is critical to identify the factors that initiate this process and to characterize the molecular mechanisms that underpin microbiota - immune crosstalk during ageing.

Despite the distinct differences between the invertebrate gut, and its associated microbiota, and that of mammalian models and humans, striking similarities in the relationship between dysbiosis, immune function and intestinal decline, in particular intestinal permeability, are apparent. These similarities are relevant in the context of both disease models and ageing. Consequently, while we must be cautious in drawing direct parallels between any model system and humans, these findings demonstrate the value of the invertebrate models as discovery tools. The strength of invertebrate studies lies in the rapid identification of potential associations, markers, candidate genes or pathways, or other molecular processes for targeted testing in more complex and costly model systems. For example, a key finding from invertebrate studies has been an age-related increase in bacterial load [54,57,9,50]. To our knowledge, the occurrence of changes in bacterial load in the mammalian intestine has not been fully investigated. Moving forward, a consideration of bacterial load, in addition to species composition, may be critical in understanding the impact of the microbiota on the aging intestine.

The host-microbota association brings together a complex microbial ecosystem with host metabolic, immune and repair systems to form an intricate network of interacting parts. Identifying specific cause and effect relationships between microbial dynamics and host health outcomes, and the mechanistic basis of these relationships, therefore represents a significant challenge. In addressing this complexity, the experimental systems provided by the invertebrate models are a critical part of our toolkit.

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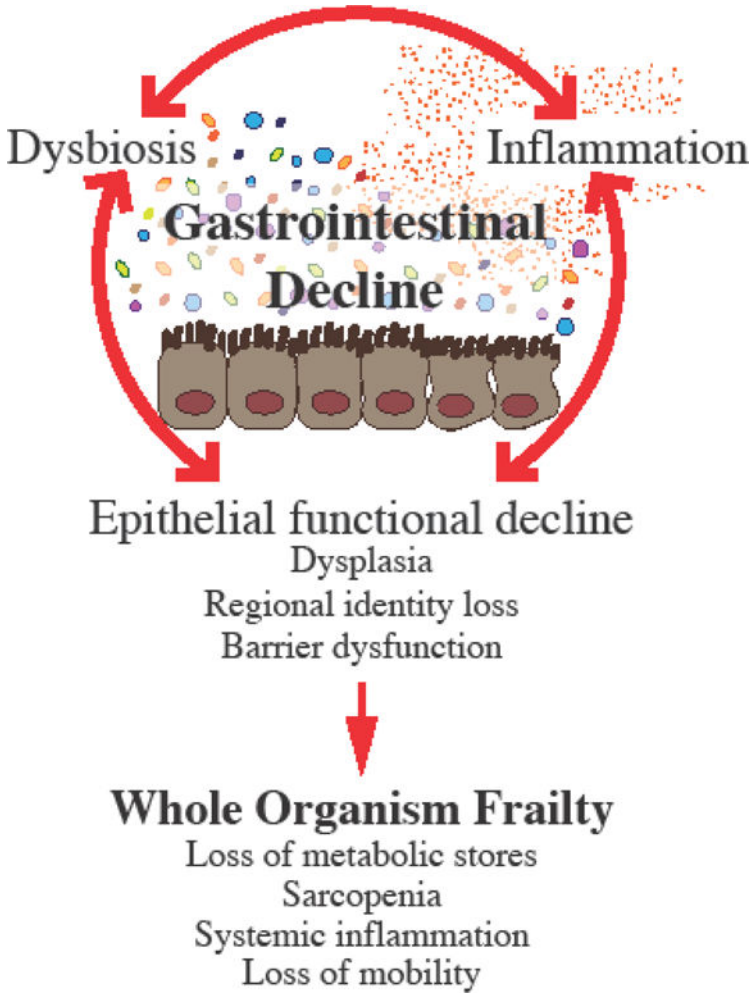

Figure 1. Age-related gastrointestinal decline drives whole organism frailty

The cause and effect relationships between age-related dysbiosis, immune activation and functional decline of the intestinal epithelium are unclear. The experimental systems available in the worm and fly are currently being used to identify the molecular mechanisms that underlie these complex relationships.