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OPINION ARTICLE

Gut microbiota as a candidate for lifespan extension: an ecological/evolutionary perspective targeted on living organisms as metaorganisms

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Abstract An emerging central concept in evolutionary biology suggests that symbiosis is a universal characteristic of living organisms that can help in understanding complex traits and phenotypes. During evolution, an integrative circuitry fundamental for survival has been established between commensal gut microbiota and host. On the basis of recent knowledge in worms, flies, and humans, an important role of the gut microbiota in aging and longevity is emerging. The complex bacterial community that populates the gut and that represents an evolutionary adapted ecosystem correlated with nutrition appears to limit the accumulation of pathobionts and infections in all taxa, being able of affecting the efficiency of the host immune system and exerting systemic metabolic effects. There is an urgent need to disentangle the underpinning molecular mechanisms, which could shed light on the basic mechanisms of aging in an ecological perspective. Thus, it appears possible to extend healthy aging and lifespan by targeting the host as a metaorganism by manipulating the complex symbiotic ecosystem of gut microbiota, as well as other possible ecosystems of the body.

Keywords Gut microbiota · Aging · Longevity · Hormesis · Worms · Flies · Humans · Symbiosis evolution

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Introduction

According to the assumption that the basic mechanisms of aging have been shared across species during evolution and within the emerging ecological perspective that symbiosis is a pervasive characteristics of living organisms (McFall-Ngai 2008), we will critically reviewed data on the role of gut microbiota (GM) in modulating lifespan in classical model systems (worms and flies), as well as in humans. GM, despite its crucial role at the crossroad among nutrition, infection or immunity and metabolism, has not received an adequate attention as a major possible regulator of lifespan. A fragmented set of data collectively suggests that manipulation of GM increases lifespan in model systems, suggesting an

evolutionary-based possible strategy to extend healthy aging in humans, where profound alterations of GM occur with age.

Evolutionary forces that shaped the human microbiota co-evolution

With a density of 10^{12} organisms per gram of luminal content diversified in <1000 bacterial species (Turnbaugh et al. 2007; Garrett et al. 2010), the human GM is indubitably the biggest, the most diverse, specific, and temporary stable symbiont microbial community of our body (Costello et al. 2009; Turnbaugh et al. 2010). In recent years, an immense scientific effort allowed a better comprehension of the complexity and biological role of GM in the biology and pathophysiology of human beings (Turnbaugh et al. 2010). The increasing perception of the fundamental role exerted by GM in human physiology culminates in the revision of human beings as metaorganisms, result of a close symbiotic relationship with microorganisms living in the gastrointestinal tract (Ley et al. 2008).

The 90% of the human GM is constituted by members belonging to two dominant divisions, *Firmicutes* and *Bacteroidetes*, while *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia* are the only subdominant divisions that populate the human gastrointestinal tract. Even, if only few divisions colonized the human gastrointestinal tract, they differentiated 1,800 genera and 16,000 phylotypes at species level, of which, each person, possesses a dynamic and specific subset of 160 species (Rajilić-Stojanović et al. 2007).

Essential for the metabolism of complex plant polysaccharides, the biosynthesis of vitamins and the regulation of fat storage, our microbial counterpart increases our capacity to extract energy from diet (Neish 2009; Candela et al. 2010). Recent studies carried out on germ free and gnotobiotic mice demonstrated that the development, education, and homeostasis of the intestinal immune system strictly depend on the intense and dynamic cross-talk with the intestinal microbiota (Sansonetti and Medzhitov 2009). Finally, precluding the colonization from allochthonous microorganisms and strengthening the gastrointestinal epithelial barrier, GM defends the host from colonization by pathogenic microorganisms.

Human aging is characterized by a decline or remodelling in the functionality of the immune system due to a process known as "immunosenescence" that favours a chronic low-grade inflammatory status called "inflamm-aging" (Franceschi 2007; (Franceschi et al. 2007); Larbi et al. 2008; Ostan et al. 2008). From this perspective, aging can be considered as an immune disorder. Taking into account the strong impact of GM on the physiology of immune responses (Kau et al. 2011), it can be predicted that this complex micro-ecosystem can have a profound influence in the process of human aging and immunosenescence, as well as in a variety of diseases, including of age-related syndromes such as frailty (Biagi et al. 2010, 2011; Candela et al. 2011; Kau et al. 2011).

Owing to its complex long adaptive history, a comprehensive evolutionary perspective is necessary in order to appreciate the remote causes of the dynamics that govern the impact of GM on human longevity. The "Neolithic revolution" (10,000 years ago) witness the transition from small and isolated hunting gathering populations to the high dense Neolitic agricultural societies (De Filippo et al. 2010). With the introduction of agriculture and animal husbandry, food resources became more abundant and constant and, for the first time in human history, the population size dramatically increased. Such a concentration of a large population in a limited area created the selective pressure for the appearance of pathogens specialized in colonizing the human host (Blaser and Kirschner 2007). Moreover, the rapidly changing human environment characteristic of these new emerging human societies increased the complexity of the environmental antigenic load, challenging the homeostasis of human beings. On the other hand, according to the "grandmother hypothesis" (Ley et al. 2008), complex Neolithic societies favoured for the first time in human evolution post-menopausal longevity in our ancestors. The support of grandmothers in the nourishment of children allowed more pregnancies in the daughters, and thus a greater reproductive fitness. Within this context the microbial counterpart became of greater importance for human longevity. We surmise that the immunomodulatory properties of GM likely favoured post-menopausal longevity by counteracting "inflamm-aging" and "immunosenescence" (Biagi et al. 2010, 2011). Furthermore, symbiont intestinal microorganisms

provided a strategic fitness advantage for the human beings living the Neolithic agricultural revolution by protecting the host from pathogen colonization and enhancing the plasticity of the immune system. Finally, dietary change in the Neolithic agricultural societies due to agricultural practice likely induced a substantial re-adaptation of GM, favouring microbial communities capable to ferment these new complex polysaccharides to short chain fatty acids (Hehemann et al. 2010).

Human microbiota in modern societies

Modern societies and industrialization exert a dramatic impact on the microbial ecology of human environments (Blaser and Falkow 2009). According to the "hygiene hypothesis" (Blaser and Falkow 2009), modern western-type societies favoured changes in human ecology that strongly reduced the microbial diversity of the human microenvironments, including the GM. The widespread use of antibiotic, sanitation, increase in Cesarian section, clean water, and increased use of bathing and showering concur in a profound decrease of the biodiversity of the human microenvironments. According to the "old friend" hypothesis, the simplification of the human microenvironments prompted a general shrinkage of the microbial communities inhabiting the human body. Moreover, the western-type diet reach in sugars, animal fat, and calorie-dense foods, is slowly reshaping the human GM by reducing its complexity and biodiversity (Turnbaugh et al. 2009). Thus, the mixture of dietary and environmental changes in globalized western-type societies is prompting a progressive simplification and reduction of the overall biodiversity of the human GM (De Filippo et al. 2010). It has been recently hypothesized that this shrinkage of the intestinal microbiota is probably on the basis of several new and emerging immunological diseases in western developed countries. The progressive disappearance of the functional microbial component of the human immune system can contribute to the decrease of its resilience and homeostasis, and to the emerging of disorders, such as allergy, autoimmune disorders, obesity, inflammatory bowel diseases, and type II diabetes (Rawls 2007; Jia et al. 2008; Neish 2009; Candela et al. 2010; Kau et al. 2011; Maslowski and Mackay 2011).

In order to avoid such a tendency to a reduction of the GM biodiversity, attention should be paid to modulate diet with the aim of feeding the GM with complex polysaccharides contained in plant material and starches.

GM, diet, and immunity in *Caenorhabditis elegans* longevity: an hormetic perspective

The nematode *C. elegans* has been originally used since 1970, as a model system to study the genetic control of development (Brenner 2009), but it soon became widely used also to study apoptosis and aging (Hengartner 1997).

The discovery that *C. elegans* can be infected and killed by pathogenic bacteria, such as *Pseudomonas aeruginosa, Micobacterium nematophilum*, or *Salmonella typhimurium* (Tan et al. 1999; Hodgkin et al. 2000; Labrousse et al. 2000), and that in turn, it possesses an inducible innate immune system to defend itself against bacterial infection (Mallo et al. 2002), made *C. elegans* a fundamental model organism to study the host-pathogen interaction. Since, then the straightforward *C. elegans* genetics, which allows to make detailed epistatic analyses and to monitor changes in its gene expression profile (Irazoqui et al. 2008; Shivers et al. 2008), along with the fact that in common laboratory settings, worms are cultivated on bacteria and their persistence or accumulation into the animal intestine can be easily quantified, permit the detailed study of host-pathogen interactions at the organism, cellular, and molecular levels.

So far, only two papers have directly investigated the effects on *C. elegans* longevity and resistance to infection, when feeding it with *Lactobacilli* and *Bifidobacteria* (LAB), the most common form of non-pathogenic microbiota (Ikeda et al. 2007; Komura et al. 2010). In their first study, the authors fed worms either with standard bacterial *Escherichia coli* or with *Lactobacilli* or with *Bifidobacteria* and look at animal lifespan and resistance to *Salmonella enterica* infection (Ikeda et al. 2007). They fed worms for three days on regular *E. coli* and then transferred animals on plates containing *Lactobacilli* or *Bifidobacteria*. All animals shifted on LAB had significantly extended lifespan compared to animals fed with non-pathogenic bacteria for their entire life.

Moreover, while animals infected with *S. enterica,* seven days after feeding on non-pathogenic bacteria rapidly died, LAB feeding also significantly retarded death after *Salmonella* infection. The protective role of LAB against host infection was further supported by results showing that feeding with *Bifidobacteria* prevented worm infection and death by *Legionella pneumophila,* in comparison to animals fed with *E. coli* (Komura et al. 2010).

Four possible non-mutually exclusive mechanisms could explain the protective effect exerted by probiotics against aging and infection (Naidu et al. 1999).

(i) Reduced pathogenicity: The increased animal defense and longevity could be due to decreased probiotics pathogenicity. Yet, Ikeda et al. (2007) showed that heat killed non-pathogenic bacteria increased animal lifespan, but not as much as LAB did, and therefore there must be factors other than intrinsic bacterial pathogenicity which explain LAB prolonged longevity.

(ii) Altered diet regimen*:* Nematodes have the ability to discriminate between good and bad source of bacterial food (Rankin 2006; Shtonda and Avery 2006), and can only eat bacteria of certain size (Avery and Shtonda 2003; Fang-Yen et al. 2009). Therefore, it is possible that they might not like or might not be able to eat certain probiotic bacteria and undergo a sort of diet restriction.

(iii) Direct protective activity: LAB may directly have a positive effect on immune response acting as protective barrier, but the authors suggest this is unlikely in their experimental setting in that LAB were digested as food (they did not recovered them from the animals) (Ikeda et al. 2007). The authors also exclude that LAB protective activity is exerted by bactericidal factors expressed or released by LAB, because they found that the number of *Salmonella* cells recovered from worms fed LAB was the same as that recovered from worm grown on non-pathogenic bacteria. LAB could nevertheless exert their antibacterial action by expressing or releasing protective factors, such as wall cell components, which act at the level of bacteria-host interaction, or activate host defense or prevent/clear the accumulation of pathogen toxic components.

(iv) Hormesis: the process by which beneficial and protective biological response to low exposures to stressors that at a higher intensity are harmful has been proposed as a potential strategy to prevent or delay the onset of diseases, as well as aging (Calabrese et al. 2007). This phenomenon has also been referred to as conditioning or adaptive response, or hormesis (Calabrese et al. 2007; Le Bourg and Rattan 2008; Rattan 2008). Many of the environmental factors that improve health and prolong lifespan (i.e. dietary restriction, exercise, cognitive stimulation) exert their beneficial effects through hormesis-like mechanisms (Arumugam et al. 2006). Probiotic bacteria may also induce a hormetic-like phenomenon by mildly stimulating the immune system to be more effective in responding to subsequent infection of pathogenic bacteria. In *C. elegans* daf-16/FOXO and p53/cep-1 regulate the hormetic extended longevity in response to different kind of mild stressors (Cypser et al. 2006; Ventura et al. 2009) and they are both required for animal defense against infection (Evans et al. 2008; Fuhrman et al. 2009).

As in higher eukaryotes, *C. elegans* immune system efficiency declines with aging (Kurz et al. 2003; Laws et al. 2004). As animals grow older they are more sensitive to bacterial infection (Laws et al. 2004), and even non-pathogenic bacteria (OP50) accumulate more easily in old worms and become opportunistic (due to difficulty to properly grind bacteria and decreased antimicrobial intestinal content). Animals grown on heat- or UV-killed OP50 bacteria live longer than those fed live bacteria (Garigan et al. 2002). In laboratory settings, different components of the worm diet (Collins et al. 2006; Yang et al. 2009), different sources of non-pathogenic bacterial food (Reinke et al. 2010), and of bacterial constituents (Lenaerts et al. 2008; Saiki et al. 2008) can modulate worm longevity. Different forms of dietary restriction were shown to increase *C. elegans* lifespan impinging on common and unique longevity-regulatory pathways (Greer and Brunet 2009).

It is interesting to note that in *C. elegans*, as in higher eukaryotes, an intense communication between the nervous and the immune systems occurs

(Zhang and Zhang 2009). The structural and functional simplicity of the two systems in *C. elegans* are facilitating our understanding of neuronal-immune coordination at molecular, cellular, and organism levels. The emerging scenario is that the different signalling pathways that are activated likely depend on the site of infection (intestine or epidermis) and on the type of pathogen, with the coordinated action of the nervous system.

Thus, also in light of the very few experimental evidences utilizing LAB as food source in *C. elegans*, one strategy to ameliorate resistance to pathogens and concurrently prolong healthy lifespan could be through manipulation of animal diet. Clearly, a more thoughtful investigation of the interaction between animal diet and the neuroimmune system is necessary in order to unravel mechanistic aspects of LAB on animal longevity.

GM, diet, and immunity in insect longevity

Several papers addressed the relationship between bacteria and insects in term of defense (e.g. insect pathogens and antimicrobial peptides) (Mandrioli et al. 2003; Brivio et al. 2005; Schmidt et al. 2005; Brown and Hancock 2006; Lemaitre and Hoffmann 2007; Lazzaro 2008; Müller et al. 2008; Mandrioli 2009; Malagoli and Mandrioli 2010).

The interaction between insects and bacteria has been studied with particular attention to non-pathogenic bacteria, including ecto- and endo-symbionts (Dillon and Dillon 2004), and GM resulted to be involved not only in the degradation of specific substances in the food (Brummel et al. 2004), but also in other complex interactions protecting the host from invasion by pathogenic microorganisms (a process known as "colonization resistance") and modulating the insect immune system (Dillon and Charnley 1996; Ryu et al. 2008). These interactions seem to be altered during insect aging and to affect their lifespan (Brummel et al. 2004; DeVeale et al. 2004).

The study of colonization resistance in the desert locust *Schistocerca gregaria* showed that locust gut microbiota reflects the environment and the relationship between host and microbes is mutualistic (Dillon and Charnley 1996), providing an additional barrier to protect the host from invasion by pathogenic microorganisms.

In germ free locusts, axenic populations died prematurely due to infection of pathogens such as *P. aeruginosa*, *Penicillium* spp., and *Bacillus subtilis* (Charnley et al. 1995; Dillon and Charnley 1996; Dillon and Charnley 2005), suggesting that they are more susceptible to infection than normal insects (Dillon and Charnley 2005). Axenic locusts are deprived of a non-specific immunization normally carried out by the resident GM, and GM itself could exert a protective function as gut bacteria can outcompete potentially harmful organisms (Dillon et al. 2005). The involvement of GM in the colonization resistance is intriguing, since the composition of the bacterial community that populate the insect gut is not stable, but can change during lifespan due to variation in the nutritional composition of the food and the aging process (DeVeale et al. 2004), and indeed changes in the GM composition affect the longevity and the fitness of *Drosophila* (Min and Benzer 1997; Fry and Rand 2002; Star and Cline 2002).

In *Drosophila,* experiments using axenic cultures and antibiotic treatment showed that the presence of bacteria during the first week of adult life enhanced longevity by 30–35%. Conversely, the presence of bacteria in the last stage of life caused a slight decrease (Brummel et al. 2004). Long-lived flies mutants EcR^{v559fs} for ecdysone receptor were slightly affected by presence or absence of bacteria, whilst long-lived mutants *DJ817* presented a beneficial effect from early bacteria stimulus, suggesting that genetic enhancers and suppressors mediating the effect of bacteria on longevity.

In addition, a growing number of recent studies in *Drosophila* directly examined the relationships between microbes, gut, and aging. As a whole, these studies demonstrated that during natural aging the gut of *Drosophila* undergoes dramatic alterations in immune and homeostatic properties, both in terms of the regulation of pathways important to these processes (Biteau et al. 2008; Choi et al. 2008; Buchon et al. 2009) and in the health and maintenance of the tissue integrity (Biteau et al. 2010). Interestingly, this age-related deterioration of gut homeostasis is not only associated with shifts in GM composition and density (Ryu et al. 2008; Buchon et al. 2009), but appears to be directly linked to the presence of GM, as germ free flies do not exhibit these age-related phenotypes (Buchon et al. 2009).

GM, diet, and immunity in *Homo sapiens* longevity

Does the human intestinal microbiota age? How does it change with aging? To answer these questions, culture-independent molecular characterization techniques have been recently utilized to investigate the dynamics of aging of the human GM (Rajilić-Stojanović et al. 2009; Biagi et al. 2010; Claesson et al. 2011). Even, if it is impossible to define exactly an "age threshold" for the starting of GM aging, it is generally accepted that >70–80 years could represent a limit beyond which an aged GM is present (Biagi et al. 2011).

Indeed, a great individual variability in reaching such a turning point can be predicted, as a consequence of different genetic background and ethnicity, socio-economic status, and lifestyle, diet, and health status. Molecular studies revealed that an aged human GM shows unbalances among the principal bacterial phyla such as *Firmicutes*, *Bacteroidetes*, and facultative anaerobes. In the *Firmicutes* domain, a decrease of bacteria belonging to *Clostridium* cluster XIVa has been reported in subject aged 74–94 years and this dysmicrobism correlated with frailty (Mäkivuokko et al. 2010). Bacteria belonging to the *Faecalibacterium prausnitzii*, a subset of the *Clostridium* cluster IV, have been reported to decrease significantly in aged human GM (Müller et al. 2006). At variance with *Firmicutes*, *Bacteoidetes* the second most abundant phyla in human GM, showed an age-related trend which is apparently highly country-dependent. While Rajilić-Stojanović et al. (2007) reported a decrease in *Bacteroidetes* in aged people from Northern Europe, Müller et al. (2006) showed an inverse tendency in German population. In the literature, there is a general agreement to report a significant increase of facultative anaerobes in the aged human GM (Gavini et al. 2001; Woodmansey et al. 2004; Müller et al. 2006; Mariat et al. 2009; Rajilić-Stojanović et al. 2009; Mäkivuokko et al. 2010). Facultative anaerobes include *Streptococci*, *Staphylococci*, *Enterococci*, and most important *Enterobacteria*. This last group includes pathobionts, potential pathogens that are subdominant in a healthy GM, but which in certain circumstances, such as immunological failure or major dysbiosis can overgrowth and cause diseases (Sansonetti 2011).

To understand how dysbiosis of the aged human GM impacts on the longevity of the host, we must consider the architecture and dynamics of the cross-talk between intestinal microorganisms and host immune system. The close association with an astonishing number of bacterial cell living in proximity with the intestinal mucosal surfaces forced the evolution of a gut-associated lymphoid tissue (GALT) capable to control and simultaneously to tolerate intestinal microorganisms (Hooper and Macpherson 2010). Enterocytes play a primary role in such a process by monitoring proximity and density on intestinal bacteria, thus, coordinating the GALT immunological barriers to tolerance or responsiveness, depending on the perceived degree of treats (Sansonetti and Medzhitov 2009).

The largest part of the resident microbiota lives away from the epithelial surface as a complex biofilm embedded in the soft upper portion of the mucus layer. These luminal commensals, such as members of the *Clostridium* cluster XIVa and *Bacteroidetes*, prompt epithelial cells to secrete tolerance signals that maintain the local dendritic cells in a quiescent state (Macdonald and Monteleone 2005; Neish 2009). When such cells present antigens to native CD4+ T-cells, they drive the differentiation of specialized regulatory CD4+ T-cells (Treg) population besides the effectors pro-inflammatory CD4+ T-helper cells (TH1, TH2, and TH17). Anti-inflammatory Treg promotes tolerance by preventing inflammatory response through the biosynthesis of anti-inflammatory cytokines (Hooper and Macpherson 2010). Concomitantly, antigen presentation to B-cells drives their differentiation to IgA secreting plasma cells. Strain specific secretory IgAs are synthesized and bound to the mucus layer coating epithelial surface. By preventing adherence of microorganisms and neutralizing toxins or enzymes, IgAs exert an important role to restrict microorganisms in the intestinal lumen. At variance with the majority of luminal commensals, subdominant pathobionts can venture deeper in the mucus layer and establish a close interaction with the epithelial surface. In this context, enterocytes rise a pro-inflammatory response that drive dendritic cells to differentiate of effectors TH1 and TH17 cells that induce a strong inflammatory response to face and control pathobionts (Maynard and Weaver 2009).

The dynamics of cross-talk signals between GM and the GALT immune system allows the host to tolerate and to control the whole microbial complexity

of GM by a "constitutive low grade physiological inflammation" state. This continuous level of a low physiological inflammatory tone, essential to preserve the symbiotic nature of the microbiota-host relationship, is also indispensable for the development, education, homeostasis, and functionality of the human immune system (Noverr and Huffnagle 2004). However, under pathological circumstances, pro-inflammatory pathobionts escape surveillance, compromise homeostasis, and consolidate the inflammatory state. The bloom of pathobionts tip the balance from the low physiological inflammation to a high inflammatory state (Round and Mazmanian 2009), rising a self-sustained pro-inflammatory response that impacts the entire microbial ecology of human GM. Within such a scenario, we can interpret the impact of GM on human longevity assuming that an healthy GM, largely dominated by commensal *Firmicutes* and *Bacteroidetes* damps inflammation and promotes host homeostasis by consolidating a "constitutive low grade physiological inflammation". The immunomodulatory properties of a healthy human GM could face and slow down "inflamm-aging" and "immunosenescence", thus favouring longevity. Conversely, an aged GM, enriched in pathobionts and anaerobes, and depleted in anti-inflammatory *Firmicutes*, such as *Clostridium* cluster XIVa and *F. prausnitzii*, will contribute to the development of an overall pro-inflammatory profile (Biagi et al. 2010, 2011). A pro-inflammatory microbial community can contribute to a systemic inflammation and promote the process of "inflamm-aging", by establishing a self-sustained inflammatory loop detrimental for host longevity. Indeed, the age related proliferation of pathobionts has been positively correlated to an increase of pro-inflammatory signals, such as IL-6 and IL-8 (Biagi et al. 2010). Even, if a direct involvement of the GM in "inflamm-aging" has still to be experimentally determined, inflammatory disorders, such as inflammatory bowel diseases and irritable bowel syndrome have been associated with pro-inflammatory unbalances of the intestinal microbiota analogous to the ones that characterized an aged GM (Neish, 2009). It is thus reasonable to predict that GM aging has a strong impact on aging and age-related diseases (Biagi et al. 2010, 2011; Cevenini et al. 2010; Candela et al. 2011).

We surmise that GM likely have a complex and largely underestimated role in human aging, owing to its complex interaction with "immunosenescence" and "inflamm-aging", as well as in energy availability and metabolism, which in turn appear to play a major role in the aging of most organs and tissues, as well as in most common age-related diseases (De Martinis et al. 2006; Ostan et al. 2008). While, an healthy profile of the intestinal microbial community support human longevity, its transition to and aged type contributes to aging. Since, there is not a fixed "age threshold" after which the human microbiota become "aged", it is of primary importance to understand the genetic and environmental factors that impact the aging of the human GM. In this perspective, it is of primary importance to investigate how environmental or behavioural variables, such as the lifestyle, nutritional habit, and ethnicity, besides genetics, concur to define the individual "age threshold" at with GM is affected by the aging process, with the aim to preserve as long as possible GM integrity. Studies in this direction will allow to implement dietary interventions aimed to preserve the health profile of the GM during human aging (Franceschi 2007).

Final remarks

On the whole, the data here reviewed suggest that a new approach, targeted on living organisms as meta-organisms is possible to maintain healthy aging and prolong lifespan. Until recently, the most studied symbiotic ecological system has been the GM, owing to its crucial importance for nutrition, immunity, and infectious diseases. However, there are other microbial ecosystems in other districts of the body (skin, respiratory, and reproductive organs, among others), which are waiting for a similar approach regarding their possible contribution to the aging phenotype. In particular, the composition and richness of the GM appears to be an important component that interacts with the host immune system, capable of affecting fertility, fitness, and lifespan in three major ways. First, an healthy GM prevents death by infections and increases longevity ("whatever doesn't kill you makes you stronger"). Second, the healthy GM can limit the accumulation of pathogen-related molecules that could be toxic (Candela et al. 2011). Third, changes in the composition of GM from an healthy profile to an aged one impinge upon the activity or function of the immune system affecting host lifespan by modulating

"immunosenescence" and "inflamm-aging" (Weksler et al. 2009). On the whole, it emerges that during animal evolution, an ancestral, integrative circuitry of increasing complexity, crucial for survival and healthy aging, and involving nutrition, GM and immunity has been established and maintained. In view of such a conservation of the role of GM, it could be possible to plan experiment aimed to extend healthy aging and lifespan by targeting the host as a metaorganism. Peculiar dietary interventions, such as age specifically oriented pre- and pro-biotics, as well as new possible strategies (transplants of appropriate GM; engineering of GM bacterial species to produce specific age-oriented products or metabolites) can and likely should be employed for a rational manipulation of the complex symbiotic ecosystem of GM.

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