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STATE-OF-THE-ART REVIEW

'Inside Out'– a dialogue between mitochondria and bacteria

Bing Han[1,2], Chih-Chun Janet Lin[2,3,4], Guo Hu[2,3] and Meng C. Wang[2,3,5]

1 Children's Hospital, Fudan University, Minhang, Shanghai, China
2 Huffington Center on Aging, Baylor College of Medicine, Houston, TX, USA
3 Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA
4 Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY, USA
5 Howard Hughes Medical Institute, Houston, TX, USA

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Correspondence
M. C. Wang, Huffington Center on Aging, Baylor College of Medicine, One Baylor Plaza MS: BCM230, Houston, TX 77030, USA
Fax: +1 713-798-4161
Tel: +1 713-798-1566
E-mail: wmeng@bcm.edu

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Mitochondria play crucial roles in regulating metabolism and longevity. A body of recent evidences reveals that the gut microbiome can also exert significant effects on these activities in the host. Here, by summarizing the currently known mechanisms underlying these regulations, and by comparing mitochondrial fission–fusion dynamics with bacterial interactions such as quorum sensing, we hypothesize that the microbiome impacts the host by communicating with their intracellular relatives, mitochondria. We highlight recent discoveries supporting this model, and these new findings reveal that metabolite molecules derived from bacteria can fine-tune mitochondrial dynamics in intestinal cells and hence influence host metabolic fitness and longevity. This perspective mode of chemical communication between bacteria and mitochondria may help us understand complex and dynamic environment–microbiome–host interactions regarding their vital impacts on health and diseases.

Introduction

As described by the predominant endosymbiotic theory, the origin of intracellular organelles, mitochondria, can be traced back to bacterial cells that accidentally form a symbiotic relationship with some methanogenic archaea billions of years ago [1–3]. While relying on carbon organics provided by the host cells, the proto-mitochondria also conducted respiration to pay back with considerably more energy, leading to an enormous evolutionary advantage and eventually gave rise to the present thriving kingdom of eukaryotes. Numerous comparative molecular studies have demonstrated that mitochondria evolved from Rickettsiales bacteria [4–9] (Fig. 1). In addition to this obligate endosymbiosis, eukaryotes possess their 'external symbionts' – hundreds of bacterial species that colonize body surfaces and cavities [10]. The gut microbiome inhabiting the digestive tract is a good reprehensive of these symbionts, which shows stable composition over time in healthy adults [11] and exerts a substantial impact on the host physiology and pathology [12].

In particular, mitochondria and the gut microbiome both play crucial roles in regulating host metabolism and longevity. Mitochondria and bacteria also share commonalities in terms of intercommunications. Our recent findings further reveal chemical communications between bacteria and host mitochondria, and the specific involvement of these communications in the

Abbreviations
3OC12, *N*-(3-oxo-dodecanoyl)-L-homoserine lactone; AHL, *N*-acyl homoserine lactone; AI-2, autoinducer 2; DRP1, dynamin-related protein 1; MFN, mitofusin; UPR^{mt}, mitochondrial unfolded protein response.

control of metabolic and aging processes. Inspired by these findings, we tentatively propose the hypothesis that mitochondria still possess the remnant abilities of communicating with extracellular bacteria, and the impacts of symbiotic bacteria on the host act largely through modulating mitochondrial activities. We also describe the merits of using the nematode *Caenorhabditis elegans* as a model system in deciphering this microbiome–mitochondria communication.

Mitochondria with bacterial origin signal to the nucleus

The endosymbiotic relationship between mitochondria and eukaryotic cells have been continuously strengthened by evolutionary pressure, resulting in an extensive gene transfer between the two genomes [13,14]. Now in eukaryotic cells, a vast majority of mitochondrial proteins are encoded in the nucleus and transported into mitochondria for maturation following cytoplasmic translation. Mitochondria coordinate many vital metabolic functions such as fatty acid oxidation and oxidative phosphorylation, and serve as the powerhouse to carry out ATP production. Interestingly, these metabolic functions are also

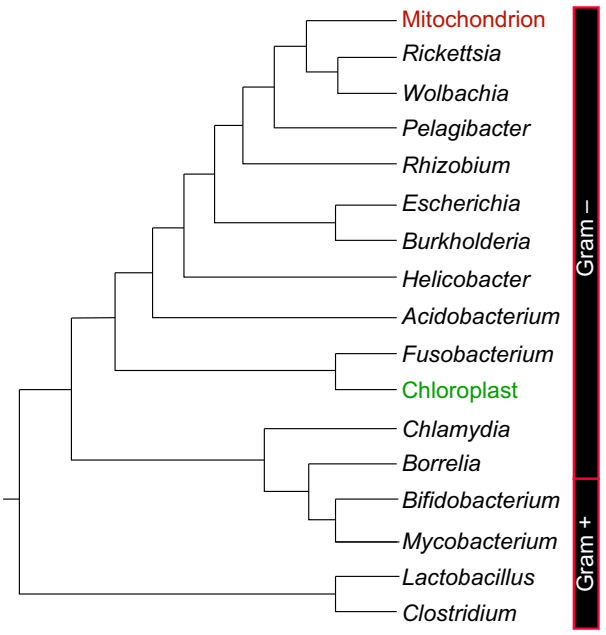

Fig. 1. The cladogram of bacteria showing the origin of mitochondria. This phylogenetic relationship among representative genera of clinical or ecological significance is inferred from previous comparative molecular studies [8,9], with mitochondria highlighted in red. Green color shows chloroplasts, result of another endosymbiosis event from some cyanobacteria. Side bars label the division between Gram negative and positive taxa.

associated with the signaling role of mitochondria in the control of nuclear activities. Retrograde signals from mitochondria act through various transcriptional and epigenetic factors to actively modulate gene expression in the nucleus, such as alpha-ketoglutarate metabolites, reactive oxygen species (ROS), and mitochondrial unfolded protein responses (UPR^{mt}) [15] (Fig. 2). In particular, UPR^{mt} senses the perturbation of the protein-folding environment in mitochondria, and directs the translocation of transcription factors into the nucleus to activate expressions of specific chaperones and proteases [16–18]. This UPR^{mt} signaling process helps restore organelle functionality of mitochondria under different stress conditions [19,20], and consequently plays crucial roles in the regulation of organismal longevity [21,22].

Mitochondrial dynamics regulates metabolism and longevity

Mitochondria are highly dynamic organelles. Although generally depicted as discrete organelles, multiple mitochondria frequently interconnect with each other, forming a large intracellular reticulum and mixing their membrane, matrix, and nucleoid contents [23–25]. At the same time, mitochondria divide constantly to facilitate organelle degradation and recycling [26,27]. A number of guanosine triphosphate hydrolases mediate mitochondrial dynamics: Mitofusin (Mfn1 and Mfn2) dimeric complexes and optic atrophy protein 1 mediate the connection between adjacent mitochondria to facilitate fusion [28,29]; while dynamin-related protein 1 (DRP1) forms ring-like structures to constrict mitochondria where the fission of organelles occurs [30,31]. The matter and information exchange resulting from mitochondrial fusion helps alleviate negative influences from impaired individual organelles [32,33]. On the other hand, selective degradation of damaged mitochondria through mitophagy requires mitochondrial fission [34–37]. Overall, these fusion and fission events keep mitochondria in a dynamic balance and ensure their quality and quantity controls, which are crucial for maintaining a healthy functional mitochondrial network.

Mitochondrial fission–fusion dynamics is tightly linked to mitochondrial bioenergetic functions and metabolic health of cells and organisms [38]. Generally, mitochondrial fusion can greatly increase the efficiency of ATP synthesis [39]. In cultured cells, nutrient withdrawal has been found to promote mitochondrial elongation through inhibiting mitochondrial fission by protein kinase A-mediated DRP1 phosphorylation [39,40] or through facilitating mitochondrial fusion by

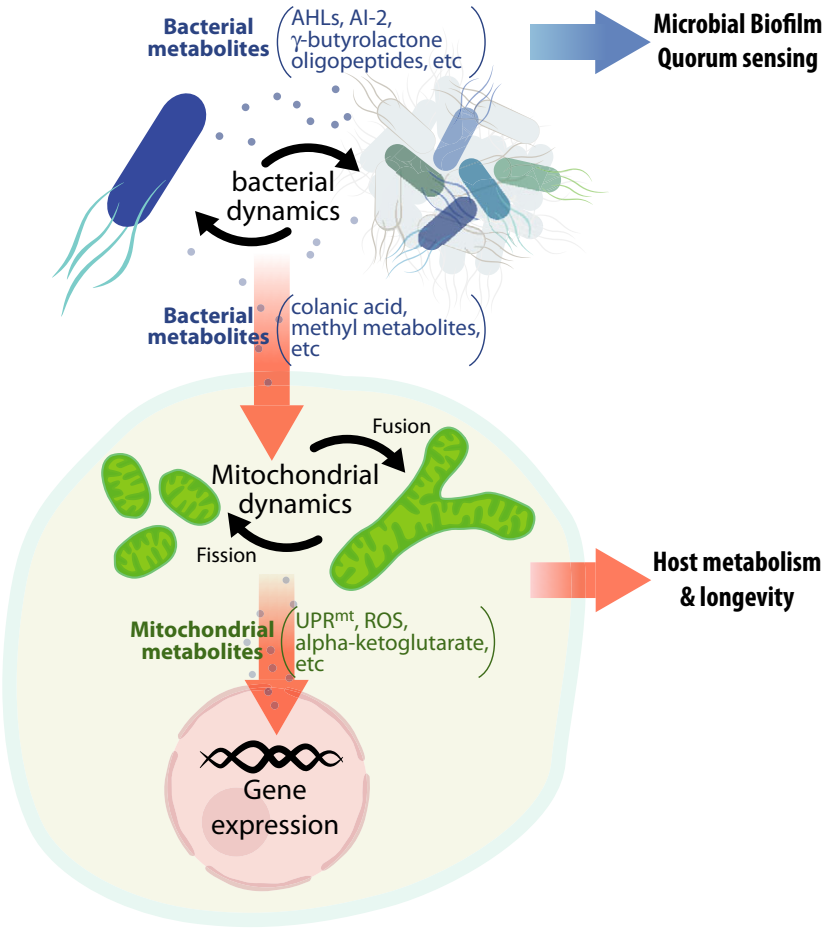

Fig. 2. Molecular communications between bacteria and mitochondria are vital for symbiotic bacteria to regulate metabolism and longevity in the eukaryotic host. Bacteria communicate with each other through biofilm formation and quorum sensing that can be mediated by specific metabolites, such as AHLs, AI-2(furanosyl borate diester), oligopeptides, and Y-butyrolactones. On the other hand, mitochondria undergo organellar fission and fusion and communicate through these dynamic processes. Interestingly, new discoveries reveal that mitochondrial fission–fusion dynamics in the eukaryotic host cell can be regulated by chemical signals from symbiotic bacteria in the form of colanic acid and methyl metabolites. These metabolite-mediated cross-kingdom communications are crucial for host metabolism and longevity.

MFN1 deacetylation [41]. This starvation-induced mitochondrial elongation increases ATP synthesis capacity and efficiency, which sustains the energy demand required under nutrient-limited environments [39]. In contrast, excess nutrients can lead to mitochondrial fragmentation. For example, glucose overload promotes mitochondrial fragmentation in a DRP1-dependent manner [42], and animals feeding on a high-fat diet display reduced levels of MFN2 and enhanced mitochondrial fragmentation [43–46]. Thus, mitochondrial dynamics can be actively influenced by environmental signals and coupled with cellular metabolic status [44,47].

Mitochondrial dynamics is also closely associated with the aging process [48–50]. With senescence, mitochondrial dynamics tends to shift toward fission more than fusion in most of the tissues [50–52], which is likely due to cumulated damages in mitochondria. The fragmentation of mitochondrial network facilitates mitophagy as a protective mechanism [53,54]. However, with advancing age, mitochondrial biogenesis becomes less effective [55], and the ability to maintain the plasticity of fission–fusion dynamics declines. As a result, superfused and swollen mitochondrial morphology is often detected [56–60], which is proposed to compensate for both quality and quantity decreases [48].

Interestingly, manipulation of mitochondrial dynamics is sufficient to modulate both glucose and lipid metabolic homeostasis systemically, and also influences organism longevity. For example, mitochondrial fragmentation driven by MFN2 deletion in muscle and hepatic cells disturbs glucose homeostasis and leads to obesity in aged animals [61]. In contrast, impairment of mitochondrial fission by DRP1 deletion in liver

protects animals from high-fat diet-induced obesity and metabolic disorders [62]. On the other hand, alterations in mitochondrial electron transport chain activities modulate lifespan and healthspan in a variety of organisms, through interplaying with diverse longevity regulatory mechanisms such as insulin and mammalian target of rapamycin signaling, dietary restriction, and autophagy [63–67]. In *C. elegans*, dietary-restricted, AMP-activated, protein kinase-mediated longevity is associated with alterations in mitochondrial fission–fusion dynamics and consequent changes in peroxisome activities [52,68]. It is also shown that mitochondrial fusion is essential for the lifespan extension conferred by reduced insulin/insulin-like growth factor-1 signaling [69]. More recently, studies in *C. elegans* and *Drosophila melanogaster* further discover that a mild induction of mitochondrial fission specifically in intestinal cells is sufficient to promote organism longevity systemically [70,71]. Therefore, mitochondria communicate through their fission–fusion dynamics, which safeguards the homeostasis of these essential cellular organelles and plays a pivotal role in the control of metabolic health and longevity [72].

Bacteria live in a community

The community of bacteria is highly dynamic and interactive. Although conventionally considered unicellular and isolated, bacteria do communicate and cooperate with each other, resembling those cells in multicellular organisms. One typical example in point is myxobacteria. To survive harsh environments, multiple myxobacterial cells can aggregate to form 'swarms' by contact-mediated signaling, for the sake of better moving, feeding, and reproducing [73]. In fact, the interactions between bacterial cells are not limited to a single taxonomical group, as evidenced by formation of biofilms ubiquitously found on our planet, either on abiotic surfaces or in the animal gut. A great variety of bacteria secrete a matrix of extracellular polymeric substances that helps adhesion and links cells together to form a colonial group [74], a process typically triggered by unfavorable environmental factors such as antibiotics [75]. Once embedded in this complex biofilm structure, bacterial cells undergo a lot of behavioral changes, differentially regulate many genes, and frequently exchange their genetic materials [76,77]. As a result, biofilms provide not only protection but also opportunities of communication among otherwise isolated bacterial cells.

Moreover, virtually all bacterial species constitutively produce diffusible chemical signals to alter gene expression of others, referred to as quorum sensing. These signal molecules include certain oligopeptides, *N*-acyl homoserine lactones (AHLs), and autoinducer-2 (AI-2, furanosyl borate diester) that stimulate synthesis and release of themselves among different cells [78,79]. Quorum sensing implies a response to population density, allowing multiple bacterial cells to adjust their growth and activities accordingly. Moreover, this communication is required for multiple bacteria to synchronize their gene expression so that macroscopic effects can be achieved by these tiny organisms. For instance, quorum sensing plays a central role in the production of bioluminescence and in the biofilm formation [80,81]. Although quorum sensing takes place mostly among members of the same species, it is intriguing to note the existence of interspecies communications via quorum sensing. For example, *Escherichia coli* encodes proteins of the LuxR family for detection of AHLs, a quorum-sensing signal released only by other microbes [82]. Moreover, AI-2 is a universal signal mediating interspecies quorum sensing because it is secreted and perceived by a great variety of bacteria [79]. Thus, a bacterial community is highly dynamic and communicative, not only comprising diverse species but also adjusting their activities, sending and receiving signals constantly.

Microbiome influences host metabolism and longevity

Gut microbiome, consisting mainly of bacteria, inhabits the digestive track of the host. An ever-growing body of evidences suggests that the composition and metabolism of the gut microbiome influence metabolic health and aging. First of all, gut bacteria generate metabolic products that directly act on the host. They are responsible for the synthesis of various vitamins to maintain metabolic health of the host [83]. Gut bacteria can also break down many carbohydrates that are otherwise nondigestible, and ferment them into short-chain fatty acids as nutrients to the host, which regulate fatty acid, cholesterol, and glucose metabolism [84,85]. Without them, germ-free mice are significantly leaner than normal mice [86–88]. In addition, primary bile acids are processed by gut bacteria into secondary bile acids that feed back to the liver and influence lipogenesis, gluconeogenesis, and insulin sensitivity in the host [89–92]. Moreover, changes in the host's diet, lifestyle, and medication with antibiotics and other drugs dramatically influence transcriptomic, proteomic, and biochemical profiles of gut bacteria [93–96]. These bacterial changes in turn modulate the susceptibility of the host to environmental insults, dietary intervention, and diseases.

Human gut microbiome is dominated by two major bacterial phyla, Firmicutes, and Bacteroidetes [97]. It is

intriguing that both diet- and genetic-induced obesity are associated with a reduction in Bacteroidetes and a proportional increase in Firmicutes [98–101]. These obese animals also display a less diverse microbiome [102,103]. Conversely, the phylogenetic composition of gut bacteria can determine the onset and progression of obesity, through modulating the efficiency of energy uptake [100,104] and inflammatory responses in the host [105–111]. On the other hand, dietary inputs not only reshape the phylogenetic structure of gut microbiome but also reprogram gene expression and metabolite production in these bacteria [96,112]. The regulatory loop among the environment, gut microbiome and the host is dynamic and complex, which can be mediated by different signaling mechanisms [113,114].

Similarly, changes in gut microbiome are also associated with the aging process in the host [115]. The reduction in bacterial number and diversity especially that of *Bifidobacterium* spp. and *Bacteroides* spp. in the elderly has been reported [116–118]. Furthermore, the microbiome composition is significantly correlated with increased frailty and age-related chronic conditions among old individuals, and diet-driven microbiome alterations have been shown to improve health in elderly people [119]. Studies in model systems show that the growth, proliferation and diversity of gut bacteria are good predictors of longevity [120,121]. Moreover, transplantation of gut microbiome from young to middle-aged killifish prolongs lifespan and healthspan [122]. Not only different bacterial species but also individual bacterial genes are correlated with the longevity regulation in the host. Specific bacterial mutants have been shown to play a causative role in prolonging host lifespan and healthspan [123–126]. Interestingly, some of these beneficial effects are directly linked to specific bacterial metabolites [123–126]. Therefore, an active chemical communication between gut bacteria and the host is essential for organism fitness during aging.

Evidences emerge for a communication between microbiome and mitochondria

Because of their critical roles in determining metabolic health and longevity, both mitochondria and gut bacteria become hot targets in biological and medical investigations. However, studying them with the cellular resolution at the organism level is highly challenging, especially in mammalian models. First, fixation of mammalian tissues for microscopic observations undoubtedly interferes with the regulation of mitochondrial dynamics, and may give limited or misleading results. Secondly, mammalian microbiome is complex, composed of 300–1000 bacterial species with a total number even exceeding that of host cells [127–129]. Plus tremendous individual compositional variations [130,131], isolating any bacterial components for causative or mechanistic analyses would be extremely hard.

The nematode *C. elegans* has been extensively used as a model organism. These soil-dwelling worms exhibit many merits for laboratory manipulations, including their short life time, low price in rearing, known genome as well as the availability of numerous mutants and transgenic lines. Most importantly, some innate features of *C. elegans* make them ideal for studying mitochondrial and bacterial activities that influence host physiology. First of all, their bodies are colorless and transparent. After fluorescently labeling of mitochondrial-targeting sequences, mitochondrial dynamics can be directly viewed *in vivo* with high resolution at the organism level [26]. With a rapid technical progress on lattice light-sheet microscopy [132], an even more detailed real-time super-resolution monitoring of mitochondrial structure and dynamics becomes feasible using *C. elegans* [133].

Furthermore, the gut of *C. elegans* is naturally colonized by a complex community of commensal bacteria whose composition is influenced but distant from the environment [134,135]. This relationship between the host and microbiome resembles that in humans, implicating a valid model. More remarkably, a strain of *C. elegans* has been tamed in laboratories [115]. This strain is reared monoxenically, feeding on and accommodating in the gut a single bacterial clone, which, therefore, carries an accurately defined microbiome. At the same time of enjoying these merits, one should also take necessary cautions to interpret conclusions obtained using *C. elegans*, partly because the typical bacteria used in laboratories, for example, *E. coli* OP50, only colonize aging individuals and this colonization is associated with bacterial pathogenesis [120,121,136]. However, with the simple manipulation of gut bacteria and some proved conservation [137], *C. elegans* still represents an ideal model for studies of microbiome–host interaction. Evidently, utilizing the system of *C. elegans* and their symbiotic bacteria, a lot of insights on microbe–host interactions have been gained [137,138], especially the microbial contributions to metabolism and aging [139–142].

Using *C. elegans*, our recent studies bring light into the interaction between bacteria and mitochondrial dynamics in the gut of the host. These communications are mediated by chemical signals from intestinal bacteria (Fig. 2). In one case, a cluster of bacterial metabolites including betaine, methionine, and homocysteine initiate a signaling cascade that triggers the nuclear

receptor 5A nuclear receptor and activates hedgehog signaling to regulate mitochondrial fission–fusion balance in intestinal cells. This bacteria–mitochondria communication ultimately regulates fat storage homeostasis in the host [112]. In another, a slime polysaccharide named colanic acid, a major biofilm component of *E. coli*, is secreted from intestinal bacteria. After entering the host cytoplasm via endocytosis, colanic acid increases the fragmentation of intestinal mitochondria in a DRP-1-dependent fashion, as well as enhances UPR^{mt} mediated by the transcription factor ATFS-1 in response to mitochondrial stress. These signaling effects of bacterial colanic acid on mitochondrial dynamics and UPR^{mt} consequently lead to lifespan extension and protection against age-associated pathologies, like germline tumor progression and toxic amyloid-beta accumulation, in the host [123]. Together, these results consistently show that mitochondria undergo chemical communication with bacteria, a process modulating metabolic and senescent states of eukaryotic cells.

This view can also be strengthened by our unbiased search for bacterial factors involved in the regulation of host longevity [123]. This genome-wide analysis implicates YceO and LsrC, two bacterial proteins important for biofilm formation and AI-2 transport, and several proteins controlling the level of colanic acid [123]. AI-2 is a key quorum-sensing molecule that has been recorded to interact with eukaryotic cells [143,144], although no mechanisms have been specified. As undergoing exclusive intracellular lives, mitochondria likely preserve their capabilities of, and possibly are responsible for, perceiving quorum-sensing signals. This view gains recent supports from the fact that a signaling molecule secreted by *Pseudomonas aeruginosa* accumulates within mitochondria and regulates cellular functions. In this bacteria–mitochondria interaction, *P. aeruginosa* secrets *N*-(3-oxo-dodecanoyl)-L-homoserine lactone (3OC12), which is hydrolyzed by lactonase paraoxonase 2 in mitochondria to attenuate its toxicity. In the hydrolyzed form, 3OC12 acid stays in the mitochondria and mediates calcium release and stress signaling through intracellular acidification [145]. Collectively, based on these new discoveries, it is reasonable to hypothesize that the microbiome may affect the host by directly interacting with mitochondria through bacterial metabolites and specific signaling mechanisms.

Future perspectives

With our findings and other sporadic evidences, a model that merges functionalities of mitochondria and microbiome is not only merely plausible but also probable. Within the context of our model, we propose that the mitochondria are the mediators for this cross-domain chemical dialogue. This is not to deny the existence of indirect communications from bacteria to mitochondria, such as by regulating nuclear gene expression. But following the Law of Parsimony, a conserved and widespread direct interaction is most likely. A systematic search for signaling molecules sent by gut microbiome, transporting mechanisms across the plasma membrane, and receptors on mitochondrial outer membrane would be essential to confirm this communication.

This model may help us understand many aspects of physiological and pathological regulations by host–microbiome interactions. For example, gut microbiome has been indicated to play vital roles in a number of neurological disorders [146]. Clearly, these bacterial effects on neurons have to occur via cell nonautonomous mechanisms. Other than a way of indiscriminately releasing certain molecules into body fluid, we propose that the dialogue between bacteria and mitochondria likely is the underlying mode of action. On one hand, patients with mutations in several mitochondrial dynamic regulators display neurological symptoms [147–150]; likewise, neurodegeneration and many other diseases have been linked to dysregulation of mitochondrial dynamics [151]. On the other hand, mitochondria within different cells have been shown to communicate with each other, resulting in a cell nonautonomous effect [152]. Hence, the proposed crosstalk exhibits high explanatory power for the function of microbiome in modulating systemic responses of the host, as exampled by metabolism and aging.

There have been quite a few biological phenomena following a 'non-Darwinian' pattern lacking mechanistic explanations. Interesting to note, mitochondria are inherited maternally, and the founding colonies of microbiome in newborns are also from a maternal source [153]. It would be intriguing to hypothesize that the microbiome-mitochondria axis also plays a role in mediating those maternal effects. By many means, a chemical dialogue across the cell membrane, orchestrated by mitochondria and symbiotic bacteria, is promising to broaden our views on biological sciences. We anticipate an era where the mitochondria-microbiome communication is fully characterized, which would shed great light on improving metabolic health and healthy aging.

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