PLOS PATHOGENS

PEARLS

# Microbiome evolution during host aging

**Francisco Daniel Davila Aleman, Dario Riccardo Valenzano***

Max Planck Institute for Biology of Ageing, Cologne, Germany

* dvalenzano@age.mpg.de

## Host–microbiota interactions

Commensal microbes and their multicellular eukaryotic hosts constitute a highly integrated system—termed the holobiont [1]—which undergoes dynamic changes through time as it integrates and responds to signals from the environment.

Dwelling at the interface between host epithelia and the external environment, commensal microbes actively modulate development, nutrient absorption, and disease onset in the host. Host metabolism is significantly modulated by commensal microbes, and the gut microbial composition significantly affects blood metabolite composition [2].

Microbial communities differ among epithelia, reaching the highest complexity and taxonomic diversity in the oral cavity and in the gastrointestinal tract [3, 4]. Environmental factors, such as diet, drug use, and social environment, shape the composition of epithelia-associated microbiota [5–7], and environmental heterogeneity—rather than host genetics—can explain much of the interindividual differences in microbiota composition in humans [8]. The assembly of specific host-associated communities, however, is also dictated by the host cell composition and activity, by the molecular components of the mucus layer, by the gut peristaltic contractility [9], and by epithelial integrity [10]. In primates, recent evidence supports that host phylogenetic relatedness and gut physiology are overall better predictors of microbiota composition than diet [11]. Together, the microbiota is a dynamic community, subject to changes in conjunction with host evolution and through the lifetime of individual hosts.

## Microbiota changes through time

Just as the composition of the microbiota varies within and between tissues [12], microbial consortia do also vary through time within individual tissues. Microbial composition in the gut of newborns is dramatically shaped by diet and varies depending on whether the infant is fed with maternal milk [13] or formula [14]. Drug administration and antibiotic use importantly shape the host gut microbiota, leading to significant community shifts and increased abundance of otherwise rare microbial taxa [15]. Although individual gut microbiota are largely unstable in the first years of life, they become more stable during adulthood [13, 16] and undergo dramatic changes in richness and composition upon onset of disease and frailty [17, 18]. The onset of specific diseases, such as cancer, obesity, diabetes, or inflammatory bowel disease (IBD), is associated with specific microbial signatures [19, 20]. Studies in humans and laboratory model organisms, such as flies, fish, and mice, have additionally shown that the composition of the gut microbiota dramatically changes during aging and is associated with host health and life span [17, 21–24]. In mice, e.g., lipopolysaccharide (LPS) from gut microbiota can accelerate age-dependent inflammation ("inflammaging") [25], and mice lacking Toll-Like receptor 4 (TLR4), which is the LPS receptor, are protected from age-dependent inflammation [26], showing that a microbial-specific substrate induces aging-specific phenotypes. Inflammaging can be further





**Citation:** Aleman FDD, Valenzano DR (2019) Microbiome evolution during host aging. PLoS Pathog 15(7): e1007727. https://doi.org/10.1371/journal.ppat.1007727

**Editor:** John M. Leong, Tufts Univ School of Medicine, UNITED STATES

**Published:** July 25, 2019



**Funding:** The authors received no specific funding for this study.

**Competing interests:** The authors have declared that no competing interests exist.

exacerbated in germ-free mice by gut microbiota transfers from aged donor mice [27], showing a direct causal relation between age-specific microbial communities and host aging.

Using deep learning to analyze human microbiome data helped build a human microbiome aging clock, which predicts host age with an accuracy of about 4 years [28]. While during adulthood microbial composition contributes to cellular and tissue homeostasis [29, 30], age-dependent changes in the microbial composition may contribute to increasing frailty and disease onset in later life. The causes leading to the changes in microbiota composition and function during host aging are still poorly understood and possibly include direct or indirect microbial selection by the host and microbe–microbe interactions, as well as microbial evolution.

## Host aging induces shifts to the microbial niche

As they age, organisms accumulate molecular damage (e.g., in DNA and proteins) [31, 32], dysfunctional organelles [33], and senescent cells [34] and undergo compositional changes in the extracellular compartment [35, 36]. Together, these molecular and functional changes lead to organ and systemic decline, which ultimately results in death. Constantly exposed to a changing environment, the microbiota dynamically respond by altering both metabolic function and individual bacterial species composition. The immune system of the host plays a key role in shaping commensal microbial communities by selectively eliminating pathogens and allowing commensals to thrive. During aging, progressive or sudden immune dysfunction and generalized inflammation lead to improper surveillance at the interface between the host and the microbiota, which can result in dysbiosis—an imbalance in bacterial community composition [37]. In humans, young-associated microbiota are enriched with bacterial taxa shown to have immune-modulatory functions, such as Clostridiales and *Bifidobacterium*, whereas old-associated bacterial communities are enriched with pathobionts—e.g., Enterobacteriaceae—and, overall, have a higher representation of Proteobacteria [23, 38]. Here, we argue that the shifting host environment occurring in the time scale of host life is compatible with inter- and intraspecies microbial competition and with the evolution of novel bacterial strains that could become overrepresented in older hosts, leading to emergence of pathogenic strains that may contribute to age-dependent host decline (Fig 1). Age-dependent immune decline could therefore enable the evolution of bacterial strains responsible for elderly-specific bacterial infections.

## Evolution in commensal bacteria

Studies in both germ-free and conventionally raised laboratory mice, which carry a taxonomically complex microbial community, have shown that bacteria in the gut acquire several advantageous mutations, de facto evolving [39] both in short (months) and long (years) time scales [40]. Changes in mutation rates, emergence of novel individual gene variants, and widespread horizontal gene transfer are essential for microbial adaptations, enabling evolution of drug (e.g., antibiotics) resistance and dynamic response to dietary changes [41]. Experiments in mice colonized with *Escherichia coli* have shown clonal interference and parallel phenotypic evolution in the gut, occurring from the emergence of several adaptive genetic variants that reach intermediate frequencies, rather than reaching fixation (i.e., maximum frequency), within individual bacterial species. The coexistence of several strains carrying adaptive variants, each at intermediate frequencies (also known as soft sweeps), sustains genetic diversity within bacterial species of the microbiota [39]. Microbial adaptation in the gut in response to specific selective regimes, such as antibiotics, shows convergent evolution at the gene-variant and functional level [40]. In humans, gut commensal microbes undergo local adaptation and bona fide evolution of new strains via nucleotide substitution and recombination in short time scales, whereas ecological dynamics—consisting in species replacement—are the dominant mechanisms over longer time

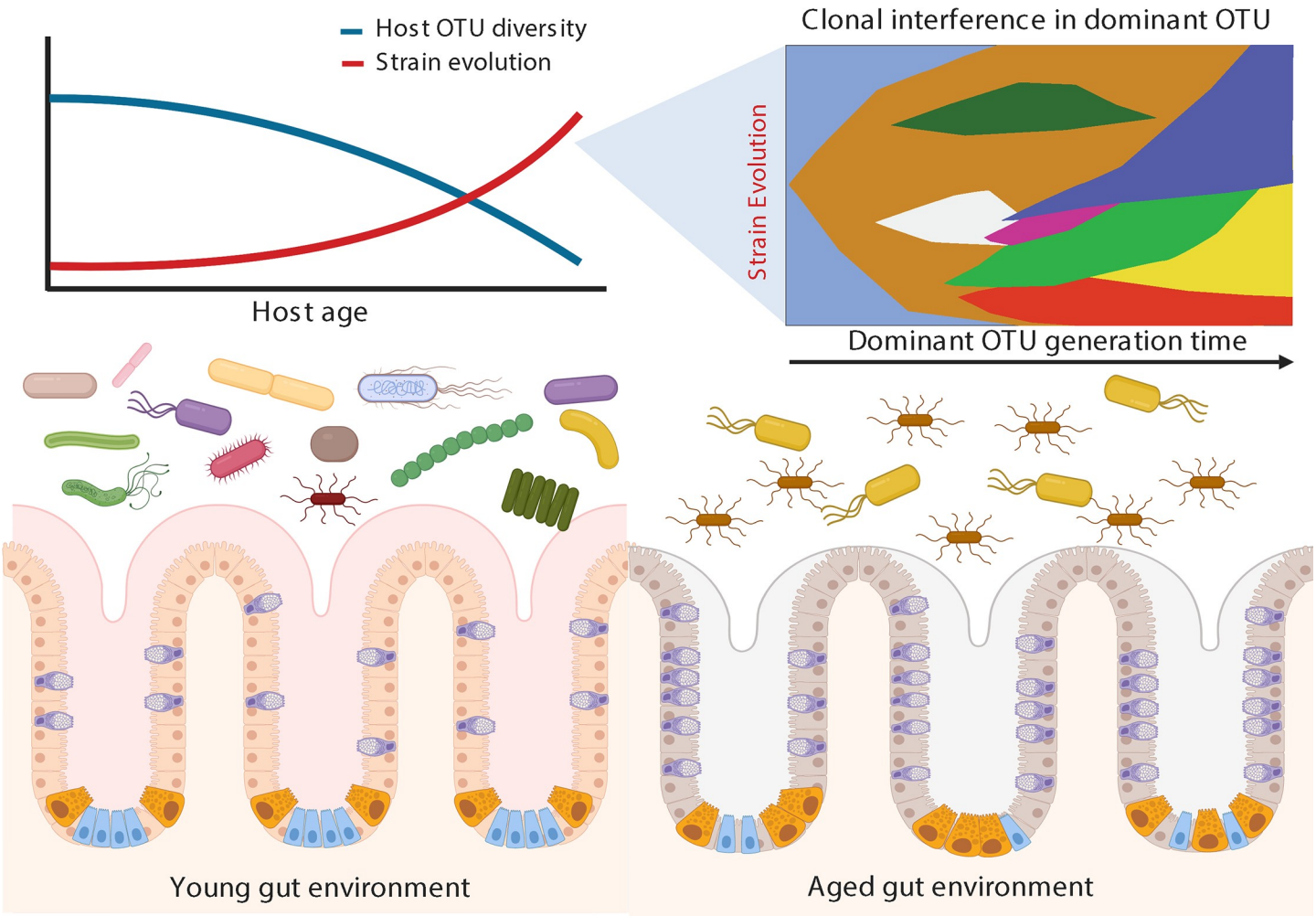


**Fig 1. The gut microbiota undergoes dynamic changes during host aging.** Changes in host intestinal cell composition and architecture occurring during aging are matched by a decrease in the microbiota taxonomic diversity. Age-related decrease in taxonomic diversity in the commensal community leads to larger population size for a few age-associated microbial species, increasing the chances for the evolution of novel potentially pathogenic microbial strains. OTU, Operational Taxonomic Unit. This figure was generated wtih Biorender.

https://doi.org/10.1371/journal.ppat.1007727.g001

scales, e.g., decades [42]. Multiple independent lineages of *Bacteroides fragilis*, each carrying independent small and large-scale genetic variants, are detected in healthy humans [43], showing unique within-individual evolutionary trajectories of commensal microbes.

## Microbial evolution during host aging

Although we are now starting to understand how bacterial taxonomic composition and diversity change during different stages of individual life—including during the aging process—we still know very little about whether bacterial evolution plays an important functional role that can impact host phenotypes and ultimately fitness. We have limited understanding on whether the changes in taxonomic composition of host microbiota occurring through host life in healthy individuals are uniquely due to ecological processes (e.g., species replacement) or whether they are, at least in part, due to bacterial evolution. We still do not know whether bacterial evolution participates in the changes in microbiota composition that occur upon the onset of aging-associated diseases. If bacterial evolution does affect host phenotypes, e.g., by

enabling specific bacterial taxa to escape immune surveillance or by modulating antibacterial responses, do bacterial strains keep evolving across multiple hosts, or is bacterial evolution always local and ends with host death? Studying bacterial evolution within individual host-associated microbiota and throughout the time scale of individual host life presents several technical challenges, but it is becoming ever more accessible due to the increased throughput, accuracy, and resolution reached in genome sequencing and analysis [44]. Furthermore, the integration of multi-omics approaches, which combine genomics and metabolomics of gut microbiota, enables accurate identification and phenotyping of commensal bacteria associated with a broad set of host physiological states [45]. Experimental work done in nematode worms has shown that the resident microbiota can foster mutualism (i.e., reciprocal benefit) with the host by evolving novel defense mechanisms that serve the purpose of excluding potential pathogens [46]. However, it is not clear whether evolution of novel microbe-mediated microbial exclusion also contributes to the community shifts in microbial composition observed during host aging. Screening a library of mutant *E. coli* for effects on nematode worm survival and aging has shown that a set of mutant strains beneficially affect host mitochondrial unfolded protein responses via the secretion of the polysaccharide colanic acid, resulting in increased worm life span [47]. Similar to the way experimenters test sets of different mutants under laboratory conditions, ongoing microbial evolution in healthy hosts leads to the continuous emergence and extinction of bacterial strains that may have either anti- or pro-longevity effects. However, while experimental nematodes are generally fed a specific *E. coli* strain (OP50) [48], complex microbiota likely mask the impact on host fitness of individual bacterial strains emerging within specific bacterial species. For a bacterial strain to impact host physiology and fitness, it is necessary to first succeed among competing strains, including the ancestral strain, and then become a functionally relevant member of the microbiota. It is therefore likely that novel strains may have higher chances to succeed in simple microbial communities, characterized by lower taxonomic complexity. Since during aging and frailty the overall microbial taxonomic diversity declines, it may indeed become more likely for new strains within dominant taxa to sweep to high frequency and affect the host.

## Aging modulation via young-associated gut microbes

Whether microbial evolution in the time scale of individual life affects homeostatic processes within the host is still an open question. Experimental research provides us with important insights into how manipulating the microbiota can significantly affect host health. Combining a specific diet with genetically engineered *E. coli* that bind colorectal cancer cells, it was recently possible to achieve cancer prevention and regression in a mouse model of colorectal cancer [49]. Genetically engineering microbes could indeed be a therapeutic strategy to compensate for genetic and metabolic deficiencies and potentially improve host health [50]. Commensal microbes have been proposed as a therapeutic target for cancer immunotherapy [51] and could be even targeted for interventions aimed at counteracting the metabolic dysfunctions occurring during aging. Recent work in model organisms indicates that host-associated bacteria have the potential to beneficially modulate host health, aging, and life span [18, 23, 52]. Commensal microbes do play a key role in several phenotypic and metabolic changes associated with aging. For instance, the age-dependent onset of insulin resistance has recently been associated with the action of commensal microbes with the host immune system [18]. Work with the naturally short-lived African turquoise killifish (*Nothobranchius furzeri*) [53, 54] has shown that acute transfer of gut microbes from young donor individuals to middle-age recipients, after antibiotic treatment, is sufficient to significantly extend life span and delay behavioral aging [23]. Metabolic and cellular changes occurring during aging, coupled with

immune senescence and inflammaging [55], generate new metabolic and cellular niches, which could lead to competition and potentially create novel selective constraints for the evolution of new strains within dominant bacterial taxa.

## Conclusion

The interactions between the host and its commensal microbes reach homeostatic balance during youth and adulthood, resisting insults from several external factors, including pathogens. Perturbations to this homeostatic balance can derive from changes in the environment, in diet, and from exposure to drugs such as antibiotics. However, challenges to the host–microbiota balance can also derive from intrinsic factors within the host, i.e., from the vast constellation of alterations that occur during the aging process, including cellular senescence, inflammation, and cancer. On the other hand, microbe–microbe interactions within the host could in principle also lead to host–microbiota disbalance, which could in turn contribute to host aging. Whether the microbiota adapt to the physiological changes occurring during host aging, or whether they actively participate to host dysfunction, remains an important open question. Understanding host–microbiota dynamics during host aging will critically inform future therapeutic interventions. If the microbiota exacerbate the cellular, tissue, and systemic changes that occur during host aging, then targeting the microbiota could, in theory, help therapeutically relieve some of the aging-related pathologies but would, in principle, not impact systemic aging. On the other hand, if the microbiota causally participate in triggering host aging, then interventions that target the microbiota could result in systemic, preventative, and bona fide anti-aging interventions.

## References


1. Margulis L, Fester R. Symbiosis as a source of evolutionary innovation. Speciation and Morphogenesis.: MIT Press; 1991.
2. Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. Proc Natl Acad Sci U S A. 2009; 106 (10):3698–703. Epub 2009/02/24. https://doi.org/10.1073/pnas.0812874106 PMID: 19234110; PubMed Central PMCID: PMC2656143.
3. Human Microbiome Project C. Structure, function and diversity of the healthy human microbiome. Nature. 2012; 486(7402):207–14. Epub 2012/06/16. https://doi.org/10.1038/nature11234 PMID: 22699609; PubMed Central PMCID: PMC3564958.
4. Clemente JC, Pehrsson EC, Blaser MJ, Sandhu K, Gao Z, Wang B, et al. The microbiome of uncontacted Amerindians. Sci Adv. 2015; 1(3). Epub 2015/08/01. https://doi.org/10.1126/sciadv.1500183 PMID: 26229982; PubMed Central PMCID: PMC4517851.
5. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014; 505(7484):559–63. Epub 2013/12/18. https://doi.org/10.1038/nature12820 PMID: 24336217; PubMed Central PMCID: PMC3957428.
6. Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. Nature. 2018; 555(7698):623–8. Epub 2018/03/21. https://doi.org/10.1038/nature25979 PMID: 29555994; PubMed Central PMCID: PMC6108420.
7. Song SJ, Lauber C, Costello EK, Lozupone CA, Humphrey G, Berg-Lyons D, et al. Cohabiting family members share microbiota with one another and with their dogs. Elife. 2013; 2:e00458. Epub 2013/04/20. https://doi.org/10.7554/eLife.00458 PMID: 23599893; PubMed Central PMCID: PMC3628085.
8. Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, et al. Environment dominates over host genetics in shaping human gut microbiota. Nature. 2018; 555(7695):210–5. Epub 2018/03/01. https://doi.org/10.1038/nature25973 PMID: 29489753.
9. Rolig AS, Mittge EK, Ganz J, Troll JV, Melancon E, Wiles TJ, et al. The enteric nervous system promotes intestinal health by constraining microbiota composition. PLoS Biol. 2017; 15(2):e2000689. Epub 2017/02/17. https://doi.org/10.1371/journal.pbio.2000689 PMID: 28207737; PubMed Central PMCID: PMC5331947.

10. Donaldson GP, Lee SM, Mazmanian SK. Gut biogeography of the bacterial microbiota. Nat Rev Microbiol. 2016; 14(1):20–32. Epub 2015/10/27. https://doi.org/10.1038/nrmicro3552 PMID: 26499895; PubMed Central PMCID: PMC4837114.

11. Amato KR, J GS, Song SJ, Nute M, Metcalf JL, Thompson LR, et al. Evolutionary trends in host physiology outweigh dietary niche in structuring primate gut microbiomes. ISME J. 2018. Epub 2018/07/12. https://doi.org/10.1038/s41396-018-0175-0 PMID: 29995839.

12. Sommer F, Backhed F. Know your neighbor: Microbiota and host epithelial cells interact locally to control intestinal function and physiology. Bioessays. 2016; 38(5):455–64. Epub 2016/03/19. https://doi.org/10.1002/bies.201500151 PMID: 26990415.

13. Stewart CJ, Ajami NJ, O'Brien JL, Hutchinson DS, Smith DP, Wong MC, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature. 2018; 562(7728):583–8. Epub 2018/10/26. https://doi.org/10.1038/s41586-018-0617-x PMID: 30356187.

14. Forbes JD, Azad MB, Vehling L, Tun HM, Konya TB, Guttman DS, et al. Association of Exposure to Formula in the Hospital and Subsequent Infant Feeding Practices With Gut Microbiota and Risk of Overweight in the First Year of Life. JAMA Pediatr. 2018; 172(7):e181161. Epub 2018/06/06. https://doi.org/10.1001/jamapediatrics.2018.1161 PMID: 29868719; PubMed Central PMCID: PMC6137517.

15. Hildebrand F, Moitinho-Silva L, Blasche S, Jahn MTT, Gossmann TI, Heuerta Cepas J, et al. Antibiotics-induced monodominance of a novel gut bacterial order. Gut. 2019. Epub 2019/01/20. https://doi.org/10.1136/gutjnl-2018-317715 PMID: 30658995.

16. Bokulich NA, Chung J, Battaglia T, Henderson N, Jay M, Li H, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci Transl Med. 2016; 8(343):343ra82. Epub 2016/06/17. https://doi.org/10.1126/scitranslmed.aad7121 PMID: 27306664; PubMed Central PMCID: PMC5308924.

17. O'Toole PW, Jeffery IB. Gut microbiota and aging. Science. 2015; 350(6265):1214–5. Epub 2016/01/20. https://doi.org/10.1126/science.aac8469 PMID: 26785481.

18. Bodogai M, O'Connell J, Kim K, Kim Y, Moritoh K, Chen C, et al. Commensal bacteria contribute to insulin resistance in aging by activating innate B1a cells. Sci Transl Med. 2018; 10(467). Epub 2018/11/16. https://doi.org/10.1126/scitranslmed.aat4271 PMID: 30429354.

19. Fulbright LE, Ellermann M, Arthur JC. The microbiome and the hallmarks of cancer. PLoS Pathog. 2017; 13(9):e1006480. Epub 2017/09/22. https://doi.org/10.1371/journal.ppat.1006480 PMID: 28934351; PubMed Central PMCID: PMC5608396.

20. Ni J, Wu GD, Albenberg L, Tomov VT. Gut microbiota and IBD: causation or correlation? Nat Rev Gastroenterol Hepatol. 2017; 14(10):573–84. Epub 2017/07/27. https://doi.org/10.1038/nrgastro.2017.88 PMID: 28743984; PubMed Central PMCID: PMC5880536.

21. Clark RI, Salazar A, Yamada R, Fitz-Gibbon S, Morselli M, Alcaraz J, et al. Distinct Shifts in Microbiota Composition during Drosophila Aging Impair Intestinal Function and Drive Mortality. Cell Rep. 2015; 12(10):1656–67. Epub 2015/09/01. https://doi.org/10.1016/j.celrep.2015.08.004 PMID: 26321641; PubMed Central PMCID: PMC4565751.

22. Langille MG, Meehan CJ, Koenig JE, Dhanani AS, Rose RA, Howlett SE, et al. Microbial shifts in the aging mouse gut. Microbiome. 2014; 2(1):50. Epub 2014/12/19. https://doi.org/10.1186/s40168-014-0050-9 PMID: 25520805; PubMed Central PMCID: PMC4269096.

23. Smith P, Willemsen D, Popkes M, Metge F, Gandiwa E, Reichard M, et al. Regulation of life span by the gut microbiota in the short-lived African turquoise killifish. Elife. 2017; 6. Epub 2017/08/23. https://doi.org/10.7554/eLife.27014 PMID: 28826469; PubMed Central PMCID: PMC5566455.

24. Thevaranjan N, Puchta A, Schulz C, Naidoo A, Szamosi JC, Verschoor CP, et al. Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction. Cell Host Microbe. 2017; 21(4):455–66 e4. Epub 2017/04/14. https://doi.org/10.1016/j.chom.2017.03.002 PMID: 28407483; PubMed Central PMCID: PMC5392495.

25. Kim KA, Jeong JJ, Yoo SY, Kim DH. Gut microbiota lipopolysaccharide accelerates inflamm-aging in mice. BMC Microbiol. 2016; 16:9. Epub 2016/01/17. https://doi.org/10.1186/s12866-016-0625-7 PMID: 26772806; PubMed Central PMCID: PMC4715324.

26. Ghosh AK, O'Brien M, Mau T, Yung R. Toll-like receptor 4 (TLR4) deficient mice are protected from adipose tissue inflammation in aging. Aging (Albany NY). 2017; 9(9):1971–82. Epub 2017/09/13. https://doi.org/10.18632/aging.101288 PMID: 28898202; PubMed Central PMCID: PMC5636669.

27. Fransen F, van Beek AA, Borghuis T, Aidy SE, Hugenholtz F, van der Gaast-de Jongh C, et al. Aged Gut Microbiota Contributes to Systemical Inflammaging after Transfer to Germ-Free Mice. Front Immunol. 2017; 8:1385. Epub 2017/11/23. https://doi.org/10.3389/fimmu.2017.01385 PMID: 29163474; PubMed Central PMCID: PMC5674680.

28. Galkin F, Aliper A, Putin E, Kuznetsov I, Gladyshev VN, Zhavoronkov A. Human microbiome aging clocks based on deep learning and tandem of permutation feature importance and accumulated local effects. bioRxiv. 2019. https://doi.org/10.1101/507780.

29. Belkaid Y, Harrison OJ. Homeostatic Immunity and the Microbiota. Immunity. 2017; 46(4):562–76. Epub 2017/04/20. https://doi.org/10.1016/j.immuni.2017.04.008 PMID: 28423337; PubMed Central PMCID: PMC5604871.

30. Hergott CB, Roche AM, Tamashiro E, Clarke TB, Bailey AG, Laughlin A, et al. Peptidoglycan from the gut microbiota governs the lifespan of circulating phagocytes at homeostasis. Blood. 2016; 127 (20):2460–71. Epub 2016/03/19. https://doi.org/10.1182/blood-2015-10-675173 PMID: 26989200; PubMed Central PMCID: PMC4874226.

31. Morimoto RI, Cuervo AM. Protein homeostasis and aging: taking care of proteins from the cradle to the grave. J Gerontol A Biol Sci Med Sci. 2009; 64(2):167–70. Epub 2009/02/21. https://doi.org/10.1093/gerona/gln071 PMID: 19228787; PubMed Central PMCID: PMC2655025.

32. Vaidya A, Mao Z, Tian X, Spencer B, Seluanov A, Gorbunova V. Knock-in reporter mice demonstrate that DNA repair by non-homologous end joining declines with age. PLoS Genet. 2014; 10(7):e1004511. Epub 2014/07/18. https://doi.org/10.1371/journal.pgen.1004511 PMID: 25033455; PubMed Central PMCID: PMC4102425.

33. Zhou C, Slaughter BD, Unruh JR, Guo F, Yu Z, Mickey K, et al. Organelle-based aggregation and retention of damaged proteins in asymmetrically dividing cells. Cell. 2014; 159(3):530–42. Epub 2014/11/25. https://doi.org/10.1016/j.cell.2014.09.026 PMID: 25417105.

34. Childs BG, Durik M, Baker DJ, van Deursen JM. Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nat Med. 2015; 21(12):1424–35. Epub 2015/12/10. https://doi.org/10.1038/nm.4000 PMID: 26646499; PubMed Central PMCID: PMC4748967.

35. Ewald CY, Landis JN, Porter Abate J, Murphy CT, Blackwell TK. Dauer-independent insulin/IGF-1-signalling implicates collagen remodelling in longevity. Nature. 2015; 519(7541):97–101. Epub 2014/12/18. https://doi.org/10.1038/nature14021 PMID: 25517099; PubMed Central PMCID: PMC4352135.

36. Elderman M, Sovran B, Hugenholtz F, Graversen K, Huijskes M, Houtsma E, et al. The effect of age on the intestinal mucus thickness, microbiota composition and immunity in relation to sex in mice. PLoS ONE. 2017; 12(9):e0184274. Epub 2017/09/13. https://doi.org/10.1371/journal.pone.0184274 PMID: 28898292; PubMed Central PMCID: PMC5595324.

37. Li H, Qi Y, Jasper H. Preventing Age-Related Decline of Gut Compartmentalization Limits Microbiota Dysbiosis and Extends Lifespan. Cell Host Microbe. 2016; 19(2):240–53. Epub 2016/02/13. https://doi.org/10.1016/j.chom.2016.01.008 PMID: 26867182; PubMed Central PMCID: PMC5106289.

38. Quercia S, Candela M, Giuliani C, Turroni S, Luiselli D, Rampelli S, et al. From lifetime to evolution: timescales of human gut microbiota adaptation. Front Microbiol. 2014; 5:587. Epub 2014/11/20. https://doi.org/10.3389/fmicb.2014.00587 PMID: 25408692; PubMed Central PMCID: PMC4219431.

39. Barroso-Batista J, Sousa A, Lourenco M, Bergman ML, Sobral D, Demengeot J, et al. The first steps of adaptation of Escherichia coli to the gut are dominated by soft sweeps. PLoS Genet. 2014; 10(3): e1004182. Epub 2014/03/08. https://doi.org/10.1371/journal.pgen.1004182 PMID: 24603313; PubMed Central PMCID: PMC3945185.

40. Lescat M, Launay A, Ghalayini M, Magnan M, Glodt J, Pintard C, et al. Using long-term experimental evolution to uncover the patterns and determinants of molecular evolution of an Escherichia coli natural isolate in the streptomycin-treated mouse gut. Mol Ecol. 2017; 26(7):1802–17. Epub 2016/10/19. https://doi.org/10.1111/mec.13851 PMID: 27661780; PubMed Central PMCID: PMC5734618.

41. Sousa A, Frazao N, Ramiro RS, Gordo I. Evolution of commensal bacteria in the intestinal tract of mice. Curr Opin Microbiol. 2017; 38:114–21. Epub 2017/06/08. https://doi.org/10.1016/j.mib.2017.05.007 PMID: 28591676.

42. Garud NR, Good BH, Hallatschek O, Pollard KS. Evolutionary dynamics of bacteria in the gut microbiome within and across hosts. PLoS Biol. 2019; 17(1):e3000102. Epub 2019/01/24. https://doi.org/10.1371/journal.pbio.3000102 PMID: 30673701.

43. Zhao S, Lieberman TD, Poyet M, Groussin M, Gibbons SM, Xavier RJ, et al. Adaptive evolution within the gut microbiome of individual people. bioRxiv. 2018. https://doi.org/10.1101/208009.

44. Pasolli E, Asnicar F, Manara S, Zolfo M, Karcher N, Armanini F, et al. Extensive Unexplored Human Microbiome Diversity Revealed by Over 150,000 Genomes from Metagenomes Spanning Age, Geography, and Lifestyle. Cell. 2019. Epub January 17, 2019. https://doi.org/10.1016/j.cell.2019.01.001.

45. Zierer J, Jackson MA, Kastenmuller G, Mangino M, Long T, Telenti A, et al. The fecal metabolome as a functional readout of the gut microbiome. Nat Genet. 2018; 50(6):790–5. Epub 2018/05/29. https://doi.org/10.1038/s41588-018-0135-7 PMID: 29808030; PubMed Central PMCID: PMC6104805.

46. King KC, Brockhurst MA, Vasieva O, Paterson S, Betts A, Ford SA, et al. Rapid evolution of microbe-mediated protection against pathogens in a worm host. ISME J. 2016; 10(8):1915–24. Epub 2016/03/16. https://doi.org/10.1038/ismej.2015.259 PMID: 26978164; PubMed Central PMCID: PMC5029159.

47. Han B, Sivaramakrishnan P, Lin CJ, Neve IAA, He J, Tay LWR, et al. Microbial Genetic Composition Tunes Host Longevity. Cell. 2017; 169(7):1249–62 e13. Epub 2017/06/18. https://doi.org/10.1016/j.cell.2017.05.036 PMID: 28622510; PubMed Central PMCID: PMC5635830.

48. Girard LR, Fiedler TJ, Harris TW, Carvalho F, Antoshechkin I, Han M, et al. WormBook: the online review of Caenorhabditis elegans biology. Nucleic Acids Res. 2007; 35(Database issue):D472–5. Epub 2006/11/14. https://doi.org/10.1093/nar/gkl894 PMID: 17099225; PubMed Central PMCID: PMC1669767.

49. Ho CL, Tan HQ, Chua KJ, Kang A, Lim KH, Ling KL, et al. Engineered commensal microbes for diet-mediated colorectal-cancer chemoprevention. Nature Biomedical Engineering. 2018; 2:27–37. https://doi.org/10.1038/s41551-017-0181-y PMID: 31015663

50. Donia MS. A Toolbox for Microbiome Engineering. Cell Syst. 2015; 1(1):21–3. Epub 2016/05/03. https://doi.org/10.1016/j.cels.2015.07.003 PMID: 27135687.

51. Zitvogel L, Ma Y, Raoult D, Kroemer G, Gajewski TF. The microbiome in cancer immunotherapy: Diagnostic tools and therapeutic strategies. Science. 2018; 359(6382):1366–70. Epub 2018/03/24. https://doi.org/10.1126/science.aar6918 PMID: 29567708.

52. Gould AL, Zhang V, Lamberti L, Jones EW, Obadia B, Korasidis N, et al. Microbiome interactions shape host fitness. Proc Natl Acad Sci U S A. 2018; 115(51):E11951–E60. Epub 2018/12/05. https://doi.org/10.1073/pnas.1809349115 PMID: 30510004; PubMed Central PMCID: PMC6304949.

53. Harel I, Valenzano DR, Brunet A. Efficient genome engineering approaches for the short-lived African turquoise killifish. Nat Protoc. 2016; 11(10):2010–28. Epub 2016/09/23. https://doi.org/10.1038/nprot.2016.103 PMID: 27658015.

54. Hu CK, Brunet A. The African turquoise killifish: A research organism to study vertebrate aging and diapause. Aging Cell. 2018; 17(3):e12757. Epub 2018/03/25. https://doi.org/10.1111/acel.12757 PMID: 29573324; PubMed Central PMCID: PMC5946070.

55. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018; 14(10):576–90. Epub 2018/07/27. https://doi.org/10.1038/s41574-018-0059-4 PMID: 30046148.