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Targeting microbiota-mitochondria inter-talk: Microbiota control mitochondria metabolism

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Abstract

Our aim is to highlight the subtle relationship that exists between microbiota and mitochondria. Microbiota targets mitochondria by modulating the Reactive Oxygen Species (ROS) production and the mitochondrial activity through interactions with toxins, proteins or other metabolites released by gut microbiota. The intriguing relationship that exists between mitochondria and microbiota is strengthened by the probable prokaryotic origin of mitochondria. Emerging data implicates a role for ROS, nitric oxide, Short Chain Fatty Acids and hydrogen sulfide in the cross-talk between microbiota – mitochondria and REDOX signaling. Several studies have shown that microbiota act and modulate mitochondrial activity, and use it as a relay to strengthen host-microbiotal interaction. This modulation depends on the gut bacterial strain quality and diversity to increase its pathogenic versus beneficial effects. Furthermore, based on conclusions from new studies, it is possible that microbiota can directly interact with the host cell gene expression by favoring bacterial and mitochondrial DNA insertion in the nuclear genome. The emerging knowledge of mitochondria-microbiota interaction may be of great importance to better understand the mechanism of mitochondrial and metabolic diseases, and the syndromes associated with change in quality and quantity of microbiotal species. We suggest that microbiota *via* mitochondrial modulation influence cell homeostasis and metabolism. The challenge will be to find strategies to modulate the quality and diversity of microbiota rather than acting on microbiota metabolites and microbiota related factors. The medicine of tomorrow will be completely personalized. Firstly there will be a test to show the quality, quantity and diversity of microbiota, and secondly a preventive or therapeutic strategy will be administrated (probiotics, diet, prodrug or fecal transplantation). The era of digital medicine is here.

Key words: Microbiota, mitochondria, oxidative stress, inflammation, personalized medicine.

Introduction

Animals and plants host a large colony of multi species bacteria named microbiota. Human microbiota consist of 10^{13} cells and 1500 different species. How these large prokaryotic colonies interact with their host is now an important topic discussed in numerous papers and scientific meetings. Microbial activity plays an important role in the development of a functional intestine and aides the digestion of food, providing nutrients for growth and well- being (1). Colonization of the gut by microorganisms is also necessary for edification of a well- balanced immune system (2). In addition, the gut microbiota interacts with the enteric nervous system and may modulate brain activities (3,4). The quality and diversity of microbiota species (in particular the relative amount of Bacteroidetes and Firmicutes) has been associated with several diseases such as depression, inflammatory bowel disease, obesity, diabetes etc. Knowledge of how microbiota control host cells and immune response to maintain their presence in the organism or to promote infection is essential to better understand diseases related to microbiotal change in quality and diversity. Several observations and experiments have highlighted the important role of mitochondria during this host-microbiotal crosstalk, suggesting that mitochondria can be targeted by microbiota to modulate interaction with its host (5–7). Interestingly, this control may be favored by the prokaryotic origin of mitochondria (8). Most phylogenetic studies pointed out a α-proteobacteria as an ancestor of mitochondria. Mitochondria and microbiota share several common features including a circular genome, a ribosome with a clear prokaryotic signature sensitive to antibiotics, a maternal Inheritance, and the fact that both structures are able to trigger autophagy through activation of the Formyl Peptide Receptor (FPR) system. Autophagy is known to be induced in response to several pathologic conditions including cancer or the presence of drugs such as clofibrate (9,10). Furthermore, mitochondrial and microbiotal DNA insertion in the nuclear genome may continuously occur in the somatic tissues. Our aim is to present the subtle modulation of microbiota over mitochondria and its role in cell function and in microbiota-associated pathologies.

Targeting mitochondrial activity and cellular homeostasis by microbiota

Several observations highlight the mitochondria-microbiota relationship. Patients with mitochondrial diseases are more prone to bacterial infection (11). Change in microbiota quality and diversity are associated with mutation of the mitochondrial DNA (mtDNA) (12). Moreover, modulation of the diet can induce variation in mitochondrial functions associated with the modification of quality and diversity of the microbiota (13). Furthermore, several groups have recently and independently associated the presence of altered mitochondrial DNA molecules or bacterial DNA in the serum and tissue of patients with metabolic disorders (14,15). In this

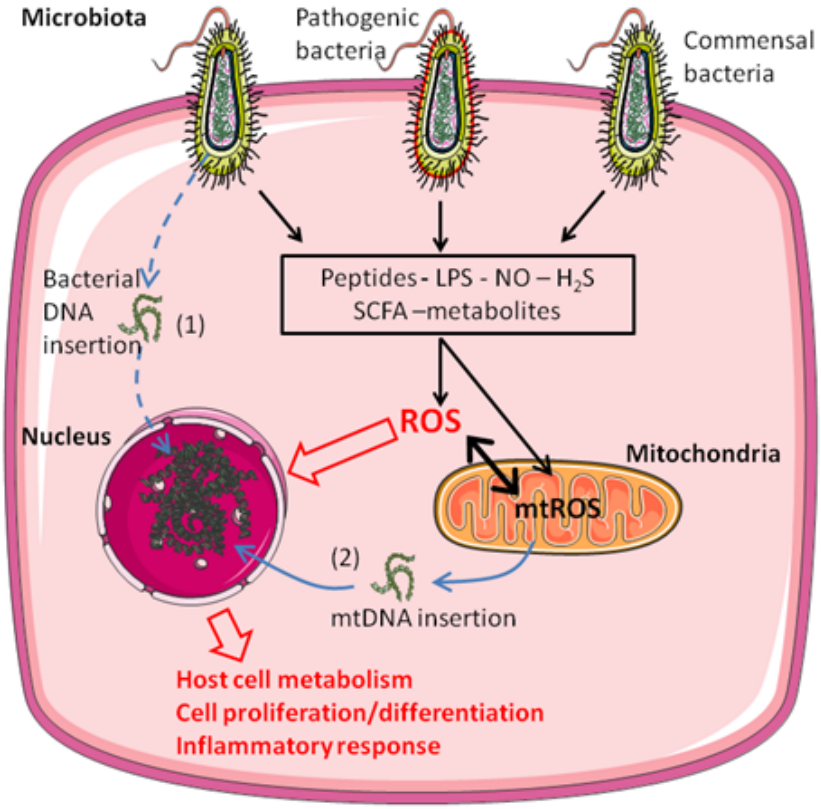

Figure 1. Microbiota - mitochondria intertalk : Commensal and pathogenic bacteria release factors that promote or decrease the mitochondrial activity and the subsequent cellular ROS concentration. High ROS production, due to unbalanced release of microbiotal factors, is able to trigger cell proliferation or differentiation, as well as an inflammatory response. Moreover, it can also promote mitochondrial biogenesis in case of mitochondrial fragmentation. Furthermore, microbiota can trigger mitochondrial and bacterial DNA insertion in the nuclear genome leading to alteration of cellular gene expression. (1) Arrow 1: Bacterial DNA insertion into the nucleus. (2) Arrow 2: mitochondrial DNA insertion into the nucleus.

paper we detail how microbiota target mitochondria to influence cell homeostasis. Three independent mechanisms are presented in figure 1.

Microbiota can control mitochondrial activity and REDOX homeostasis

Abundant evidence suggests that mitochondria are crucial in maintaining the innate immune system and inflammation (16). During infection, the peptides, toxins, or lipopolysaccharides (LPS) released by microbiota induce mitochondrial reactive oxygen species (ROS) production through activation of the pattern recognition receptor (Figure 1). The increased ROS level leads to the proliferation of stem cells followed by cell differentiation. A high cellular level of mitochondrial ROS blocks cell differentiation and promotes the inflammatory response. Inflammation is, among other things, a result of the activation of the inflammasome because of the re-localization of the NOD-like receptor family, pyrin domain containing 3 (NLRP3) to the mitochondrial membrane. Its subsequent activation leads to the release of cytokines and initiates an inflammatory response and adaptive immunity. In addition, ROS production activates a signaling pathway which induces antioxidant and detoxification gene expression through the transcription factor Nuclear factor E2 relater factor 2 (NRF2), or promotes mitochondria biogenesis through activation of the unfolded protein response.

Therefore, regulation of the mitochondrial activity and homeostasis is a key point of the microbiota-host cells crosstalk. For example, in *C elegans,* bacterial toxins impair the mitochondrial import and allow the re-localization of Activating Transcription Factor associated with Stress (ATFS-1) from mitochondria to the nucleus, where it activates the mitochondrial unfolded protein response genes (17). This specific gene activation re-establishes the mitochondrial homeostasis and activates the innate immune response. Similar mechanisms exist in mammal's cells. Alternatively, the production of carbon monoxide (CO) by a host can also induce mitochondrial biogenesis. A high concentration of CO inhibits the mitochondrial transport electron chain. However, ROS signaling due to interaction with the microbiota induces the release by the host of low concentration of CO which positively influences mitochondrial biogenesis and favors the clearance of pathogens from the gut (18).

Commensal bacteria such as *Lactobacillus johnsonii* BS15 directly control the mitochondrial activity. These bacteria decrease the content of mitochondrial uncoupling protein-2 and increase cytochrome *c* level in obese mice. These protein levels can increase ATP production and restore mitochondrial homeostasis. They are associated with reduced levels of serum lipopolysaccharide and attenuate local inflammation (19). Numerous pathogenic bacteria can directly reduce mtROS production. *M. tuberculosis* downregulates the lipopolyssacharide mediated signaling pathway and subsequent ROS production (20). Alternatively, *E chaffeensis* toxins can up-regulate activity of the mitochondrial detoxification enzyme MnSOD, which results in a lower ROS content and reduces the host cell apoptosis as seen in (21).

Interestingly, some bacteria can directly affect the mitochondrial electron transfer chain. Leschelle et al. have shown that microbiota produce large quantities of hydrogen sulfide (H_2S), which is known to inhibit cyto-

chrome oxidase, a major complex of the mitochondrial respiratory chain (22). Microbiota also releases nitric oxide (NO) which reduces the acetyl-CoA production and therefore downregulates the energy metabolism. Short Chain Fatty Acids (SFCA), released by microbiota due to the fermentation of dietary fiber, is an additional example of the modulation of energy metabolism (23). For example, butyrate can enter the TCA cycle to reduce NAD+ to NADH, a donor of mitochondrial electron transfer chain. Butyrate can be used as the only source of carbon by the colonocyte mitochondria even in presence of glucose (24). Moreover, butyrate not only regulates mitochondrial activity, but also promotes the release of signaling hormones such as GLP-1, which decreases food intake (25). Interestingly, the addition of butyrate to high fat diets of mice prevents the induced obesity generally observed (26). In addition, administration of human milk to rats compared to cow milk increases the fecal butyrate concentration associated with enhanced mitochondrial activity (13). To summarize, molecules released by the microbiota modulate mitochondrial activity and biogenesis. Depending on their concentration, these molecules promote or affect the mitochondrial homeostasis that controls different cellular functions, in particular ROS signaling, innate immune response and energy metabolism.

Microbiota may affect nuclear gene expression by promoting bacterial DNA insertion

Bacterial DNA insertion in the nuclear genome of a host cell is well known with plants. For example, *Agrobacterium tumefaciens* injects DNA, provoking plant tumor growth and changes in host cell metabolism. These changes induce optimal growth conditions for bacteria. Recent studies have pointed out the possible ongoing lateral transfer gene between the bacterial DNA and the host nuclear genome in humans (27). Bacterial DNA insertion to the nuclear genome occurs primarily in the somatic tissue. These insertions are significantly higher in cancer cells. We can hypothesize that the presence of microbiota increase these bacterial DNA insertions into the nucleus and induce change in gene expression and/or promote mutagenesis that favors bacteria-host interaction and causes diseases (Arrow 1 figure 1). However, this transfer remains controversial because such transfers occur mainly in somatic cells. Some possible contamination of the nuclear genome by bacterial DNA during DNA samples preparation may occur (27). We are planning experiments to test this particular mechanism.

Mitochondrial DNA insertion occurs in human somatic cells and may be trigger by microbiota activity

Many studies show that mitochondrial DNA insertion in the nuclear genome continues to occur even if almost all mitochondrial genes have already been transferred to the nucleus (28). This transfer is dependent on DNA double strand breaks reparation. Such mitochondrial DNA insertions have been shown to preferentially target coding or regulatory sequences associated with several human diseases (28). It is known that bacterial infection induces high ROS production and promotes the mitochondria membrane alteration as observed during *listeria* infection (29). Mitochondrial alteration is associated with the release of mitochondrial DNA into the cytoplasm. We can hypothesize that the release of mitochondrial DNA fragment associated with high cytoplasmic ROS may favor mitochondrial DNA insertion in nuclear genome. In such cases, microbiota can trigger bacterial DNA insertion into the nucleus genome and alter nuclear gene expression (Arrow 2, figure 1).

Altogether, microbiota may alter gene expression through modulation of ROS production by mitochondria. Furthermore, as opposed to the release of microbiotal factors that control the mitochondrial activity, the modulation of host response toward microbiota may also be linked to the direct control of the nuclear genome integrity. At this point, we are lacking data that allows us to know whether control of the nuclear genome through bacterial DNA insertion is dependent on the mitochondrial activity.

Discussion

The role of mitochondria during the host microbiota cross-talk is essential in order to modulate the innate immune response. Microbiotal species tend to control mitochondrial activity in order to favor interaction and infection. Indeed, the response of host cells toward microbiotal presence is dependent on the presence of factor released by microbiota which increases (SCFA…) or decreases (NO; MnSOD…) mitochondrial activity and ROS production. Unknown mechanisms by a variety of metabolites originating from the microbiota may be relevant for mitochondrial homeostasis and remain to be discovered. The balance between these factors may trigger an adequate host response. Imbalance between bacterial species among the microbiota may increase mitochondrial ROS production and the inflammatory response, generating disease. Difference in microbiota quality and diversity has been associated with several diseases including bowel inflammatory disease and obesity (30,31). Alternatively, based on current available data, bacterial species can also trigger insertion of bacterial or mitochondrial DNA within the host genome and induce mutation of somatic cells independent of mitochondria.

In considering these effects, it is tempting to think that targeting microbiota can be useful to manage intestinal ROS, oxydative stress, inflammation and metabolic anomalies due to the alteration of the microbiota as we previously reported (5–7). The objective will be to modulate the quality and diversity of the microbiota of each person, rather than acting on the microbiota metabolites and the microbiota related factors (ROS, NO, H2S, SCFA). Probiotics, diet or fecal transplantation are new emerging strategies to modulate the quality and diversity of microbiota. The medicine of tomorrow will be completely personalized. The first step will be to analyses the quality, quantity and diversity of microbiota. Based on this analysis, preventive or therapeutic strategy (probiotics, diet, fecal transplantation) will be administrated to patients. The era of digital medicine is open.

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