Aging: An evolutionary competition between host cells and mitochondria

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ABSTRACT

Here, a new theory of aging is proposed. This new theory is referred as the Host-Mitochondria Intracellular Innate Immune Theory of Aging (HMIIITA). The main point of this theory is that the aging is rooted from an evolutionary competition, that is, a never ending coevolutionary race between host cells and mitochondria. Mitochondria are the descendants of bacteria. The host cells will inevitably sense their bacterial origin, particularly their circular mtDNA. The host intracellular innate immune pressure (HIIIP) aims to eliminate mtDNA as more as possible while mitochondria have to adapt the HIIIP for survival. Co-evolution is required for both of them. From biological point of view, the larger, the mtDNA, the higher, the chance, it becomes the target of HIIIP. As a result, mitochondria have to reduce their mtDNA size via deletion. This process has last for 1.5–2 billion yeas and the result is that mitochondria have lost excessive 95% of their DNA. This mtDNA deletion is not associated with free radical attack but a unique trait acquired during evolution. In the postmitotic cells, the deletion is passively selected by the mitochondrial fission-fusion cycles. Eventually, the accumulation of deletion will significantly jeopardize the mitochondrial function. The dysfunctional mitochondria no longer provide sufficient ATP to support host cells’ continuous demanding for growth. At this stage, the cell or the organism aging is inevitable.

Introduction

Aging seems to be an inevitably irreversible process. This is particularly valid for higher metazoans which do not possess large numbers of stem cells. Some species have a long lifespan, whereas, some exhibit the accelerated aging, thus, live shorter, while others are aging at an intermediate velocity. All of these lifespan variations lead to the marvelous diversity of life histories in creatures inhabiting earth. However, humans represent the only species who care about aging, tries to extend life and to maintain healthy state. Starting from our ancestors several thousand years ago, the pursuit of longevity has not been stopped yet. As a result, at least, 300 plus theories and hypotheses which are related to aging have been formulated [1] and many animal studies as well as computer simulations have been performed in attempts to prove these theories and hypotheses. Even though countless efforts have been made and considerable amounts of money have been spent, no fundamental breakthrough on aging research has been achieved till now. It appears that the aging research will continue forever.

Among the aging hypotheses, the “Mitochondrial Theory of Aging” (MTA) [2] has gained ground. MTA can be considered as an extension of the free radical theory of aging which was proposed by Denham Harman [3]. He hypothesized that aging might be a result of accumulated cellular damage inflicted by free radicals. Mitochondria are a major source of free radicals or other reactive oxygen species (ROS) [4,5]. Moreover, researchers had assumed that mitochondrial DNA (mtDNA) in contrast to nuclear DNA (nDNA) is naked without protection by histone and, thus, is more vulnerable to ROS attack [6,7]. In addition, the repair mechanisms for mtDNA are less efficiency than those in nDNA [8]. These factors were supposed to cause high mutation rate in mtDNA compared to nNAD. The accumulation of mutant mtDNA was concluded to finally result in the dysfunction of mitochondria and therefore, in phenotypes of aging at cellular and organismal levels [9,10].

MTA, however, cannot plausibly explain some obviously contradictory phenomena of aging. For example, several long-lived species have higher levels of metabolic rate and generate more ROS than short-lived species [11]. Many studies have failed to find accumulated oxidative damage in mtDNA of old animals or even of humans [12,13]. Prolonged supplementation with mitochondrially targeted antioxidant did not attenuate age-related oxidative damage and rescue the loss of muscle mass and function associated with aging [14]. In addition, mtDNA is not as poorly protected as previously thought. On the contrary, mtDNA is well protected by a robust protein coating with mitochondrial transcription factor A (TFAM) and proteins, including antioxidant enzymes [8,15,16]. All these factors let us to reconsider the merits of MTA.

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Here, we propose a new theory of aging which is also associated with mitochondrial mutation accumulation, but which is not primarily related to the free radical theory. We classify this theory as the Host-Mitochondria Intracellular Immunity Theory of Aging (HMIITA). A main point of this theory is based on the intracellular innate immune capacity of organisms. As it will be outlined below, the innate arm of the immune system has been shown to not only act in terms of intercellular interactions, but to also play an important intracellular role. I hypothesize that aging is rooted in intracellular innate immune processes which can be understood as a long lasting competition between host cells and mitochondria.

Co-evolution of host cells and mitochondria

Based on the endosymbiotic theory, the precursor of the mitochondrion has been an alphaproteobacterium which has been taken up by the protoeuakaryotic cell. It is impossible to decide whether the host cell has actively taken up the bacterium endocytically by attempting predation of a prey that escaped from becoming digested, or whether the bacterium intruded the host cell by inducing endocytosis, in order to persist as a parasite. Processes of uninvented intrusion as occurring in recent pathogenic bacteria may serve as models or not. Endosymbiosis has taken place many times in evolution, in which other bacteria or eukaryotes became endosymbionts of host cells. Well-known examples are cyanobacteria that have transformed into plastids, or the so-called P-symbionts in bacteriocytes of insects [17]. Some eukaryotic cells, especially those which carried plastids, have also turned into endosymbionts of other uni- or multicellular organisms, which thereby acquired so-called secondary plastids [18,19]. For instance, the dinoflagellate _Kryptoperidinium foliaceum_ carries a second nucleus belonging to a diatom-derived symbiont [20]. Even tertiary plastids caused by three successive endocytic events are known [21]. In these cases of secondary and tertiary endosymbiosis, a parasitic intrusion into the host appears rather unlikely. The concept of epibiotic symbiogenesis, in which epibiotic symbiosis precedes endosymbiosis [22], would also not be easily compatible with parasitic intrusion. However, such a preceding epibiotic stage seems less likely in cases of endosymbiogenesis of free-swimming partners, such as dinoflagellates and diatoms. With regard to the uptake of bacterial precursors of endosymbionts, a parasitic intrusion into host cells is not certain, but cannot be excluded. Close associations of archaean, which have been discussed as possible precursors or relatives of eukaryotes, and bacteria are well-known. This includes alphaproteobacteria, a taxon from which mitochondria have originated. Such associations have been studied in mixed biofilms found in the marine environment [23] in continental subsurface rocks [24], and in various other habitats. Multispecies biofilms are characterized by intra- and interspecific communication, both quorum and community sensing, exchange of extracellular membrane vesicles, cheating and competition with, sometimes, battle-like dimensions under conditions of limited resources [25]. Therefore, the situation in an ancient pre-endosymbiotic phase of evolution may have allowed both friendly and aggressive interactions.

Regardless of the mode of interaction between host and bacterial ancestor, the relationship between them has not been free from problems. During the course of evolution, the proto-endosymbiont, whether intruder or prey, has evolved into the mitochondrion [26]. This event might occur some 1.5–2.0 billion years ago [27]. At that time, the unicellular organisms had already evolved defense mechanism to against unwelcome intruders, such as virus and bacteria. This mechanism is referred as the intracellular innate immune response [28]. Thus, from the appearance of the early true eukaryotes there is a battle of host cells and the intruders and this is also applied to the precursor of mitochondrion. Independently of the mode of uptake as either a prey or an uninvited intruder, the bacterium and its descendants had and still have to avoid lysosomal digestion as well as any attack from the cytosolic side of the host. They have to mask themselves as “self” to the host cells by cheating.

The easiest and economically most fitted way is camouflage. For the bacterium, the most promising procedure might have been to cover itself with a membrane containing, at the surface exposed to the host’s cytosol, components of the host’s membrane, i.e., markers that seem to indicate “self”. Traditionally, the outer mitochondrial membrane is interpreted as a descendant of the endosomal membrane, which contains host membrane proteins that are specific for the inner face of the plasma membrane. This may be sufficient for preventing detection as “nonself” and attack from the cytosol, but it would not yet avoid lysosomal digestion, because the normal fate of an endosome is fusion with a lysosome. However, avoidance of lysosomal digestion has been described for alphaproteobacteria of the genus _Wolbachia_ [29], which have been regarded by some investigators as genetically close relatives of mitochondria [30]. In _Wolbachia_, the endosymbiont associates with Golgi-derived vesicles and is preferably found in the endoplasmic reticulum [29]. Another method of avoiding lysosomal digestion would be lysis of the endosomal membrane before fusion with the lysosome, a strategy used, e.g., by _Listeria_ [31].

The inner membrane of mitochondria still preserves the trait of a bacterial membrane by containing 20% cardiolipin (CL), which is characteristic of bacteria, especially, at this high concentration [32–36], thus, to cover this bacterial originated inner membrane is necessary. How the outer mitochondrial membrane was formed, may still be debated. The assumption of a derivative of the ancient endosomal membrane may have some likelihood, but lacks a direct proof. Other intracellular membranes that are able to fuse with endosomal membranes may also be considered, e.g., Golgi-derived vesicles or parts of the endoplasmic reticulum. Lysosomes as one kind of Golgi derivatives can only be taken into account, if the early proto-endosymbiont is sufficiently protected against digestion and low pH. This is possible in several recent pathogenic bacteria. Some of them such _Legionella pneumophilia_ secrete effector molecules that prevent phagosome maturation [34], whereas others such as _Chlamydia_, _Anaerospila_ and _Mycobacterium_ species prefer to hijack host lipids that prevent the endosome/lysosome fusion [35]. Whether an ancestral proto-endosymbiont may have been capable of hijacking the host’s membrane synthetic machinery to _de novo_ produce a membrane according to own requirements would only be conceivable in cases of prior endosomal lysis, as in _Listeria_ and may be rather unlikely. For alternative possibilities of proto-endosymbiont incorporation see Fig. 1.

After entry of the mitochondrial ancestor into the proto-eukaryote cell, a remarkable process of mitochondrial remodeling started. In morphological terms, the enlargement of the inner mitochondrial membrane took place, in favor of increased ATP production. The enlargement and associated folding may not be that much surprising as it may appear at first glance. In bacteria including _E. coli_, experimental overexpression of membrane proteins leads to membrane curvatures, intracellular membrane formation, and shifts in lipid-to-protein ratio and cardiolipin content [36]. In addition, the most importantly, it was the host similarity outer membrane formation.

For a long term of residents, the membrane modification is not sufficient to avoid HIIP. Host cells still can sense clues of the foreign material covered by the outer membrane. The intruders must fundamentally change themselves to eliminate their bacterially originated materials as more as possible. Among them, DNA is the only one which can be evolved and inherited by next generation. Thus, modification of DNA is the best choice for this purpose. Under the HIIP, the intruder has initiated the longest and most expensive modification on their genes by the process referred as the DNA deletion. In other hand, these deleted DNA segments (genes) have to be integrated and expressed in the host’s genomes, otherwise, the intruder also cannot thrive or survive by malfunctions due to the gene loss. It is known that the extent of horizontal gene transfer between the endosymbiont and the host. Such processes are generally common in endosymbiotic systems. They are well-known from plastids, though to a smaller extent than in
mtDNA erosion can have been associated with two different fates of the removed segments, (a) transfer into the nucleus and incorporation into nuclear chromosomes or (b) uptake into lysosomes via splice variants of LAMP2 proteins and degradation, a process known as DNAutophagy [46,47]. The decision between these possibilities may depend on the mechanism of mobilization. As soon as a gene copy has been transferred to the nucleus, by whatever mechanism, it becomes superfluous in the mitochondrion and can be deleted without disadvantage (Fig. 2).

After uptake of the proto-endosymbiont, one of the driving forces leading to mitochondrial gene erosion may be the host intracellular innate immune pressure (HIIPP).

Host intracellular innate immune pressure (HIIPP)

The terminology of intracellular innate immunity used here is different from the adaptive innate immune activity which is performed primarily by the specific immune cells. The terminology here is to refer the immune activity that occurs virtually in all individual cells and it is also referred as cell-autonomous immunity by some scientists [48]. This intracellular innate immune response has been present in the unicellular organisms [49] and it has been acquired before the appearance of the adaptive immunity in the multicellular organisms. This cellular self-defense has the potential to confer antimicrobial protection on most, if not all, cells.

Since Intracellular defense has to have existed beginning from the most ancient times of evolution, it is difficult to judge which of the early defense strategies are still at work or may have been transformed into modern cell-protective mechanisms. It also seems important to distinguish between different scenarios, such as (1) invasion of a bacterial parasite that actively leaves the endosome; (2) the presence of an intracellular bacterium within host membrane structures, e.g., modified endosomes prevented from fusion with lysosomes, and Golgi- or ER-derived vesicles; (3) the appearance of bacterial proteins or nucleic acids in the host cytosol; and (4) dysfunctional endosymbionts including mitochondria. Under condition (1), surface molecules can be more easily detected by the host and, additionally, components released from the parasite may induce alarm mechanisms. This may be more difficult in case (2), but is highly likely in (3). Under condition (4),
dysfunctionality must lead to signaling towards the host, in order to remove the problem. Under these perspectives, it seems necessary to distinguish between pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [50]. The most typical PAMPs are surface molecules of the bacterial cell wall or components of bacterial flagella, i.e., molecules not present in mitochondria. However, nucleic acids can be also identified as PAMPs because of differences to their eukaryotic counterparts, concerning base composition, secondary structures and enzymatic modification [50]. Recognition of non-self nucleic acids is known already from bacteria, e.g., by using restriction endonucleases, but this rather reflects antiviral strategies, whereas recognition of foreign DNA or RNA in eukaryotic cells is based on other molecules. This may also be a matter of antiviral protection, e.g., in the detection of double-stranded RNA (dsRNA), but can extend to DAMPs. Therefore, mitochondrial nucleic acids are of particular interest in the context of the intracellular innate immune system.

The innate immune system is able to detect signals from both outside and inside the cell. With regard to the topic of this article, we shall focus on the respective intracellular signals. However, the intracellular presence and detection of a foreign molecule does not necessarily mean that it has derived in an intracellular process. For instance, several toll-like receptors (TLRs) are able to detect bacterial nucleic acids: TLR3 recognizes dsRNA, TLR7 and TLR8 detect purine-rich ssRNAs, whereas TLR9 recognizes dsDNA [51]. Contrary to other TLRs, which are predominantly located in the plasma membrane, they are mainly acting in the endosomal compartment. Therefore, they come into contact with foreign molecules after these have been taken up by endocytosis. Thus, they detect external signals after internalization. One might argue that the TLRs have to reach the endosomes by trafficking through other intracellular membranous structures, from their site of synthesis (ER) via coat protein complex II (COPII)-coated vesicles to the Golgi. However, TLRs present in these other compartments are not necessarily active. As shown for TLR7, this receptor is activated in the endosome, by dimerization and proteolytic loss of its N-terminal domain [51].

In addition to DAMP recognition in endosomes or other vesicular structures, cytosolic sensors exist. Foreign RNAs can be detected in the cytosol by RIG-1 (retinoic acid inducible gene I) and MDAs5 (melanoma differentiation-associated protein 5), which both activate via the MAVS (mitochondrial antiviral-signaling protein)/IRIF3/IFN-κB pathway IFNα/β and CCR5 expression [50]. These routes are primarily seen as antiviral defense mechanisms. The mitochondrial role of MAVS is only incompletely understood. Evidence has been presented for stimulation of mitochondrial function under conditions of infections with RNA viruses [52]. An example for DNA detection in the cytosol is AIM2 (absent in melanoma 2), a component of the respective inflammasome and, thereby, inducer of proinflammatory cytokines [53]. Again, the function of AIM2 is mainly seen in the context of antiviral, but also antibacterial defense. The relationship to mitochondria may be restricted to mitophagy [54].

Another cytosolic detector of foreign DNA is cGAS (cyclic GMP-AMP synthase). The second messenger 2′,3′-cGAMP activates the ER protein STING (stimulator of IFN genes), which leads to the formation of proinflammatory cytokines, especially interferons. Cytokine release indicates extracellular actions, findings that are compatible with a primary role in antiviral defense, which is in accordance with observations in Cgas or Sting deficiencies. However, cGAS also detects mtDNA when appearing in the cytosol [50]. In this context, a surprising aspect of aging was detected. In murine and human fibroblasts, depletion of cGAS and STING counteracted cell senescence and prevented SASP (senescence-associated secretory phenotype) [55]. In turn, this indicates that mtDNA detection in the cytosol by cGAS, i.e., an action of the intracellular immune system, promotes senescence. On the one hand, cGAS appears as a mediator of cell stress reactions, but on the other hand, it gives rise to the assumption to be involved in aging-related diseases [56]. This conclusion is well in accordance with recent findings on a Sting gene polymorphism that is associated with low-risk of aging-related diseases, presumably by reducing inflamming [57].

Another question is that of the conditions under which mtDNA is released to the cytosol. Unfortunately, low-rate release as has to be expected in relation to mitochondrial gene erosion has not been sufficiently studied. Instead, the current knowledge is almost exclusively based on viral or bacterial infections or on oxidative mtDNA damage that induce the cytosolic appearance of mtDNA, as recently reviewed [58]. As soon as mtDNA or, even more, oxidatively modified mtDNA appears in the cytosol, this causes NLPR3 inflammasome activation [58–60]. In other words, released mtDNA, whether oxidized or not, appears as PAMP or DAMP signals, which fuel HIIIP, with consequences to the expression of proinflammatory cytokines, to mitophagy or to apoptosis. At first glance, mitophagy may be perceived as an aggressive action of the host towards mitochondria. However, the purpose of this process is rather to maintain a functional mitochondrial status in the host cell by removing those organelles or parts of the mitochondrial network that release DAMP molecules. Mitophagy has, in fact, been interpreted as a means for warranting the host’s tolerance towards well-functioning mitochondria [50]. This conclusion contrasts with the defense against intracellular bacteria, which are removed by autophagy in order to eliminate the uninvited intruder [61,62]. The processes mentioned above occur intracellularly but in outside of mitochondria.

The discovery of widespread mtDNA deletions and of competition between wildtype nucleoids and others carrying deletions of variable lengths [63] indicate that these events occur inside mitochondria. If as we have hypothesized that mtDNA alternations is the result of HIIIP, the question is how and which of the intracellular innate immune effectors enter inside mitochondria.

One of the complications for appropriately judging the role of mutant mitochondrial chromosomes results from the fact that a typical single cell contains thousands of mt nucleoids [63], which are either distributed over many mitochondria or are present in large mitochondrial networks, which may, in the extreme of skeletal muscle fibers, extend as a single, connected structure over a syncytium derived from several cells. These numerous nucleoids are not identical, but rather represent mixed populations of wild-type and mutated chromosomes. Mutations may concern single genes, but can also comprise deletions of different extension [63]. Although increased numbers of mutations do not necessarily lead to enhanced free radical formation, as shown in aging mitochondrial mutator mice [64], age-dependent increases in mutated variants of mt chromosomes should have an effect on mitochondrial functionality. Although the nucleoids can be densely packed with proteins, especially TFAM, mitochondrial mutation rates are by a factor of 10–17 fold higher than those in the nucleus [65]. TFAM-labeled nucleoids were shown to be located adjacent to or surrounded by the intracristal space, but were also found in cristae-free matrix space [65]. Moreover, nucleoids vary in their compaction by associated molecules not present in mitochondrial networks, which may, in the extreme of skeletal muscle fibers, extend as a single, connected structure over a syncytium derived from several cells. These numerous nucleoids are not identical, but rather represent mixed populations of wild-type and mutated chromosomes. Mutations may concern single genes, but can also comprise deletions of different extension [63]. Although increased numbers of mutations do not necessarily lead to enhanced free radical formation, as shown in aging mitochondrial mutator mice [64], age-dependent increases in mutated variants of mt chromosomes should have an effect on mitochondrial functionality. Although the nucleoids can be densely packed with proteins, especially TFAM, mitochondrial mutation rates are by a factor of 10–17 fold higher than those in the nucleus [65]. TFAM-labeled nucleoids were shown to be located adjacent to or surrounded by the intracristal space, but were also found in cristae-free matrix space [65]. Moreover, nucleoids vary in their compaction by TFAM binding, dependent on their state of activity [65,66]. Therefore, their vulnerability should be assumed to vary with their functional state. Nucleoids may also appear as larger clusters, which were found to be usually not homogeneously covered by TFAM [65]. Studies on nucleoid localization indicate binding to the inner mitochondrial membrane, but it has remained uncertain as to whether this concerns all of them [65].

The heterogeneity of mitochondrial nucleoids raises the questions of possible competition between variants and driving forces for clonal selection. According to recent studies, clonal expansion of variants takes place, may be influenced by aging and diseases, and does not generally favor wild-type mtDNA [63]. For instance, mt chromosomes carrying deletions may be favored by shorter replication times. A recently proposed model assumed product inhibition by mitochondrial proteins on mRNA primers required for mtDNA replication and a
selection advantage by diminished feedback in variants with deletions concerning the genes of feedback protein [63]. The ultimate of mitochondrial heteroplasmacy can be remarkably high and the extent of deletions can concern substantial sections of the mt chromosome [63]. Whatever the selection advantage may be, clonal expansion of mtDNA variants carrying deletions lead to a decline in ATP production, mitochondrial dysfunctionality or, alternately, apoptosis.

In author’s opinion, the HIIIP may act as a major selection force for mitochondria deletion and the clonal expansion of shortened mtDNA mutants (will discussed in Section “The speculated aging process based on the HIIIP”). However, as emphasized above, reduction of mitochondrial functionality can finally lead to DAMP signals appear.

For host cells, the selection force is the increased ATP demand for thriving and for competing with their counterparts. Under the nature selection, host cells and intruders had to coevolve. The results are that the intruders have lost more than 95% of their original bacterial genetic material. Many but by far not all of these bacterial genes have been adopted by the host cells and integrated into their genomes. The host cells have become highly dependent on the abundant ATP supply provided by the endosymbionts that evolved to mitochondria. The outcome appears to be perfect. However, one should remember that there is no free lunch in biology. The seemingly perfect endosymbiotic relationship has a bad by-product, i.e., aging which appears only in the cells after they obtaining mitochondria, particularly in the multicellular organisms. I hypothesize that this aging process has originated from the innate immune competition between host cells and the mitochondria in the postmitotic stage of organisms.

Several issues related to this hypothesis

(1). Aging in organisms or at the cellular level mainly occurs in the postmitotic cells. This new role of HIIIP only applies to postmitotic cells and not to mitotic and mitotic cells due to the potentially different mechanisms related to mitochondrial fission (as will discuss later).

(2). Mitochondria still contain materials of bacterial origin which can become targets of HIIIP. These mainly include mtDNA, and cardiolipin. Cardiolipin, a typical lipid of the inner mitochondrial membrane (IMM) of bacterial origination. Insofar, it cannot represent a general HIIIP target, although its scramblase-mediated appearance in the OMM serves as a mitophagic signal. Only mtDNA has been subject to evolution and its variants can be selected. Thus, I speculated that the HIIIP is the selection force of the mtDNA modification and the principle driving force of aging.

(3). Various of cellular events trigger mitochondrial fission. For instance, the mitochondrial fission mechanisms acting during meiosis or mitosis differ from those in the postmitotic cells. During the meiosis or mitosis, mitochondrial fission serves as homogenous distribution of the genetic material (mtDNA) to the daughter mitochondria to keeps the mitochondrial population relatively uniform and healthy [67–70]. This type of fission is obvious not related to the aging process in the individuals but may be associated with the different lifespans among species (not to be discussed in the current paper). In postmitotic cells, mitochondrial fission is mainly related to the elimination of damaged mitochondrial fragments [71]. The processes of fission are well documented. Under the guidance of several elements which anchor in the mitochondrial outer membrane including mitochondrial fission 1 protein (FIS1), the dynamin-related protein 1 (Drp1) is recruited from the cytosol to the mitochondrial outer membrane [72]. The active Drp1 then initiates mitochondria fission. While mitochondrial fission is assumed to improve mitochondrial function [73]. However, fission and fusion are not exclusively related to mitophagy, but also occur independently, in both mitotic and postmitotic cells. This may be controlled by hormonal stimuli and/or calcium levels. The fission/fusion cycle has been shown to be also controlled by circadian oscillators [74]. Moreover, the fission/fusion balance is altered by mitochondrial proliferation as stimulated by metabolic sensing [75].

Interestingly, similar sizes of mtDNA mutants have the trend to segregate together, respectively [76]. This characteristic of mtDNA segregation is an important factor to enhance the deleted mutant selection during the course of aging. Due to the highly heterogenic property of the multiple mtDNA copies (wild type and mutants) in a mitochondrion, these selected mutants initially will not significantly impact the mitochondrial function. However, as the selection process is going on, the accumulation of the deleted variants finally will jeopardize mitochondrial function and result in cell incompetence.

(4). Autophagy is a typical intracellular innate immunome process that the host cells use to clean up the “foreigners” (bacteria, virus) and damaged compartments in almost all cell types [62,77]. This process is triggered either by PAMP or DAMP [78,79]. Mitophagy is the autophagy that specifically targets the damaged mitochondrial segments [71,80,81], usually generated by the mitochondrial fission in postmitotic cells. Mitophagy is the direct evidence to indicate that mitochondria are under the HIIIP. The mtDNA, especially the wild type, and the bacterially originated cardiolipin, when appearing at the OMM, are the likely triggers of mitophagy [82–85]. Additional evidence of the HIIIP against mitochondria is the inflammasome formation which is another indicator of host intracellular innate immune response [86]. The inflammasome initiator, NLRP3, is also localized in the damaged mitochondrial membrane [87]. The chronic low-grade inflammation is often associated with aging process and it is termed as inflammaging [88–90]. The mtDNA deletion and intracellular chronic low-grade inflammation triggered by mtDNA or mitochondrial cardiolipin are the twins resulting from the continuously HIIIP against the mitochondria. Mitochondria also play a critical role involving intracellular innate immune activity [50].

(5). Free radical attack on the mtDNA primarily induces point mutations. Several studies have failed to support that point mutation accumulated in the mitochondria is a substantial cause of aging, but data support the accumulation of deleted mutations being the culprit of aging in mice or in human [91,92]. Thus, free radical attack may not be the primary causative factor of aging, but it causes some diseases that will lead to accelerate the aging process. Under the normal condition, the free radical formation and the antioxidant system are in balance. The free radical and antioxidant imbalance often occurs under mitochondrial stress [93–95]. Thus, it is possible that excessive free radical production may be an active mechanism of the mitochondrial response to the unfavorable environments they have experienced. Imbalanced free radical formation causes the cascade reaction including mitochondrial permeable transient pore (mtppt) opening, cytochrome C release and host cell apoptosis. This is probably another side of the continuous battle of host cells and mitochondria. The overwhelming generation of the free radicals by mitochondria may mainly associate with some diseases and has little to do with the nature aging per se.

(6). Adaptive immune response against mitochondria has been frequently reported [96–98]. The antibodies against mitochondrial encoded proteins, mtDNA, cardiolipin, etc. have been identified in patients [99–101]. Theses adaptive immune responses are collectively classified as an autoimmune reaction. The reason is that the mitochondria are considered as part of ourselves by most of physicians. Actually, our body recognize many mitochondrial elements as the foreign antigens when the immune surveillance cells encounter with these elements. This evidence indicates that the immune response between hosts and intruders occurs at a different level (the level of intercellularly). The adaptive immune response
against mitochondria is probably not associated with the aging but the diseases.

The speculated aging process based on the HMIIITA

Immediately after birth, the newborn has mitochondria being dominated with wild type mtDNA populations. These mitochondria are obtained from mitochondrial fission during the process of meiosis from maternal and then mitosis in embryonal development. In the early life, most of the cells are still going through mitosis, as we mentioned that the mitochondrial fission in mitosis generates symmetric daughter mitochondria. After majority of the cells enter the postmitotic status, the asymmetric mitochondrial fission takes place. Mitochondrial fission at postmitotic cell separates the damaged portion of mitochondria from their relatively healthy portion. The purpose of this type fission serves as a method to eliminate damaged mitochondrial segments; however, this process also becomes a passive selection force for mitochondrial evolution in individual postmitotic cell. Many factors can cause mitochondrial damage. Here, the attention is given to the potential damage initiated by the HIIP. Due to the bacterial origin with circular structure and the unmethylated CpG islands [102], mtDNA seems the most favorite target for the HIIP. From an immunological point of view, the larger the mtDNA, the higher, the chance that it becomes the target of HIIP due to the larger mtDNA possessing more attacking sites than that of the smaller one for HIIP. Wild type probably is the largest mtDNA among the mutants of deletion. Thus, most likely, the majority of the immune actions will occur on the wild type mtDNA. To avoid this attack, mitochondria have a trait to reduce their mtDNA sizes by deletion. This is the trait that has resulted in mitochondria having emitted more than 95% of their genome during evolution. Even through the mutants of deletion in postmitotic cells cannot pass over to next generation and contribute to evolution, they have still possessed this trait acquired from maternal inheritance. As a result, mtDNA deletion occurs in a regular base in postmitotic cells. It is not unlikely that the host intracellular innate immune effectors, probably the peptides or RNAs, enter into mitochondria. If the size of these effectors are at the range of 1.5 kD or less they can enter mitochondria via the mPTP which allows such sizes of substances to across [103]. The large molecular immune effectors can also be translocated into the mitochondria by specific or non-specific translocators. As we mentioned above that TLR9 or cGAS are present intracellularly and also endosomally active. There is no reason to exclude their mitochondrially active. Both TLR9 and cGAS recognize mtDNA as PAMP and/or DAMP. If these host intracellular innate immune effectors enter mitochondria they will interact with the mtDNA to form an immune complex and/or damage it. mtDNA localizes close to the mitochondrial inner membrane and this immune attack will impact the intact of inner membrane and the ETC, reduce the membrane potential and significantly impede the mitochondrial function. Reduced membrane potential is the decisive factor to initiate the mitochondrial asymmetric fission [104,105]. The specific mitochondrial outer membrane proteins including FIS1 will first sense the altered mitochondrial membrane potential and recruit Drp1 to the mitochondrial outer membrane from cytosol. The active Drp1, then, recruits other effectors to initiate the mitochondrial fission process [106,107] (Fig. 3). This process leads to a mitochondrion dividing into two asymmetric fragments. One contains more wild type mtDNA which is heavily attacked by HIIP and it will be subjected to mitophagy to be cleaned up [105]. The remaining fragment contains more of the deleted mtDNA mutants which are less attacked by the host innate immune effectors and it is relatively healthy compared to the wild type. It then will be fused with other mitochonrdion or mitochondrial fragment via a process of mitochondrial fusion. For several fusion-fusion cycles, the mtDNA deleted mutants are selected (Fig. 3). This selection lacks any long term of survival benefit for cells and it is considered as a passive procedure accompanied with elimination of the substantially damaged mtDNA. It just selects the bad from the worst.

If the functions of the mitochondria with the selected mutants are not substantially impeded, the cells can still maintain their minimal requirements for survival and growth; however, the growth for the individuals will be slow down compared to the young ages. After removal of the wild type of mtDNA, the relatively large mutants will become the next favorable targets of the HIIP. This process continues until to the point that the selected mtDNA mutant is too small to maintain the functions of mitochondria. The dysfunctional mitochondria can no longer provide sufficient ATP for the host cell’s growth, but to generate more free radicals to further damage the cell functions. The aging becomes obvious at this point.

The testable feature and perspective

HMIIITA is testable. For example, some of indirect evident support the HMIIITA. In murine and human fibroblasts, depletion of cGAS and STING which are the host intracellular innate immune effectors primarily to attack mtDNA counteracted cell senescence and prevented senescence-associated secretory phenotype [55]. In addition, when depleting the mtDNA in unicellular organism, rh0 yeast cells, it significantly increased their longevity [108]. The association between aged phenotypes and increased resistance against cell death has also been observed in SK-Hep1 rh0 cells [109] which are mammalian cells being lack of mtDNA. The well-known immunosuppressory agents, cyclosporin A and rapamycin, both reduced aging-related disorders and prolong the life span of mammals [110–113] even the additional mechanisms were involved for their anti-aging effects, the suppression of intracellular innate immunoresponse cannot be ignored. If the new types of specific intracellular innate immunosuppressive molecules have been identified which act at different sites or pathways, judging from the current evidence the combination of these molecules might significantly slow down the aging process and prolong the life span of organisms. This may have the trade-off effects for more vulnerable to certain infectious diseases. If the adaptive immunoresponse was not impeded by these agents the infectious diseases could still be manageable due to the nature that the majority of infectious diseases are finally controled by the adaptive immunity. Thus, this opportunity was worthy of investigation.

Conclusion remarks

The HMIIITA hypothesizes that the mitochondrial gene erosion during evolution is mainly made by the HIIP via mtDNA deletion and the aging is the by-product of the coevolution of the host cell and mitochondria in the postmitotic stage under the continuously HIIP. Importantly, this theory is readily testable.

There is no doubt that aging is caused by multiple internal and external factors which have been reviewed by countless publications. In the current paper, the attention is only given to the host intracellular innate immune competition between host cells and the mitochondria. HIIP may be one of the many factors which lead to cell as well as organism aging. This HMIIITA is not aimed to replace any existing aging theory but is only the complimentary to the 300 plus aging theories. Hopefully, the HMIIITA will stimulate the enthusiasm in the field of aging research.

Conflict of interests

The author claims no conflict interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.04.007.
References


