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REVIEW

Bacteria–organelle communication in physiology and disease

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Bacteria, omnipresent in our environment and coexisting within our body, exert dual beneficial and pathogenic influences. These microorganisms engage in intricate interactions with the human body, impacting both human health and disease. Simultaneously, certain organelles within our cells share an evolutionary relationship with bacteria, particularly mitochondria, best known for their energy production role and their dynamic interaction with each other and other organelles. In recent years, communication between bacteria and mitochondria has emerged as a new mechanism for regulating the host's physiology and pathology. In this review, we delve into the dynamic communications between bacteria and host mitochondria, shedding light on their collaborative regulation of host immune response, metabolism, aging, and longevity. Additionally, we discuss bacterial interactions with other organelles, including chloroplasts, lysosomes, and the endoplasmic reticulum (ER).

Introduction

In a world seemingly dominated by our species, boasting an impressive global headcount of 8 billion, a closer examination reveals an astonishing microbial superpower that overshadows our human presence: bacteria. More than a nonillion (10^{30}) of these microorganisms inhabit our planet, encompassing millions of distinct species (Flemming and Wuertz, 2019). Some of them are disease-causing pathogens, while others are essential contributors to human health. Remarkably, a substantial portion of these microorganisms reside as our commensal companions. It is estimated that around 38 trillion bacteria thrive within or upon the average 70-kg male human, surpassing the total count of human cells in the body (~30 trillion) (Sender et al., 2016). An imbalance among commensal bacteria has been linked with pathological alterations (Cho and Blaser, 2012). For example, alterations in the gut microbiome have been associated with a spectrum of ailments, encompassing neurodegenerative diseases, cardiovascular diseases, gastrointestinal diseases, cancers, and more (Cullin et al., 2021; Fang et al., 2020; Jie et al., 2017; Trakman et al., 2022). The gut microbiome's role in modulating aging and longevity further underscores their impact on human health (O'Toole and Jeffery, 2015; Wilmanski et al., 2021).

It is interesting to note that the symbiotic interaction between humans and bacteria extends from the macroscopic to the microscopic scale. Eukaryotic cells, including human cells, harbor a variety of organelles, such as mitochondria, lysosomes, the endoplasmic reticulum (ER), and the nucleus, each with distinctive activities. Mitochondria are the powerhouse of eukaryotic cells, which provide essential energy to support all cellular processes. These organelles also dynamically interact with each other and with other organelles, playing crucial roles in cellular signaling. The prevailing hypothesis suggests that mitochondria originated through an endosymbiotic relationship between bacteria and amitochondriate eukaryote or methanogenic archaea, which eventually led to a blooming diversity of eukaryotic species (Gray et al., 1999; López-García and Moreira, 2020; Martin et al., 2015). Multiple phylogenetic studies suggest a close kinship between mitochondria and the α-proteobacteria Rickettsiales (Andersson et al., 1998, 2003; Fitzpatrick et al., 2006), although recent findings have cast a discerning light on this proposition (Geiger et al., 2023; Martijn et al., 2018; Roger et al., 2017).

Cumulative evidence reveals that pathogens can target mitochondria in the host cell to facilitate their infection, while host cells employ these very organelles in their defense against pathogenic invaders. Emerging studies also uncover that the microbiome influences host physiology through communicating with mitochondria. In this review, we summarize the communication between bacteria and mitochondria, exploring their collaborative role in regulating host disease, aging, and longevity. Furthermore, this review also provides insights into the communications of bacteria with other organelles in addition to

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mitochondria. We define bacteria–organelle communication as the process through which bacteria influence organellar architecture and/or activities, and organelle/bacteria communication as the process through which organelles/bacteria interact with each other via physical contacts and exchanging chemical molecules, such as ions and metabolites.

Origin of mitochondria

The prevailing mitochondrial origin theory, known as the endosymbiotic theory (Gray and Doolittle, 1982; Roger et al., 2017; Sagan, 1967; Schwartz and Dayhoff, 1978; Yang et al., 1985), suggests that mitochondria are descendants of free-living bacterial ancestors via the process of endosymbiosis. The Serial Endosymbiosis Theory, a version of endosymbiotic theory proposed by Lynn Margulis (Gray et al., 1999; Sagan, 1967), suggests that the aerobic mitochondrial endosymbiont, enabling oxygen detoxification and energy production, conferred advantages to the anaerobic host cell. This process eventually led to the evolution of specialized intracellular organelles. An alternative perspective within the endosymbiotic theory, the Hydrogen Hypothesis (Martin and Müller, 1998), shifts the focus away from the primacy of endosymbiosis for energy production via oxidative phosphorylation. Instead, it emphasizes that the association between the host cell and the endosymbiont is primarily driven by the exchange of hydrogen, with the eubacterial symbiont generating hydrogen for use by the hydrogen-dependent host cell. The endosymbiotic theory is supported by the striking similarities between mitochondria and bacteria, including the presence of a double membrane structure, circular double-stranded DNA, tRNA, ribosomes, and enzymes, as well as the ability to undergo replication independently (Pallen, 2011).

Phylogenetic analyses have bolstered the case of mitochondria's bacterial origins (Gray et al., 1999) and illustrated that mitochondria have an alphaproteobacterial ancestry. When considering the closest eubacterial relatives in the alphaproteobacterial taxa, most studies report parasitic Rickettsiales (Andersson et al., 1998, 2003; Fitzpatrick et al., 2006), whereas other studies suggest free-living Rhizobiales, Rhodobacterales, and Rhodospirillales (Atteia et al., 2009; Esser et al., 2004). The variation in the placement of mitochondria is likely due to different phylogenetic approaches that are used in these studies (Roger et al., 2017), as well as the high phylogenetic divergence within Alphaproteobacteria, strong statistical noise and artefactual signals, and limitation of taxonomy (Fan et al., 2020).

Bacteria–bacteria communication

Bacteria and mitochondria not only share evolutionary origins but also exhibit similar communication within their community. To understand how bacterial communities influence the homeostasis of the organelles in the host cells, especially the mitochondria, it is essential to explore how bacteria communicate with each other.

Given the small size of bacteria, it is not surprising that these microorganisms always operate as a community through their intricate communication strategies. One such form of communal existence is the biofilm, which offers various benefits to the bacteria residing within it, compared with free-living bacteria. These benefits include protection against adverse conditions, facilitation of nutrient absorption, creation of localized gradients for habitat diversity, and promotion of social interactions (Flemming et al., 2016). Within the biofilm, bacteria attach to each other and aggregate into clusters, which involves the production of extracellular polymeric substance (EPS) and the formation of the EPS matrix (Fig. 1). Bacteria residing in biofilms can contribute to infectious diseases, exacerbate chronic infections, and incite infections via medical devices by evading host immune responses and antibiotic treatments (Vestby et al., 2020).

Beyond direct cell-to-cell contact, many bacteria can also employ chemical signaling molecules, such as autoinducers, to communicate with each other, a process known as quorum sensing (QS). During QS, bacteria release autoinducers to the surrounding environment, where their external concentration corresponds to the population density (Fig. 1). As the autoinducer accumulates and reaches a critical stimulatory concentration, bacteria start to trigger specific gene expression programs that regulate community behavior (Keller and Surette, 2006; Waters and Bassler, 2005). Interestingly, QS signals in the host gut microbiome not only help inhibit potential pathogens (Piewngam et al., 2018; Wu and Luo, 2021) but also modulate host signaling transduction (Hughes and Sperandio, 2008).

Moreover, bacteria communication is facilitated by outer membrane vesicles (OMVs) originating from the outer surface of bacteria. OMVs serve as messengers, transferring various cargo, such as proteins, metabolites, nucleic acids, and toxins, between bacterial cells (Caruana and Walper, 2020). In particular, OMVs are important for the transport of hydrophobic signals that are not able to freely diffuse out of the cell to induce QS (Toyofuku, 2019; Toyofuku et al., 2017). During infection, OMVs can be internalized by host cells through the endocytosis process, releasing their cargo, such as virulence factors. This process thereby regulates molecular pathways within the host cells and functions of organelles including lysosomes, eventually causing cell damage and suppressing the immune system (O'Donoghue and Krachler, 2016). Understanding these bacteria–bacteria communication cues helps to unravel the complex interactions between bacteria and their hosts.

Mitochondria in response to pathogens

The interactions between pathogenic bacteria and their hosts play a central role in immune response. Bacterial effectors, which are proteins secreted by pathogenic bacteria into the host's cell, target mitochondria to modulate cellular death. Pathogenic bacteria also shape the host's mitochondrial network to facilitate their infection. Importantly, not only do pathogenic bacteria modulate host mitochondria for their own benefit, but the host also utilizes mitochondria for its own defense against bacterial infection.

Bacterial effectors target mitochondria to regulate apoptosis. Bacteria developed diverse secretion systems to transport proteins across their cellular membrane. These secretion systems vary in complexity and function. Type I, III, IV, and VI secretion systems are able to transport effectors across both inner and outer membranes, and even directly into the host cell in the case

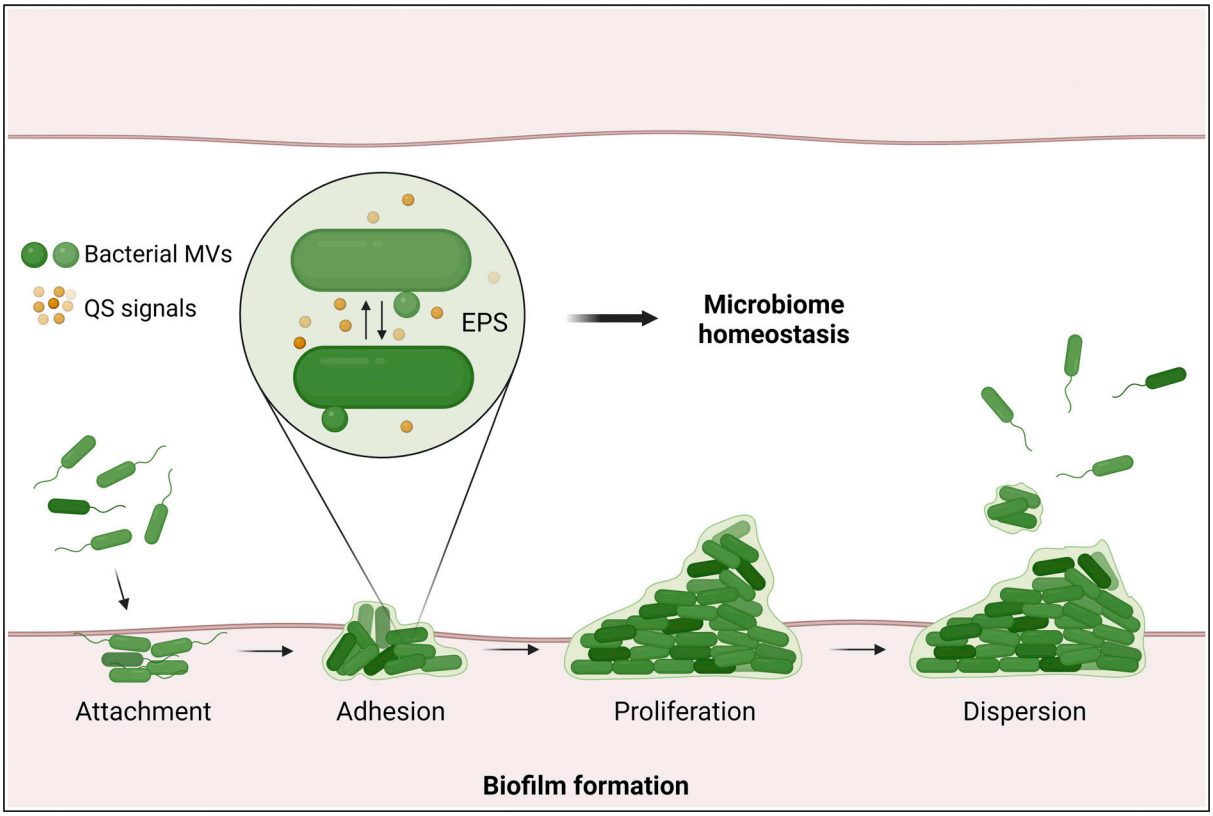


Figure 1. **Bacteria exhibit communal behavior through various communication strategies.** Biofilms serve as a form of communal existence, where bacteria aggregate, forming extracellular polymeric substance (EPS) matrices that offer protection, nutrient absorption, habitat diversity, and social interactions. Bacteria can also employ quorum sensing (QS), releasing signals to coordinate gene expression based on population density. Bacterial membrane vesicles (MVs) facilitate the transfer of diverse cargos, including hydrophobic signals involved in QS.

of type III, IV, and VI secretion systems. On the other hand, type II, V, IX, and XI secretion systems require exportation pathways to transport the effectors into the periplasm before further secretion (Arechaga and Cascales, 2022; Green and Mecsas, 2016).

The effectors of the bacterial type III secretion system (T3SS), which has been reported to be mainly utilized by gram-negative bacteria, have been found to activate or suppress the apoptosis machinery by affecting mitochondria (Nandi et al., 2021). Upon infection, the enteropathogenic *E. coli* secretes numerous effectors, including the T3SS-dependent *E. coli* secreted proteins F (EspF), mitochondrial-associated protein (Map), and *E. coli*-secreted protein Z (EspZ) (Serapio-Palacios and Finlay, 2020). Both EspF and Map possess mitochondria-targeting sequences (MTS) in their N-terminus, allowing their entry into the host mitochondria (Kenny and Jepson, 2000; Nougayrède and Donnenberg, 2004), which results in disrupted mitochondrial membrane potential and apoptosis activation (Ma et al., 2006; Nagai et al., 2005; Ramachandran et al., 2020). On the contrary, EspZ has been found to elicit an anti-apoptotic effect (Shames et al., 2010). How these effectors coordinate with each other to promote enteropathogenic *E. coli* infection remains to be explored. Moreover, the T3SS-dependent effector, invasion plasmid antigen D (IpaD), in the enteroinvasive bacteria *Shigella flexneri* (*S. flexneri*) was reported to disrupt mitochondrial membrane potential and induce apoptosis in macrophages, although its mitochondrial localization has not been confirmed (Arizmendi et al., 2016).

For the bacterial type IV secretion system (T4SS), although it is largely found in gram-negative bacteria, it has also been identified in gram-positive bacteria and archaea (Sheedlo et al., 2022). Ehrlichiosis is a tick-borne disease that is caused by infection of the obligate intracellular bacteria *Ehrlichia chaffeensis* (*E. chaffeensis*). *E. chaffeensis* secretes the T4SS-dependent effector Ehrlichia translocated factor-1 (Etf-1), which targets mitochondria via its MTS and has been reported to be anti-apoptotic (Liu et al., 2012). Interestingly, expressing the nanobody that targets Etf-1 blocks its mitochondrial localization and abrogates its inhibition of etoposide-induced apoptosis in non-human primate cell lines infected with *E. chaffeensis* (Zhang et al., 2021).

There are also non-T3SS and -T4SS effectors that target mitochondria to modulate apoptosis. For example, infection of *Helicobacter pylori (H. pylori)* causes apoptosis in gastric epithelial cells, which is mediated by the secreted vacuolating cytotoxin A (VacA). After endocytosis into the epithelial cell, VacA is imported into mitochondria at the endosome–mitochondria juxtaposition and then inserted into the inner mitochondrial membrane to form an anion-selective pore. The permeabilization of the mitochondrial outer membrane disrupts membrane

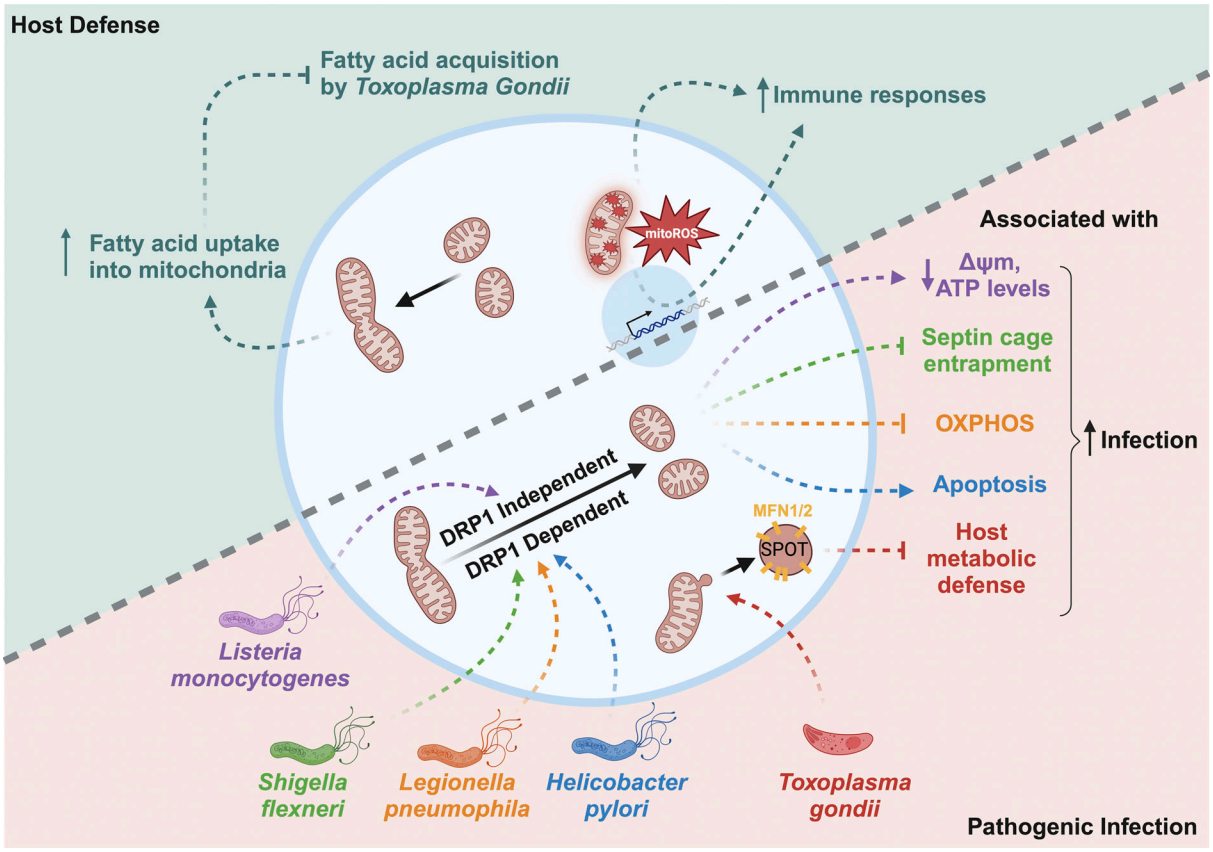


Figure 2. **Pathogens and mitochondria interact during infection.** *Shigella flexneri*, *Legionella pneumophila*, and *Helicobacter pylori* drive mitochondrial fragmentation in a DRP1-dependent manner, while *Listeria monocytogenes* do so via a DRP1-independent mechanism, facilitating pathogenic infection through various pathways. *Toxoplasma gondii* remodels the mitochondria outer membrane into SPOT structure that contains mitochondrial fusion machinery such as MFN1/2, blocking the host metabolic defense and favoring infection. On the other hand, mitochondria serve as the host intracellular response center to defend against bacterial infection via promoting metabolic reprogramming and inducing mitoROS-mediated immune response.

potential, resulting in the release of cytochrome c and the induction of apoptosis (Fig. 2) (Czajkowsky et al., 1999; Domańska et al., 2010; Galmiche and Rassow, 2010; Galmiche et al., 2000; Jain et al., 2011). It was also observed that upon incubation with VacA, Dynamin-related protein 1 (DRP1) is recruited to the mitochondria, leading to mitochondrial fission. Another example is the intracellular bacterium *Legionella pneumophila* (*L. pneumophila*) effector Lpg1137, which inhibits apoptosis through cleavage of syntaxin 17 (Stx17), a protein located at the mitochondria–ER contact site (Arasaki et al., 2017; Hamasaki et al., 2013). Mitochondria-associated ER membranes (MAMs) in the mitochondria–ER contact site have been implicated in the regulation of various crucial cellular activities, including apoptosis, calcium homeostasis, mitochondrial dynamics, and autophagosome formation. Consequently, MAMs are believed to be prime targets for pathogenic bacteria (Escoll et al., 2017a; Raturi and Simmen, 2013). It is known that Stx17 interacts with Drp1 at MAMs to promote mitochondrial fission, an early event often observed upon apoptotic cell death (Arasaki et al., 2015; Suen et al., 2008). Through degrading Stx17, Lpg1137 abrogates the Stx17-Drp1 interaction and blocks apoptosis, which could facilitate the continual replication of *L. pneumophila* (Abu-Zant et al., 2005; Arasaki et al., 2017).

Pathogenic bacteria tuning mitochondrial dynamics. The mitochondrial network maintains a dynamic equilibrium between fragmented and tubular morphologies, a balance crucially intertwined with mitochondrial metabolic activities and their interactions with other organelles (Box 1, mitochondrial fission-fusion dynamics). Manipulation of mitochondrial dynamics by pathogenic bacteria not only influences cell death but also helps them evade degradation and obtain energy for replication.

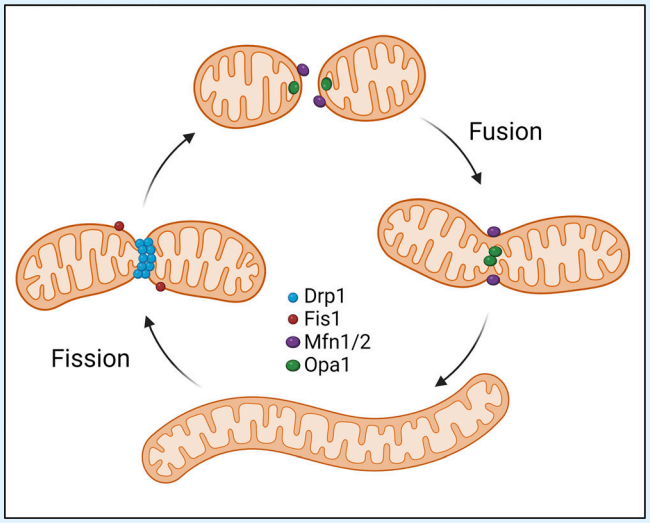
S. flexneri promotes mitochondrial fragmentation in a DRP1-dependent manner (Lum and Morona, 2014). During infection, the septin protein in the host forms a cage to trap *S. flexneri* (Mostowy et al., 2010), which is then targeted to the autophagosome for degradation (Mostowy et al., 2011). It was shown that effective trapping of *S. flexneri* by the septin cage relies on a non-fragmented mitochondrial network. Thus, *S. flexneri*-induced mitochondrial fragmentation may serve to protect the pathogen from entrapment (Fig. 2) (Sirianni et al., 2016). *H. pylori* effector VacA also promotes mitochondrial fission through a DRP1-dependent manner, leading to cell death (Fig. 2) (Jain et al., 2011). On the other hand, while *L. pneumophila* inhibits apoptosis, its infection nonetheless promotes mitochondrial fragmentation. This process is mediated by the secreted T4SS effector MitF, a Ran GTPase activator, that induces DRP1

Box 1. **Mitochondrial fission–fusion dynamics**

Mitochondria are highly dynamic organelles that constantly adapt their morphology and cellular distribution in response to stress or metabolic changes, displaying high heterogeneity at multiple levels. For instance, studies showed that severe stress such as prolonged nutrient deprivation and electron transport chain (ETC) inhibition leads to fission while mild stressors such as inhibition of RNA transcription or protein translation, UV irradiation, and moderate starvation cause fusion (Tondera et al., 2009; Toyama et al., 2016; Zemirli et al., 2018). Mitochondrial fission–fusion processes are critical for mitochondria to maintain their appropriate size, shape, and function, which is regulated by a complex network of proteins. Three dynamin-like GTPases, dynamin-related protein 1 (DRP1), mitofusins (MFN1/2), and optic atrophy protein 1 (OPA1), are key regulators of mitochondrial fission and fusion, which are activated and inactivated by posttranslational modifications and can be modulated by interactions with various regulatory proteins. Fission is initiated by DRP1 recruitment to mitochondria by several adaptor proteins such as Fission 1 (FIS1), followed by assembly into a ring-like structure that constricts the organelle and eventually divides it (Chan, 2006; Westermann, 2010). Fusion, on the other hand, is facilitated by MFN1/2 and OPA1 which mediate the tethering and fusion of two adjacent mitochondria, leading to the creation of highly interconnected networks (Chan, 2006; Westermann, 2010).

Although fission and fusion exert distinct effects on mitochondrial functions, they both play a vital role in cell and tissue homeostasis. Mitochondrial fusion enables the exchange of mitochondrial contents and DNA between mitochondria and disruption of mitochondrial fusion causes mitochondrial dysfunction (Adebayo et al., 2021; Chen et al., 2005; Yang et al., 2015). In addition, mitochondrial fusion contributes to enhancing the rate of lipid consumption by facilitating the distribution of fatty acids from lipid droplets among the mitochondrial network and consequently beta-oxidation of these fatty acids by mitochondria (Rambold et al., 2015). Also, studies in mice showed that obesity increases mitochondria fragmentation, and adipose tissue expression of Drp1 displays a positive correlation with obesity and insulin resistance (Xia et al., 2024).

On the other hand, mitochondrial fission can enable both the selective removal of damaged organelles through mitophagy and mitochondrial biogenesis (Burman et al., 2017; Kleele et al., 2021). Interestingly, mitochondrial fission and fusion dynamics also control the positioning of mitochondria within the cell to accommodate cellular metabolic needs (Han et al., 2012; Lee et al., 2023; Wakai et al., 2014) and their physical/functional crosstalk with other organelles.



accumulation to drive fission (Escoll et al., 2017b). The fragmented mitochondria in macrophages impair mitochondrial oxidative phosphorylation, and together with T4SS-independent induction of glycolysis, a Warburg-like effect is provoked. This metabolic reprogramming in host cells favors bacterial replication (Fig. 2) (Escoll et al., 2017b). In the case of *Listeria monocytogenes* (*L. monocytogenes*), it induces mitochondrial fragmentation through a DRP1-independent mechanism. Prior to bacterial entry, listeriolysin O secreted by *L. monocytogenes* forms calcium-permeable pores on the plasma membrane and causes mitochondrial fragmentation accompanied by a reduction in mitochondrial membrane potential and intracellular ATP levels (Fig. 2) (Repp et al., 2002; Stavru et al., 2011). Interestingly, this listeriolysin O–induced fragmentation of the host mitochondrial network does not require Drp1 or Opa1 but takes place at the mitochondria–ER contact site (Stavru et al., 2013).

Despite most reported cases showing fragmentation of mitochondria upon bacterial infection, tubulation of the host mitochondrial network was observed in primary cells infected by the obligate intracellular bacterium *Chlamydia trachomatis* (*C. trachomatis*) during the early phase (Chowdhury et al., 2017). This process is mediated by the downregulation of DRP1 and is associated with increased mitochondrial oxygen consumption and intracellular ATP content (Kurihara et al., 2019). However, during prolonged infection with *C. trachomatis*, mitochondrial fragmentation begins to take place (Kurihara et al., 2019), suggesting that early-phase mitochondrial tubulation may allow the pathogen to gain access to more ATP molecules, further develop, and establish the infection. Moreover, the impact of pathogenic bacteria on mitochondria is not limited to mitochondrial fission-fusion dynamics. During *Vibrio cholerae* (*V. cholerae*) infection, perinuclear clustering of mitochondria is inhibited, suppressing innate immune responses in mammalian cells (Suzuki et al., 2014). This inhibition is mediated by VopE, a T3SS effector, which binds to mitochondrial Rho GTPases Miro1 and Miro2 to interfere with their modulation of mitochondrial trafficking (Suzuki et al., 2014).

Mitochondrial responses to bacterial infection. Mitochondrial reactive oxygen species (mitoROS) is central to the cellular immune response to pathogens (Fig. 2) (Pinegin et al., 2018). Lipopolysaccharides (LPS), lipoproteins, and other toxins released by bacteria are known as pathogen-associated molecular

patterns (PAMPs), which are recognized by the host pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and Nod-like receptors (NLRs) (Tiku et al., 2020; West et al., 2011). In macrophages, the activation of TLR1, 2, and 4 induces mitoROS production and recruits mitochondria toward phagosomes (West et al., 2011). NLRX1, a member of the NLR family, is targeted to the mitochondrial matrix, and its activation enhances mitoROS production as well (Arnoult et al., 2009; Tattoli et al., 2008). The bactericidal effect of mitoROS occurs at multiple levels. mitoROS can directly exert oxidative damage to the pathogen (Abuaita et al., 2018; Geng et al., 2015; West et al., 2011). It can also activate NADPH oxidases in the phagosome to further generate ROS for bacterial killing (Kröller-Schön et al., 2014). In macrophages infected by methicillin-resistant *Staphylococcus aureus*, it was reported that mitoROS is delivered to phagosomes via mitochondria-derived vesicles upon infection-induced ER stress (Abuaita et al., 2018). Furthermore, mitoROS is a crucial signaling molecule that activates transcriptional factors such as NFkB (Chen et al., 2011; Gloire et al., 2006; Zinovkin et al., 2014), and members of the NLR family, NLRP3 and NLRC4, to upregulate proinflammatory cytokines and initiate the assembly of inflammasomes, respectively (Jabir et al., 2015; Shimada et al., 2012).

Additionally, metabolic reprogramming orchestrated by mitochondria is crucial for different aspects of immune responses. A prominent example is that macrophages undergo a metabolic shift from oxidative phosphorylation to aerobic glycolysis upon encountering bacteria (Rosenberg et al., 2022), which promotes proinflammatory responses. In LPS-activated macrophages, TCA cycle enzymes isocitrate dehydrogenase 1 (IDH1) is transcriptionally repressed (De Souza et al., 2019), and both IDH1 and aconitase are functionally inhibited (Bailey et al., 2019; Palmieri et al., 2020), leading to the accumulation of citrate and cis-aconitate. The cis-aconitate is further converted to itaconate by the mitochondrial enzyme cis-aconitate decarboxylase, and itaconate exerts its bactericidal activity by inhibiting bacterial isocitrate lyase and propionyl-CoA carboxylase, resulting in disruptions of the glyoxylate cycle and acetate assimilation that are important for bacterial survival (Berg et al., 2002; Peace and O'Neill, 2022). Interestingly, enzymes that facilitate the degradation of itaconate into pyruvate and acetyl-CoA are found in numerous pathogenic bacteria, and the genes encoding these enzymes have been shown to be essential for the survivability of some pathogens inside the macrophage (Sasikaran et al., 2014).

***Host mitochondrial association by* Toxoplasma gondii.** In addition to bacteria, another pathogen that exhibits a close association with the host's mitochondria is the intracellular parasite *Toxoplasma gondii* (*T. gondii*). It is known that upon infection, *T. gondii* resides in vacuoles and tethers host mitochondria to vacuoles via the secreted *Toxoplasma gondii* mitochondrial association factor 1 (TgMAF1) protein (Pernas et al., 2014; Sinai et al., 1997). Although the detailed mechanism remains to be explored, *T. gondii* acquires fatty acids for growth and proliferation by promoting lipid droplet incorporation into the vacuoles and inducing lipophagy in the host (Nolan et al., 2017; Pernas et al., 2018). Simultaneously, the mitochondrial network surrounding the vacuoles fuses together and becomes tubular in the early phase of the infection (Pernas et al., 2014), leading to increased fatty acid uptake into mitochondria, which competes with *T. gondii* for nutrients. When mitochondrial fusion is lacking, *T. gondii* growth and proliferation are enhanced (Pernas et al., 2018). Interestingly, the outer mitochondrial membrane (OMM) translocase TOM70 (translocase of the outer membrane 70) and the mitochondria-specific chaperon HSPA9 have been identified as the host binding partners of TgMAF1, which are required for mitochondrial tethering to vacuoles upon *T. gondii* infection (Blank et al., 2021).

More recently, the study of *T. gondii* has revealed its infection as a natural stressor that triggers the remodeling of the outer mitochondrial membrane (OMM) (Li et al., 2022). Upon infection, structures known as SPOTs (structures positive for OMM) emerge within the host cell (Fig. 2). These structures exclusively contain OMM proteins but lack proteins located in the mitochondrial matrix or the inner mitochondrial membrane. The formation of SPOTs requires TOM70, which mediates the binding between TgMAF1 and another OMM translocase SAM50 (sorting assembly machinery 50 kDa subunit). The shedding of SPOTs from the mitochondria results in the depletion of OMM proteins, including Mfn1 and Mfn2, which are required for mitochondrial fusion to compete for nutrients with the parasite. The loss of other OMM translocases required for mitochondrial biogenesis also diminishes the nutritional defense mediated by host mitochondria. Interestingly, without infection, the removal of SAM50 or the overexpression of alpha-helical OMM proteins is sufficient to induce SPOT formation, suggesting that *T. gondii* hijacks an intricate cellular response associated with OMM remodeling in the host cell for its own benefits (Li et al., 2022).

Bacteria–mitochondria communication in aging and longevity

Mitochondria communication in aging. Like their prokaryotic relatives, mitochondria also dynamically communicate with each other, characterized by fusion, fission, and trafficking (Box 1), enabling them to adapt to the cell's changing demands, ensuring optimal function and response to environmental cues. During aging, mitochondrial dynamics undergo changes, leading to a decline in the efficiency and integrity of mitochondria and ultimately contributing to the development of various age-related diseases (Liu et al., 2020; Srivastava, 2017). In particular, impaired mitochondrial dynamics caused by mitochondrial fission–fusion defects are well documented in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, Charcot-Marie-Tooth type 2A disease, and dominant optic atrophy (Alexander et al., 2000; Arduíno et al., 2012; Flannery and Trushina, 2019; Reddy, 2014; Su et al., 2010; Trimmer et al., 2000; Van Laar and Berman, 2009; Züchner et al., 2004).

Interestingly, manipulating mitochondrial fusion–fission regulators proves to be an effective way of altering lifespan and healthspan in model organisms (Table 1). Studies in the fruit fly *Drosophila melanogaster* showed that transient upregulation of Drp1 during midlife to promote mitochondrial fission prolongs healthspan, which is associated with increased mitochondrial membrane potential, youthful cristae ultrastructure, improved mitochondrial respiratory capacity, reduced levels of mitoROS,

Table 1. **Alterations in mitochondrial dynamics affect lifespan in model organisms**

Genetic manipulation	Effect on mitochondrial dynamics	Model organism	Lifespan	Reference
Transient upregulation of Drp1	Increased fission	*D. melanogaster*	Increase in lifespan	Rana et al., 2017
Parkin E3 overexpression	Increased fission	*D. melanogaster*	Increase in lifespan	Rana et al., 2017
Intestine-specific overexpression of drp-1	Increased fission	*C. elegans*	Increase in lifespan	Han et al., 2017
Mfn2 knockout in skeletal muscle	Impaired fusion, Swollen mitochondria upon aging	*Mice*	Premature aging, No change in lifespan	Sebastián et al., 2016
Knockdown of drp-1 or overexpression of fzo-1	Increased fusion	*C. elegans*	No change in lifespan	Weir et al., 2017

enhanced mitophagy, and proteostasis in aged flies (Rana et al., 2017). Reduction of mitochondrial fusion factors by overexpression of parkin E3 ubiquitin ligase in flies also improves mitochondrial activity and prolongs healthspan (Rana et al., 2013). Similarly, intestine-specific overexpression of *drp-1* extends *C. elegans'* lifespan (Han et al., 2017). In mice, Mfn2 deficiency in the skeletal muscle leads to disrupted mitochondrial dynamics and premature aging phenotypes, although the lifespan is not altered (Sebastián et al., 2016). On the other hand, in *C. elegans*, an increased mitochondrial elongation morphology, likely resulting from enhanced mitochondrial fusion, has been associated with several prolongevity pathways, including reduction of insulin/IGF-1 signaling, caloric restriction, mitochondrial ETC deficiency, mTOR inactivation, and AMPK activation (Chaudhari and Kipreos, 2017; Jacobi et al., 2015; Weir et al., 2017). However, the knockdown of *drp-1* or overexpression of *fzo-1* (MFN1/2 ortholog), both of which lead to an increase in mitochondrial fusion, does not increase *C. elegans'* lifespan (Weir et al., 2017). Thus, achieving a delicate balance between mitochondrial fusion and fission is critical for cellular health, while the connection between mitochondrial dynamics and longevity regulation is multifaceted, which may vary depending on the biological context and with tissue and age specificity.

Furthermore, mitochondria communicate with other organelles via both membrane contact and molecular exchanges, which have also been linked with longevity regulation in model organisms. Mitochondrial retrograde signaling via mitochondrial unfolded protein response (mitoUPR) plays a crucial role in *C. elegans'* longevity regulation (reviewed in Lima et al., 2022). Improvements in mitochondrial functions by increased lysosomal acidity and lysosomal lipolysis have been shown to extend lifespan in yeast and *C. elegans*, respectively (Hughes and Gottschling, 2012; Ramachandran et al., 2019). Additionally, reducing ER–mitochondria Ca^{2+} exchange by deleting inositol 1,4,5-trisphosphate receptor (IP_3R) improves both lifespan and healthspan in female mice (Ziegler et al., 2021), while in *C. elegans*, the gain-of-function mutation of IP_3R increases lifespan (Burkewitz et al., 2020).

Bacterial metabolites act through mitochondria to regulate host aging. In addition to pathogenic bacteria, trillions of non-pathogenic bacteria in the microbiome coexist with eukaryotic organisms. There is a continuous exchange of nutrients, genetic materials, and metabolites between these commensal bacteria and their hosts. The metabolic inputs from bacteria play crucial roles in modulating the host's physiological and pathological activities. Interestingly, emerging studies reveal mitochondria as key mediators of these bacteria-host metabolic interactions in regulating stress responses, metabolism, and aging.

Short-chain fatty acids (SCFAs) such as butyrate and acetate are among the best-studied metabolites produced by commensal bacteria through the fermentation of dietary fibers (LeBlanc et al., 2017). The levels of SCFAs alter during the aging process (Salazar et al., 2019), which has been implicated in neuroinflammation and various age-associated diseases (Bostick et al., 2022; Tran and Mohajeri, 2021). SCFAs' supplementation has been shown to influence age-associated pathologies through their effects on mitochondria. For example, bacteria-derived acetate modulates mitochondrial membrane potential and electron transport chain (ETC) complex II activity in mouse microglia, contributing to microglial maturation and function during the steady state (Erny et al., 2021). Bacteria-derived acetate also modulates microglial phagocytosis and hippocampal amyloid-beta pathology in the 5xFAD mouse model of AD (Erny et al., 2021). In insulin-resistant obese mice, butyrate supplementation elevates mitochondrial fusion factors Mfn1, Mfn2, and Opa1 expression in the liver and increases mitochondrial functions in liver, brown adipose tissue, and skeletal muscle, leading to improved insulin sensitivity (Gao et al., 2009; Mollica et al., 2017). In aged mice, butyrate supplementation has been shown to induce mitochondrial biogenesis in skeletal muscles and alleviate sarcopenia (Walsh et al., 2015).

In addition, bacteria can produce metabolites that are also made by the host to influence mitochondrial functions. One example is hydrogen sulfide (H_2S), an inhibitor of ETC complex IV component cytochrome oxidase (Blackstone et al., 2005), which can be produced in a large quantity by bacteria in the Enterobacteriaceae family (Murros, 2022). In a 15-year follow-up study, the abundance of H_2S is associated with increased all-cause mortality (Salosensaari et al., 2021). Carbon monoxide (CO) and nitric oxide (NO) are also endogenous ETC inhibitors, and their production from the host's microbiome promotes mitochondrial biogenesis (Hopper et al., 2020; Tengan and Moraes, 2017). Interestingly, bacteria can even modify host metabolites to regulate mitochondrial functions. In the colon, secondary bile acids (BAs) are produced by bacteria using host-derived primary BAs as substrates (Zeng et al., 2019). The

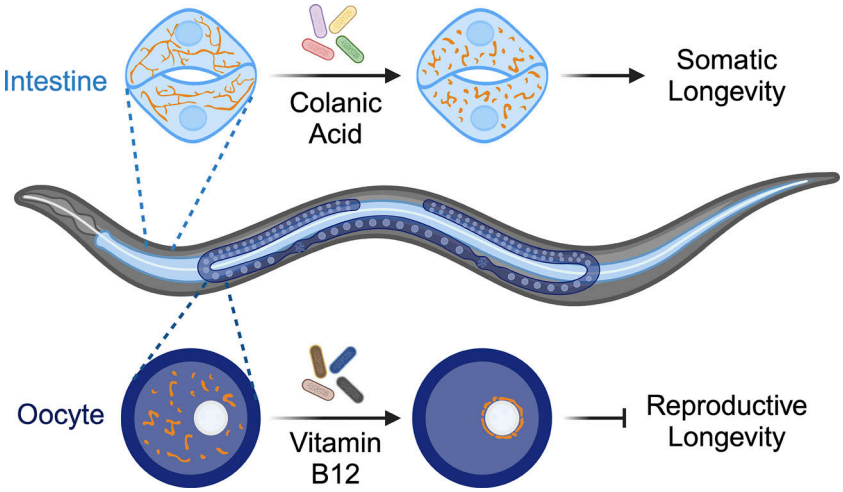


Figure 3. **Bacterial metabolites signal through host mitochondria to regulate somatic and reproductive aging in *C. elegans*.** Colanic acids released from bacteria direct the intestinal mitochondrial network toward fragmentation, promoting somatic longevity in *C. elegans*. Bacterial vitamin B12 causes perinuclear clustering of mitochondria in the oocyte, resulting in accelerated reproductive decline in *C. elegans*.

secondary BA deoxycholic acid is a well-established risk factor for colon cancer (Bernstein et al., 2011), and exposure to deoxycholic acid has been reported to induce mitochondrial oxidative stress in the human colorectal carcinoma cell line HCT116 (Payne et al., 2007). Another secondary BA, tauroursodesoxycholic acid, shows neuroprotective effects in mouse models of multiple neurodegenerative diseases (Borbolis et al., 2023; Castro-Caldas et al., 2012; Keene et al., 2002; Nunes et al., 2012) and was found to promote mitophagy by upregulating mitophagy-related proteins in neuroblastoma cells (Fonseca et al., 2017). BA supplementation has been shown to extend healthspan and lifespan in a variety of organisms (Zhou et al., 2021).

The model organism *C. elegans* can be supplied with a single bacterial source, facilitating the mechanistic investigation of microbe–host interactions, especially from a metabolic perspective. Through these studies, molecular mechanisms by which bacterial inputs signal through mitochondria to modulate the host's physiology are starting to be unveiled. Colanic acid (CA) is a bacteria-secreted exopolysaccharide produced by several enterobacteriacease species, particularly *E. coli* (Grant et al., 1969). Through genome-wide screening, *E. coli* deletion strains with increased production of CA were discovered to promote longevity in the host *C. elegans* (Han et al., 2017). Interestingly, CA supplementation leads to increased mitochondrial fission in the intestine of *C. elegans* and mammalian cells (Fig. 3), and coherently, *drp-1* is required for the prolongevity effect of CA (Han et al., 2017). Other mitochondrial factors are also involved in CA-induced lifespan extension in worms. The transcription factor ATFS-1 mediates mitoUPR activation by relocating from mitochondria to the nucleus (Nargund et al., 2012). The requirement of *atfs-1* for the CA-induced prolongevity effect suggests the involvement of the mitoUPR pathway. Additionally, mitochondrial ETC components, NUO-6 of complex I and ISP-1 of complex III, both contribute to the regulation of longevity by CA (Han et al., 2017). Recent unpublished studies from our lab have revealed that this exopolysaccharide-mediated communication with mitochondria can be extended to gram-positive *Bacillus subtilis* and gram-negative *V. cholerae*.

Vitamin B12 (VB12), also known as cobalamin, varies in its levels among different bacteria with more than 1,000-fold differences in certain cases (Watson et al., 2014). B-type *E. coli* OP50 is deficient in VB12 compared with K12-type *E. coli* HT115, K12/B hybrid *E. coli* HB101, and *Comamonas aquatica* DA1877 (Lam et al., 2021; Revtovich et al., 2019; Watson et al., 2014). When exposed to VB12-deficient OP50, *C. elegans* exhibited reduced resistance to various stresses, including heat shock, pathogenic infection, and oxidative damage (Revtovich et al., 2019). Supplementation of VB12 increases the stress resistance of worms grown on OP50, which is dependent on *mmcm-1* encoding *C. elegans* methylmalonyl-CoA mutase (Revtovich et al., 2019). Methylmalonyl-CoA mutase is a VB12-dependent mitochondrial enzyme, and this dependence suggests that bacterial VB12 functions through mitochondria to influence the stress response. Furthermore, mitochondrial fragmentation increases in intestinal and muscular cells of wild-type worms grown on VB12-deficient OP50 *E. coli* (Neve et al., 2020; Revtovich et al., 2019). For the *drp-1* worm mutant, growing on VB12-rich HT115 *E. coli* leads to excess muscular mitochondrial fusion and a high rate of embryonic lethality, which can be mitigated when growing on VB12-deficient OP50 *E. coli* (Wei and Ruvkun, 2020). Interestingly, the deacidification of lysosomes, which mediate VB12 uptake, attenuates the excess mitochondrial fusion and embryonic lethality in the *drp-1* mutant grown on VB12-rich HT115 *E. coli* (Wei and Ruvkun, 2020). These results reveal that VB12 from environmental bacteria regulates mitochondrial dynamics in somatic tissues and modulates organism survival.

More recently, we discovered that bacterial VB12 regulates reproductive aging by modulating germline mitochondrial GTP levels and, subsequently, oocyte mitochondrial distribution in *C. elegans* (Fig. 3) (Lee et al., 2023). When worms grow on VB12-rich HT115 *E. coli*, the oocyte mitochondrial network is evenly dispersed throughout the cytosol at a young age but becomes clustered in the perinuclear region at an older age. This age-associated increase in perinuclear clustering is attenuated when worms grow on VB12-deficient OP50 *E. coli* but is restored with VB12 supplementation. Furthermore, worms grown on OP50 exhibit an extended reproductive lifespan, which is suppressed by VB12 supplementation. Interestingly, the age-associated perinuclear clustering of oocyte mitochondria can be also attenuated by the inactivation of GTP-specific succinyl-CoA synthetase

(GTP-SCS). GTP-SCS is required for VB12 supplementation to shorten the reproductive lifespan, and germline mitochondrial GTP levels were increased with high bacterial VB12 levels during aging. Thus, bacterial VB12 can control mitochondrial GTP metabolism and mitochondrial positioning in the oocyte, consequently influencing organism reproductive health during aging.

Bacteria–mitochondria interaction in humans

Although most mechanistic studies on the interaction between bacteria and host mitochondria are reported in model organisms, such interactions may also occur in humans and play a role in health and diseases. Polymorphisms in mitochondrial genes have been reported to be associated with the composition of the gut microbiome in humans (Ma et al., 2014). One notable observation is that mitochondrial single nucleotide polymorphisms (mtSNPs) causing synonymous mutations in key redox genes have been associated with the abundance of butyrate-producing *Clostridia* clusters IV and XIVa (Ma et al., 2014). Another study reported that a decrease in their abundance in the gut microbiome is linked to the loss of resistance against pathogen colonization (Livanos et al., 2018). This is consistent with the finding in mice, in which mtDNA polymorphism that increases mitoROS production correlates with a less diversified gut microbiome (Yardeni et al., 2019). Interestingly, aging is generally associated with increased mitoROS production (Cui et al., 2012; Giorgi et al., 2018) and decreased microbiome diversity (Aleman and Valenzano, 2019), but the causative links are still unclear.

Inflammatory bowel disease (IBD) is a collective term referring to conditions characterized by chronic inflammation of the digestive tract over an extended period, encompassing disorders such as ulcerative colitis and Crohn's disease (CD), which have both been known to be caused by gut dysbiosis (Qiu et al., 2022). Excessive mitochondrial fragmentation (Chojnacki et al., 2023) and alterations in mitochondrial gene expression have been observed in the biopsies of patients with IBD (Haberman et al., 2019). Proteomic analysis revealed that the mitochondrial H_2S detoxification pathway is downregulated in biopsies of CD patients (Mottawea et al., 2016). Meanwhile, the relative abundance of *Atopobium parvulum* (*A. parvulum*) positively correlates with the severity of CD in these patients, and network analysis suggests that *A. parvulum* acts as a central hub co-occurring with other known H_2S-producing bacteria such as *Vagoccocus* and *Streptococcus* (Mottawea et al., 2016).

Gut dysbiosis is often observed in patients with neurodegenerative diseases such as PD and AD (Fang et al., 2020). IBD patients have been found to possess a higher risk of developing neurodegenerative disorders later in life, supporting that the microbiome alteration could lead to neurodegeneration (Kim et al., 2022). Microbiome analysis from stool samples suggests a reduced level of SCFAs-producing *Firmicutes* in PD patients (Hill-Burns et al., 2017; Keshavarzian et al., 2015; Mehanna et al., 2023; Petrov et al., 2017). Similarly, AD patients have a reduced level of *Firmicutes* and an elevated level of *Bacteroidetes* (Bustamante-Barrientos et al., 2023; Vogt et al., 2017), but the results are not always consistent among studies (Zhuang et al., 2018). Meanwhile, mitochondrial dysfunction and defective mitophagy are characteristics of both PD and AD (Kramer, 2021; Liu et al., 2019; Mary et al., 2023). However, how the microbiome interacts with host mitochondria to affect neurodegenerative disease progression remains inconclusive at this moment. It is possible that bacteria metabolite is involved in this process as levels of butyrate in fecal matter have been linked to PD in humans (Unger et al., 2016) as well as AD-like conditions in mice (Zhang et al., 2017). Additionally, although no direct evidence has been reported in humans, oral administration of the bacterial toxin β-N-methylamino-*L*-alanine results in neuronal mitochondrial dysfunction and fragmentation of the mitochondria network, as well as alpha-synuclein aggregation and dopaminergic neurodegeneration (Esteves et al., 2023). Gut dysbiosis resulting in gut leakiness could cause inflammatory responses of immune cells, which could be transmitted to the brain and give rise to multi-faceted neuropathology including mitochondrial dysfunction (Zhang et al., 2023). Since the presence of bacteria has been found in the brain tissue of PD and AD patients (Emery et al., 2017; Pisa et al., 2020), it is also possible that some bacteria travel to the brain to directly interact with mitochondria in the neurons.

Bacteria interaction with other organelles

Pathogenic bacteria targeting chloroplasts. Chloroplasts are the site of photosynthesis in plants and some algae and are considered another significant example of endosymbiosis. It is believed that the chloroplast evolved from a photosynthetic cyanobacterium, which was engulfed by a larger eukaryotic host cell (Martin et al., 2015). The cyanobacterium survived within the host cell, and over time, the two entities developed a symbiotic relationship. The host cell provided the cyanobacterium with a protective environment to carry out photosynthesis, while the cyanobacterium provided oxygen, organic compounds, and energy to its host. Over millions of years, the cyanobacterium evolved into the chloroplast, which became an essential component of plant cells and is responsible for the production of glucose and oxygen through photosynthesis. Like mitochondria, chloroplasts are surrounded by two membranes, thought to be derived from the original engulfing of the cyanobacterium, and they also contain their own DNA. Chloroplasts are not only responsible for photosynthesis but also hold essential roles in the biosynthesis of various compounds crucial for plant growth and metabolism (Song et al., 2021). The endosymbiotic origin of chloroplasts stands as a compelling example of how symbiosis and the merging of distinct organisms can drive the evolution of complex, multicellular life forms.

Pathogenic bacteria that have evolved the ability to target chloroplasts in plant cells represent a unique facet of host-pathogen interactions (Lu and Yao, 2018). Some pathogenic bacteria release effectors that target chloroplasts, often resulting in significant alterations in host physiology and disease development. One such example is *Pseudomonas syringae* (*P. syringae*), a versatile plant pathogen with a broad host range. *P. syringae* T3SS effectors such as Hopl-1 and AvrRps4 are believed to target chloroplasts and impair photosystem II function, hampering photosynthetic electron transport (de Torres Zabala et al., 2015; Jelenska et al., 2007; Li et al., 2014). There are also examples in

the *Xanthomonas* genus, which is known to infect a wide range of crops, including rice, citrus, and *Brassicaceae* vegetables. Virulence factors released from *Xanthomonas campestris* bacteria target chloroplasts, causing changes in their morphology and function, and ultimately leading to ROS accumulation in chloroplasts, photooxidative stress, and in some cases, plant death (Pierella Karlusich et al., 2017; Zurbriggen et al., 2009). The exact mechanisms by which *Xanthomonas* bacteria target and manipulate chloroplast function are not yet fully understood. In addition to *Pseudomonas* and *Xanthomonas*, another group of bacteria targeting chloroplast function is *Phytoplasms*. Once inside the plant, they infect chloroplasts, causing a range of symptoms, such as yellowing of leaves, reduced yield, dwarfing, and stunted growth (Wei et al., 2022).

Bacteria interaction with endosome, phagosomes, and lysosomes. Endosomes, phagosomes, and lysosomes are key cellular organelles of a dynamic network that governs the digestion of extracellular materials. Their interactions with bacteria play a vital role in pathogenic immune responses. First, phagocytosis and the formation of phagosomes are integral parts of the host's innate immune system. When extracellular bacteria invade host cells, they can be ingested by phagocytosis and enclosed by phagosomes. The phagosomes then fuse to lysosomes to form phagolysosomes, leading to final degradation by distinct lysosomal enzymes including lysozymes (Haas, 2007). Dysfunctions in phagosomes and lysosomes can result in compromised phagocytosis and delayed bacterial degradation, and subsequently, hinder the host's ability to combat bacterial infections (Wong et al., 2017).

Some bacteria evolve sophisticated regulatory strategies for lysosomes and phagosomes to evade lysosomal degradation (Sachdeva and Sundaramurthy, 2020). For example, *Mycobacterium tuberculosis* (Mtb) can inhibit the fusion of phagosomes with lysosomes by expressing lipoarabinomannan on their cell envelope (Gaur et al., 2014). A group of intracellular pathogenic bacteria, such as *E. coli* K1, *Leishmania donovani*, and *Salmonella enterica* also form membrane-bound vacuoles that acquire endosomal and even lysosomal membrane markers (Bakowski et al., 2010; Figueira and Holden, 2012; Garcia-del Portillo and Finlay, 1995; Kim et al., 2003; Rathman et al., 1997; Steele-Mortimer et al., 1999; Verma et al., 2017). However, these bacteria-containing vacuoles avoid the fusion with mature acidic lysosomes that carry digestive enzymes, and within the vacuole, pathogenic bacteria survive and replicate (Eswarappa et al., 2010; Kim et al., 2003; Krieger et al., 2014). These phenomena suggest that factors from these bacteria may actively inhibit endolysosomal processing and maturation. One such bacterial input identified in *E. coli* K1 is the K1 capsule, which is required for preventing the fusion of bacteria containing vacuoles and lysosomes (Kim et al., 2003). In the case of *S. enterica*, the T3SS effector SifA forms a complex with SifA and kinesin interacting protein (SKIP) and Ras-related protein 9 (RAB9) in the host cell and disrupts Rab9-mediated retrograde tracking of mannose-6-phosphate receptors, resulting in the misdirection of lysosomal enzymes and ultimately the disruption of lysosomal digestion (McGourty et al., 2012).

On the other hand, the host cell also develops adaptive responses to adjust its lysosomal homeostasis in responding to pathogenic invasion. For example, upon Mtb infection, lysosomal content and activity are greatly increased in macrophages, and this adaptive response is triggered by Mtb surface lipids sulfolipid-1 (SL-1) and mediated by mechanistic target of rapamycin complex I (mTORC1) and the transcription factor EB (TFEB) in the host (Sachdeva et al., 2020). In response to SL-1, macrophage cells also enhance the trafficking of phagosomes to lysosomes to facilitate bacterial degradation (Sachdeva et al., 2020).

Bacterial regulation of ER. In general, ER offers a secure environment for intracellular bacteria due to its nutrient-rich properties and limited bactericidal defenses (Celli and Tsolis, 2015). Some pathogens evolve mechanisms to manipulate the host ER to support their replication (Arasaki et al., 2012; Roy, 2002; Starr et al., 2012). For instance, *L. pneumophila*, an intravacuolar pathogen, enters host cells and resides in plasma membrane–derived vacuoles, which subsequently merge with ER-derived vesicles and form *Legionella*-containing vacuoles (Swanson and Isberg, 1995; Tilney et al., 2001). These vacuoles are enveloped by multilayer membranes adorned with ER-originated ribosomes, which are essential for bacteria to escape lysosomal digestion and replicate within the host cell (Abu Kwaik, 1996; Horwitz, 1983).

Furthermore, pathogenic bacterial infection often triggers ER stress responses, especially ER unfolded protein response (ER-UPR) (Celli and Tsolis, 2015). The secretion of virulence factors or toxins from bacteria can disrupt ER functions, leading to the accumulation of misfolded proteins (Pillich et al., 2012), and the elevated demand for cellular membrane biosynthesis places additional burdens on ER protein homeostasis (Bettigole and Glimcher, 2015). The host employs ER-UPR signaling pathways to induce immune responses, such as the production of proinflammatory cytokines (Celli and Tsolis, 2015; de Jong et al., 2013), the activation of innate immune factors (Richardson et al., 2010), and combat pathogenic infections. On the bacterial side, *Simkania negevensis*, a gram-negative intracellular bacterium, has been observed to inhibit ER-UPR, facilitating the fusion of its vacuoles with the ER and enabling its survival within host cells (Mehlitz et al., 2014).

Summary and future perspective

The intricate interplay between bacteria and host organelles represents a multifaceted relationship of paramount importance. Examples of interactions between pathogenic bacteria and organelles illustrate how pathogens exploit these interactions to evade the host's defenses and enhance their survival. In response, host cells leverage these connections to detect and mount defenses against pathogenic infections.

Remarkably, recent studies from our laboratory and other groups have unveiled a previously underappreciated dimension: non-pathogenic bacteria's capacity to modulate host mitochondria (Han et al., 2017; Lee et al., 2023; Lin and Wang, 2017; Revtovich et al., 2019; Wei and Ruvkun, 2020). This modulation extends to both somatic and reproductive health, particularly in the context of aging. This revelation aligns with the understanding that mitochondria themselves have a bacterial ancestry and actively participate in the regulation of lifespan through cell

non-autonomous communication between tissues (Durieux et al., 2011).

A promising future avenue of exploration lies in comprehensive and mechanistic investigations into these interactions between bacteria and mitochondria, spanning diverse host organisms. Such investigations may reveal a plethora of beneficial metabolites derived from commensal bacteria, with potential applications in promoting healthy aging, enhancing reproductive health, and preventing or treating metabolic diseases.

Furthermore, it would be equally intriguing to explore metabolite-mediated communication between commensal bacteria and other organelles, extending beyond mitochondria. A holistic exploration of these interactions promises to unravel their profound roles in host physiology and pathology. Beyond human health, the study of bacteria–organelle interactions extends to ecosystems and agriculture. Understanding how bacteria influence chloroplasts and other organelles in plants has implications for sustainable agricultural practices and environmental conservation. A deeper understanding of the intricate crosstalk between bacteria and host organelles provides a new perspective in developing approaches for promoting healthy aging and delaying age-related diseases as well as optimizing crop production and mitigating the impact of environmental stressors.

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