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Organ Reserve, Excess Metabolic Capacity, and Aging

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Abstract

"Organ reserve" refers to the ability of an organ to successfully return to its original physiological state following repeated episodes of stress. Clinical evidence shows that organ reserve correlates with the ability of older adults to cope with an added workload or stress, suggesting a role in the process of aging. Although organ reserve is well documented clinically, it is not clearly defined at the molecular level. Interestingly, several metabolic pathways exhibit excess metabolic capacities (e.g., bioenergetics pathway, antioxidants system, plasticity). These pathways comprise molecular components that have an excess of quantity and/or activity than that required for basic physiological demand *in vivo* (e.g., mitochondrial complex IV or glycolytic enzymes). We propose that the excess in mtDNA copy number and tandem DNA repeats of telomeres are additional examples of intrinsically embedded structural components that could comprise excess capacity. These excess capacities may grant intermediary metabolism the ability to instantly cope with, or manage, added workload or stress. Therefore, excess metabolic capacities could be viewed as an innate mechanism of adaptability that substantiates organ reserve and contributes to the cellular defense systems. If metabolic excess capacities or organ reserves are impaired or exhausted, the ability of the cell to cope with stress is reduced. Under these circumstances cell senescence, transformation, or death occurs. In this review, we discuss excess metabolic and structural capacities as integrated metabolic pathways in relation to organ reserve and cellular aging.

Keywords

Excess Metabolic Capacity; Organ Reserve; Cell Senescence; Mitochondria; Complex IV; Methylene blue; mtDNA; Telomeres

Introduction

Organ reserve describes the ability of an organ to endure recurring stressful conditions, especially at a young age, and restore the normal homeostatic balance and function in a relatively short recovery time (Neustadt and Pieczenik, 2008). Part of the age-related decline in physiological functions is attributed to reduction in organ reserve as presented in many of the body systems (Iliodromiti *et al.*, 2016, Goldspink, 2005, Bortz and Bortz, 1996). The functional decline in specific tissues or organs (e.g., immune-, musculoskeletal-, nervous

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systems) is a key characteristic of aging. Although organs vary in the rate of functional decline with age, this linear decline of reserve capacity with age shows values ranging from 0.5% to 1.4% per year (Bortz and Bortz, 1996, Sehl and Yates, 2001). However, the decline could accelerate by the fifth decade of age (Bortz and Bortz, 1996), which may explain, in part, the age-related increase in vulnerability to disease and infections, complications after clinical procedures, as well as frailty following exposure to stressful conditions (Savji *et al.*, 2013). These observations indicate that aging is characterized by limited organ reserve. The consequences of this decline become evident under stressful conditions.

The disease prognosis and the rate of recovery from a clinical procedure (e.g., treatments, invasive clinical procedures), as well as the health outcome of the patient in general are affected by the robustness (health and resilience) of the organ reserve of the patient. Tim Ahles and colleagues (Ahles *et al.*, 2012), showed that the aging process differentially impacts organ reserve in cancer patients. The age of cancer patients at the time of initiating chemotherapy (a cause of chemical and oxidative stress) as well as their general health appear to determine their ability to endure the treatment and predicts the prognosis for the patient. Interestingly, clinical observations revealed the variability among the same age group of patients in their ability to respond to, and cope with, a comparable stressful condition. This variability is interpreted, in part, as a variation in the organ reserve as well as the pace at which organ reserve diminishes with age (Sarkisian *et al.*, 2008, Sternberg *et al.*, 2011, Ahles *et al.*, 2012, Sloan *et al.*, 2010). The authors concluded that organ reserve correlates with the outcomes of risky, invasive, or stress-inducing procedures such as surgical treatments or chemotherapy (Ahles *et al.*, 2012). They also suggested that organ reserve could have a special significance in clinical settings when weighing on treatment for older adults.

Although, organ reserve is well-documented in the clinical settings, it is not defined at the molecular level. We were intrigued with the potential significance of excess metabolic capacity to intermediary metabolism, organ reserve, and aging. Excess metabolic capacity refers to the excess (unutilized) activity that exceeds that is required for the normal basic function to allow the biological systems to operate at the basal level with the option of readily advancing to maximal capacity if needed. Organ reserve could be, in part, a joint contribution of excess (unutilized) metabolic capacities of several metabolic pathways and biochemical structures, which we will refer to as “structural capacity,” when discussed in the following sections. We propose that excess metabolic capacity of these pathways collectively contribute to organ reserve and enhance the ability of the young cell to cope with stress and recover from injury. Decline or exhaustion of the excess capacities could diminish organ reserve and influence the aging process. In this paper, we will review some of the well-known excess capacities in specific metabolic pathways while integrating the current research to this field in the concept of excess metabolic capacity. We will also propose new structural excess capacities and discuss their role in providing metabolic advantages for stress resistance and recovery from injury.

Intermediary metabolism and excess metabolic capacity

Intermediary metabolism refers to the biochemical reactions, structures, and metabolites within the living cell. Intermediary metabolism is enriched with biochemical steps or structures that exhibit excess metabolic capacity that exceed what is required for normal basic function. In some cases, the activities of some enzymes exceed the flux capacity of the pathways they are embedded within by more than 1,000 folds (Salvador and Savageau, 2003). Traditionally, excess metabolic capacities have been repeatedly demonstrated in energy and redox systems such as glycolysis, hexose monophosphate shunt (HMS), TCA cycle, oxidative phosphorylation in addition to Na/K ATPase (Gnaiger *et al.*, 1998, Kramer *et al.*, 2014, Sansbury *et al.*, 2011, Desler *et al.*, 2012, Jones and Brewer, 2010, Eanes *et al.*, 2006, Dranka *et al.*, 2010). The energy and redox systems are the backbone for the intermediary metabolism while their intermediates are used in a variety of metabolic pathways (Houtkooper *et al.*, 2011). They are deeply connected to the structural and metabolic integrity of the young cell.

Energy metabolism depends on the integrity of mitochondrial DNA (mtDNA), which is found in multi copies per mitochondrion (Miller *et al.*, 2003). We propose that the multi copy number of mtDNA serves as a structural excess capacity that may contribute to organ reserve. Similarly, we propose that DNA repeats in telomeres could serve as structural excess capacity.

The genome of multicellular organism builds robust metabolism and mechanisms for stress response and repair that secure its metabolic integrity up to the productive age (Rattan, 1998, Rattan, 2015). These mechanisms appear to decline with age and several observations indicate that the metabolic integrity declines around the 4–5th decade (Carnes and Witten, 2014). The aging muscle, for example, exhibits reduced mitochondrial respiratory capacity that leads to a compensatory (or adaptive) increase in mitochondrial content. This increase results in ragged red fibers (RRF) harboring an abnormal accumulation of mitochondria in the aging skeletal muscle. Ragged red fibers are very rare under 40 years of age, although about half of subjects between the age of 40 and 50 possess them, their frequency exponentially increases in subjects older than 50 years (Pesce *et al.*, 2001).

Molecular damage, an increase in metabolic demand, chronic stress, or chronic loss of homeostasis could lead to hyperfunction (Zimniak, 2012). For example, pathological or stress conditions trigger adaptive mechanisms that induce hyperfunction which may lead to compensatory hypertrophy (e.g., the heart response to chronic high blood pressure). Hypertrophy if not controlled could lead to the exhaustion of the adaptive mechanisms and organ dysfunction (e.g., heart hypertrophy and failure or RFF). The molecular correlates of hyperfunction could utilize the excess metabolic capacities for the adaptive response to an increase in chronic stress, molecular damage, or functional demand (Zimniak, 2012).

The excess metabolic capacities embedded in various metabolic pathways are puzzling and give the impression of a superfluous investment in metabolic pathways. Their biological value and molecular correlates remains to be understood, particularly regarding the aging process. Organ reserve may require the contribution of excess metabolic capacities from

proteins embedded in various pathways of intermediary metabolism. For example, the product of a gerontogene could be one plausible candidate for providing a protein with excess capacity (Rattan, 1995). We will describe selected pathways that directly relate to energy metabolism and genome stability as well as present examples of excess metabolic capacities including structural reserve capacities and discuss their potential significance for organ reserve.

Excess metabolic capacity of the bioenergetics pathway

Energy drives the numerous cellular functions which maintains their activity, structural integrity, and the homeostatic set points of the normal metabolism. However, the bioenergetics system is intrinsically inefficient. It dissipates (wastes) energy in the form of heat and generates reactive free radicals and oxidants (e.g., O_2^-/H_2O_2)(Brand, 2016). The wastefulness of the bioenergetics system is proportional to its activity. Thus, it would be counterproductive if the bioenergetics system is constantly active at its maximal rate since it excessively releases heat and free radicals which would accelerate the rise in cell entropy (Hayflick, 2007). Therefore, the bioenergetics pathways evolved to allow the biological systems to operate at the basal level with the option of readily advancing to maximal capacity if needed (Dranka *et al.*, 2010). The difference between the basal and maximal respiratory activities (e.g., respiratory rate of the electron transport chain) is referred to as "respiratory reserve/excess capacity" (Dranka *et al.*, 2010).

The bioenergetics pathway instantly adjusts to the functional demand of the biological system. Such functional demand could be demonstrated during increase in metabolic, physical, and cognitive activities as well as stress. This fluctuating pattern in activity to match demand could serve to curtail excessive release of heat and production of reactive oxygen species, which keeps cellular entropy at a minimum level and may slow the process of aging (Hayflick, 2007). Thus, excess metabolic capacity could be also interpreted as a safety gauge that establishes a close match between the activities of metabolic pathways and abrupt surges in metabolic demands (Salvador and Savageau, 2003).

Interestingly, the levels of acetyl-CoA (Peleg *et al.*, 2016) and NAD (Miller *et al.*, 2017) increase in middle age in Drosophila and mice, respectively which seems to influence the lifespan by altering the epigenetics balance. The increase in acetyl-CoA and NAD could be compensatory response of the excess capacity of the bioenergetics pathway. However, these observations could also suggest that excess capacity of bioenergetics pathway intermediates affect the aging process through altering the cell epigenetic patterns. The role of metabolic capacity may extend beyond the need of increased metabolic demand.

Excess metabolic capacity of glycolysis and HMS

Excess metabolic capacity of glycolysis, over that required for basal metabolic demand, is demonstrated by excess activity in four of its enzymes; phosphoglucose isomerase, phosphoglucomutase, triosephosphate isomerase, and glycerolphosphate dehydrogenase (Eanes *et al.*, 2006, Merritt *et al.*, 2006). These enzymes are present in considerable excess capacity. Even a 5–10 times reduction below their normal activity level has no measurable

impact on the glycolytic activity and the organ function. These findings indicate that the glycolytic pathway as such has excess capacity *in vivo*.

HMS branches from glycolysis and diverts the reducing electrons from glucose to NADPH. The excess capacity of HMS is demonstrated in the excess capacity of glucose-6-phosphate dehydrogenase (G6PDH) and NADPH production (Salvador and Savageau, 2003). NADPH helps the cells resist oxidative stress after exposures to hydrogen peroxide (endogenous oxidant) or strong redox-active agent such as, primaquine or divicine (Salvador and Savageau, 2003). Thus, HMS is essential for cytosolic redox metabolism and defense mechanisms, which protects cellular functions from oxidative damage (Bolanos *et al.*, 2010, Salvador and Savageau, 2003). The redox equivalents in NADPH are also essential for the synthesis of low molecular weight metabolites (e.g., cholesterol, lipids) while ribose, one of the products of HMS, is used for the synthesis of nucleotides.

Excess metabolic capacity of the respiratory pathway

Excess capacity of mitochondrial complex IV is well-known and drives most of the respiratory capacity of the electron transport chain (ETC). The difference between coupled and uncoupled respiration correlates with the reserve respiratory capacity of mitochondria (Dranka *et al.*, 2010). Although complex IV is under tight regulation, it exists in excess relative to the other three ETC complexes. The molar ratio between complex IV and complex I in skeletal muscle is 6:1 (Schwerzmann *et al.*, 1989, Gnaiger *et al.*, 1998). However, a more moderate complex IV excess in some intact cells also has been reported *in vitro* (Villani and Attardi, 1997). Several experiments on mitochondrial respiration provided evidence that the activity of the ETC complexes and oxidative phosphorylation are also several folds in excess (Davey and Clark, 1996).

Excess capacity of complex IV appears to decline with age. Complex IV negative fibers are almost absent in subjects under 40 years of age. Their frequency is about 21% in ages between 40 and 50 and almost exponentially increase in subjects 50 years and older (Pesce *et al.*, 2001). This pattern of accumulation of tissue damage indicates reduction in (or exhaustion of) mitochondrial metabolic capacity around the 4–5th decade of age when functional decline of organs ensues (Carnes and Witten, 2014).

Aging is a multifactorial process that could differentially present among individuals of the same species and across the different species (Rattan, 2014). For example, a decrease in the reserve capacity of complex IV diminishes resilience and shortens lifespan in Drosophila melanogaster (Klichko *et al.*, 2014). Similar deficiencies in respiratory complexes in mammal cause disease if not lethal (e.g., human). Interestingly, function-reducing mutants in the respiratory complexes of the mitochondria in C. elegans extend (rather than shorten) the life span. This apparently contradictory observation is interpreted as a tradeoff of the increase in longevity with a slower (or delayed) development and decline or loss of fertility, both items would be considered disadvantageous outside the research models or in mammals (Jenkins *et al.*, 2004). It has also been proposed that metabolic compensation by an alternative metabolic pathway that bypass the mutated enzyme could explain the effect of the mutations in C. elegans on longevity (Rea and Johnson, 2003). Interestingly, the existence of an “alternative pathway” in C. elegans could be a backup that emulates the

concept of “excess capacity”. However, mammals and flies seem to lack specific alternative metabolic pathways that bypass, and thus compensate for, the deficient mitochondrial function. It is conceivable that evolutionary, metabolic, developmental, and habitat could account for the different outcomes of longevity in response to interferences with specific pathways among the various species (Rea and Johnson, 2003). These differences indicate that the pathway that could be considered a universal initiator of the aging process is not clear (Rattan, 2014).

Excess capacity of mitochondrial DNA (mtDNA)

Among the 37 genes of mitochondrial DNA (mtDNA), 13 code for proteins that serve as subunits in the ETC and ATP synthase (Kogelnik *et al.*, 1998). mtDNA-encoded subunits provide the catalytic activities in complexes I, III, and IV as well as ATP synthase. Coordinated gene expressions of mtDNA and nuclear DNA are necessary for the assembly of the four ETC complexes and ATP synthase. Therefore, mtDNA is fundamental for maintaining physiologically competent oxidative phosphorylation and ATP production with minimal production of oxidants. mtDNA is also critical for maintaining excess respiratory capacity.

mtDNA copies per mitochondrion are estimated between 2 to 10 copies (Veltri *et al.*, 1990, Wiesner *et al.*, 1992). Therefore, a nucleated cell with 1000 mitochondria is estimated to contain on average 2000–10000 copies of mtDNA. The total number of mtDNA per muscle fiber and cardiac cell *in vivo* is between 3500 and 7000 (Miller *et al.*, 2003). The redundancy in mtDNA (i.e., the genes of mtDNA) could be viewed as a reserve capacity (Scheme 1). The potential functional significance for the increase in the copy number of mtDNA could be that of reducing the impact of mutations on energy metabolism by having the genes of mtDNA in excess (Scheme 1). Given that the damage to mtDNA increases with age, reduced mtDNA stability negatively impacts the reserve capacity of mitochondrial respiration and thus the aging process. Increasing evidence suggests an important role of accumulating mtDNA mutations in the pathogenesis of many age-related neurodegenerative diseases as well as a number of age-related pathological alterations of heart, skeletal muscle, and vascular system (Herrera *et al.*, 2015).

Telomeres reserve capacity

Telomeres consist of a tandem TTAGGG repeats and are located at the terminals of a linear DNA string of chromosomes. Telomeres, with the nucleoprotein complexes, function to protect the genetic material by preventing chromatid fusion or degradation by exonucleases. Interestingly, each time a normal somatic cell divides a segment of the repeated sequence is eroded. Short telomeres trigger replicative senescence. Furthermore, exposure to oxidizing agents (e.g., free radicals, radiation, high O_2 tension) or mitochondrial dysfunction cause telomeric DNA damage and telomeres dysfunction (Fumagalli *et al.*, 2012, Liu *et al.*, 2002). Persistent damage to telomeric DNA as well as telomere attrition induces persistent DNA damage response (DDR), triggering replicative senescence (Fumagalli *et al.*, 2014, Rossiello *et al.*, 2014). Thus, telomeres may help maintain the integrity of the genome to preserve optimal intermediary metabolism and the normal activities of the cell and organ function.

The normal activity of the cell requires telomeres length to be above a threshold or the absence of persistent DNA damage response.

Telomeres could be viewed as reserve (excess) capacity of the repetitive DNA sequence TTAGGG (Scheme 2). In this regard, sustained (length or function) telomeres excess capacities maintains genome stability, preserves normal gene expression, and delays cell senescence (Scheme 2). Genome integrity, especially telomeres, is necessary for avoiding transformation, apoptosis, or cell senescence. Maintaining these metabolic functions is essential for an organ to recover from injury and to tolerate a stressful condition. Telomeres excess capacity is essential for delaying cell senescence. There are at least two ways that cell senescence could negatively impact the function of an organ and its ability to recover from injury and cope with stress, which are important characteristics of organ reserve. First, senescent cells lose their function and fail to divide, which impair their ability to replace dead or injured cells. Second, they adopt Senescence-Associated Secretory Phenotype (SASP), refers to the secretion of inflammatory cytokines, growth factors, and proteases from senescent cells (Watanabe *et al.*, 2017). Through SASP, senescent cells could impair the normal function of the somatic cells in their surrounding as well as progenitor cells, which impair recovery from injury. Dysfunctional telomeric DNA and short telomeres have been tied to cell senescence in aging as well as in age-related disorders and organ dysfunction (Kong *et al.*, 2013, Bernadotte *et al.*, 2016, Jeyapalan *et al.*, 2007). Interestingly, methylene blue (MB), most effective agent that delays cell senescence, slows the attrition rate of telomeres (Atamna *et al.*, 2015).

Metabolic reserve of the neuronal systems

Neural ion homeostasis is maintained by the sodium potassium ion ATPase (Na/K ATPase). Following neuronal activity, the Na/K ATPase re-establishes the ionic homeostasis allowing neurons to create repetitive action potentials and release neurotransmitters, which are critical for neuronal plasticity and establishing cognitive reserve. The Na/K ATPase exhibits large reserve capacity that exceeds the basic physiological demand *in vivo* (Knudsen and Johansen, 1990). Furthermore, Na/K ATPase is energy consumes close to 2/3 of the cell energy, making it dependent on the bioenergetics reserve capacity (Howarth *et al.*, 2012, De Lores Arnaiz and Ordieres, 2014). The activity of the Na/K ATPase declines with age, which may contribute to decline in neural excess capacity. Neural excess capacity is essential for brain plasticity and cognitive function (De Lores Arnaiz and Ordieres, 2014, Wyckelsma and Mckenna, 2016).

The antiaging effects of metabolic excess capacities and organ reserve

Excess metabolic capacities could include forms of enzymatic activities (e.g., complex IV), copy number (e.g., mtNDA), and/or repeats (e.g., telomeres). Potential additional candidates to excess metabolic capacities could be distributed across the intermediary metabolism. For example, in the absence of direct evidence for a clear programmed aging process or aging-specific set of genes, alternative platforms to understand aging were proposed in the form of gerontogenes, which determine hemodynamic space for the cell, and “network entropy” (Rattan, 1995, Manke *et al.*, 2006). Gerontogenes could encompass a set of genes that are

involved in the maintenance and repair of various cellular functions. Thus, gerontogenes and hemodynamic space overlap with the concept of excess capacity and together could provide, in part, a metabolic frame of adequate metabolic functions to sustain longevity assurance for the organism. Most importantly, this frame does not contradict the notion of the nonadaptive nature of the aging process (Rattan, 2015).

Excess capacity could also rely on the functional resilience of a biochemical network. The functional resilience of a biochemical network was evaluated following random perturbations induced by reducing the activity of specific proteins (Kamath *et al.*, 2003). Interestingly, it has been found that these perturbations do not result in any phenotypic variations in a large number of networks (in yeast and *c. elegans*). Building on these observations, Demetrius et al. used statistical mechanics and large-scale protein interaction screens to characterize the diversity of possible pathways in terms of “network entropy”; a collective measure for the diversity in the molecular interactions in a network. In this regard, “network entropy” refers to the natural structural diversity embedded in macromolecules (e.g., polymorphism), which influence their properties (e.g., redundancies in binding, activity, function etc.). At the structural level, a network with higher “network entropy” (diversity) disintegrate less rapidly under random perturbations. Network entropy is based on the dynamical diversity of the microscopic processes underlying the macroscopic cellular state and correlate with the macroscopic robustness of a system (Demetrius *et al.*, 2009). Demetrius et al. concluded that network entropy is advantageous to cell survival by allowing the network to tolerate and resist perturbations in gene expression or activity-reducing mutations (Manke *et al.*, 2006, Demetrius *et al.*, 2009). Thus, network entropy could provide additional approach to understand the process of aging and a rationale to study proxies of biochemical network resilience to random perturbations. The network resilience to perturbations and grontogenes could carry elements of redundancy and thus may provide some evolutionary bases to the origin of excess capacity and organ reserve.

These various potential sources for excess capacities could collectively contribute to organ reserve and the aging process (Scheme 3). We propose that excess metabolic capacities are interconnected and influence each other through a synergy or additive effects (e.g., redox/bioenergetics excess capacity and mtDNA). Excess metabolic capacities and organ reserve provide an opportunity to consider the collective contribution of many factors to the aging process.

Bioenergetics excess capacity lowers cellular entropy

In general, “entropy” refers to stochastic events that increase the randomness and degree of disorder in a system, which correlates with its level of damage and disintegration. Biological systems employ proteins, nucleic acids, and cofactors, which are also subject to age-related increase in cellular entropy (e.g., stochastic covalent modifications or mutations) and disintegrations. Cellular repair and maintenance systems work to counter the increase in cellular entropy” (Hayflick, 2007). Excess capacity of complex IV could lower the pace of free radical production by the ETC in the mitochondria. Complex IV is a terminal oxidase that is responsible for consuming more than 95% of the oxygen that enters the cell (Ferguson-Miller *et al.*, 2012). It catalyzes the four electrons reduction of O_2 to H_2O, which

is a key step in energy extraction from nutrients. Excess reserve of complex IV (Diamond and Hammond, 1992) consumes most of the O_2 that reaches the mitochondria, making it a key player in determining the mitochondrial concentration of O_2. Oxygen effectively dissolves in membranes (Shiva *et al.*, 2001). Thus, high O_2 concentration in the inner-membrane of the mitochondria increases the risk of partial O_2 reduction by the redox centers of the ETC, leading to the formation of free radicals and oxidants (e.g., O_2^- and H_2O_2). Interestingly, ETC-dependent free radical production increases under hyperoxia (Sanders *et al.*, 1993). Partially reduced O_2 intermediates are formed only by the redox centers upstream of complex IV. Therefore, high activity of complex IV oxidizes the upstream centers and lowers the risk of oxidants formation. Several studies showed that the production of free radicals by the mitochondria, negatively correlates with the activity of complex IV, which could be attributed to low mitochondrial [O_2] (Guidot *et al.*, 1993). Thus, excess complex IV capacity could slow H_2O_2/O_2^- production (Xin *et al.*, 2003), thus reducing cellular entropy and slowing the aging process. Complex IV negative fibers sharply increase after the fifth decade of age (Pesce *et al.*, 2001). A decrease in complex IV reserve capacity diminishes resilience of Drosophila melanogaster and shortens lifespan (Klichko *et al.*, 2014). Furthermore, the level of complex IV decreases in Alzheimer's patients and with aging (Jones and Brewer, 2010).

Interestingly, Hekimi et al demonstrated that the heterozygote phenotype of MCLK (*mclk*$^{+/-}$) causes partial reduction in Coenzyme Q synthesis (Lapointe and Hekimi, 2008). However, the levels of coenzyme Q were not affected by this phenotype. *mclk*$^{+/-}$ mice exhibits marginal decline in the activities of some of the mitochondrial enzymes (ranges between 10–33%) in addition to mitochondria-specific oxidative stress. This oxidative stress is absent in cytosol, nucleus, and membranes (Lapointe and Hekimi, 2008). The authors also found that the genotype *mclk*$^{+/-}$ creates a phenotype resembles CR. The real effect of *mclk*$^{+/-}$ is not clear, however the authors propose that the mitochondrial mild stress could have hormetic effect by inducing compensatory mechanisms that protect from oxidative stress in the cytosol, nucleus, and membranes.

mtDNA damage and mutations increase sharply after the fifth decade of age (Herbst *et al.*, 2016). Major causes for mtDNA susceptibility to mutations include high rate of production of oxidants by the ETC (e.g., when complex IV reserve capacity diminishes), mtDNA close location to ETC, and limited repair of mtDNA (Lee and Wei, 2005). The mutation rate of mtDNA exceeds that of nuclear DNA by 10 folds. Furthermore, aging reduces the copy number of mtDNA (Mao and Reddy, 2011). Environmental factors can also contribute to increasing mtDNA instability and thus influence the aging process (Aiken *et al.*, 2015). The large copy number of mtDNA per cell provides substantial excess capacity and resistance to the outcome of the age-related modifications to mtDNA (Scheme 1). Excess reserve of mtDNA helps preserve gene expression and slows the decline in bioenergetics metabolism. Mitochondrial dysfunction contributes to telomeres shortening and to the process of senescence in somatic cells (Atamna *et al.*, 2015, Liu *et al.*, 2002). Heteroplasmy, a variation in mtDNA sequence due to mutations within a single cell, it results from the increased copy number of mtDNA. Heteroplasmy is an indication for the buffering capacity and the functional significance of excess capacity of mtDNA. The functional consequence of heteroplasmy occurs after a threshold of mtDNA mutation is reached (usually estimated >

50%) (Sobenin *et al.*, 2014), which mostly affects energy demanding tissues such as neurons or muscles (e.g., MELAS; mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes and MERRF; mitochondrial encephalopathy with ragged red fibers). Each of the factors discussed above could compromise the bioenergetics reserve capacity, increase cell entropy, trigger cell senescence, accelerate the process of aging, and increase the risk of age-related disorders.

Excess telomeres capacity preserves genome stability and delays cell senescence

The length of telomeres varies among individuals, between young and old, thus it may correlate with longevity and healthy aging (Monaghan, 2014). The length of telomeres in human cells varies and ranges between 10–15 kb (Kong *et al.*, 2013, Callen and Surralles, 2004). By the time the cell ages due to natural causes, the length of telomeres decreases on average below 10 kb (Madonna *et al.*, 2011). Interestingly, telomere length is highly heritable, longer in women than in men (Gardner *et al.*, 2014) and correlates with chronological age and the risk of chronic diseases of aging. A correlation between telomere length, the quality of aging, and the risks for age-related disorders has been demonstrated in several studies among various species (Kong *et al.*, 2013, Bernadotte *et al.*, 2016, Jeyapalan *et al.*, 2007).

The large number of telomere repeats per cell provides excess capacity that helps the cell resist the age-related erosion or damage in DNA ends (Scheme 2). Intact telomeres maintain DNA integrity and genes expression, which are the basis for optimal intermediary metabolism and excess metabolic capacity. Furthermore, telomeres excess capacity allows the cell to gain large number of doublings and extends the ability to divide when needed to replace dead cells, such as in adaptive compensatory hyperplasia, which allows tissue regeneration.

Telomeres attrition or dysfunction occurs with each round of somatic cell division or as a result of persistent damage, respectively. Oxidative stress could also drive telomere erosion, probably due to the high content of deoxyguanosine. Deoxyguanosine forms a complex with redox active metals (e.g., Fe, Cu) or heme (Henle *et al.*, 1999, Noblitt *et al.*, 2007, Saito *et al.*, 2012), which could catalyze site-directed oxidative damage to telomeres (Shay and Wright, 2005). Oxidative damage contributes to the erosion of telomeres that leads to cellular senescence and premature aging (D'adda Di Fagagna *et al.*, 2003, Liu *et al.*, 2002).

The biology of telomeres length and longevity should be viewed in relation to telomerase expression and subtelomeric regions (Calado and Dumitriu, 2013). For example, the maximum life span in human exceeds several folds that of mouse while telomeres in mouse are about 10 times longer than the telomeres in human. These facts appear to contradict the protective role of telomeric reserve capacity. However, the mouse somatic cells constitutively express high level of telomerase, which is repressed in human somatic cells (Calado and Dumitriu, 2013). Thus, telomeres correlate with replicative senescence in human cells but not in mouse cells, which make it difficult to correlate telomeres length and longevity in these species. It seems as if the constitutive telomerase activity in mouse represent an "excess metabolic capacity" that compensates for the increase in oxidative

defense and DNA repair mechanisms found in telomerase-repressed and short telomere in human.

Discussion

Excess metabolic capacities could serve as an innate defense system that help intermediary metabolism cope with increase metabolic demand, and chronic or acute stresses, and recover from injury (e.g., excessive oxidation, excitotoxicity, ischemia, hypermetabolism, inflammation, chemotherapy, surgical procedure, or physical trauma) (Thorburn and Kuchel, 1985, Gong *et al.*, 2003, Hill *et al.*, 2009, Dranka *et al.*, 2010, Choi *et al.*, 2009, Yadava and Nicholls, 2007, Kingsley-Hickman *et al.*, 1990). Therefore, we propose that organ reserve could be established, in part, by a joint contribution of several metabolic and structural excess capacities. If the excess metabolic capacity is impaired, the ability of the organ to cope with stress and recover from injury is reduced, thus contributing to the process of aging. Under these circumstances, cell death, transformation, or cell senescence occur. Cell senescence leads to tissue dysfunction, impairs organ reserve, and contributes to the aging process (Kong *et al.*, 2013, Bernadotte *et al.*, 2016, Jeyapalan *et al.*, 2007).

Excess metabolic capacity could be embedded in multiple systems and processes throughout intermediary metabolism. We discussed excess metabolic capacities in bioenergetic systems, mtDNA, and telomeres. Additional metabolic platforms that could enhance excess metabolic capacity include gerontogenes (Rattan, 2015) and functional resilience and redundancy through “network entropy” (Demetrius *et al.*, 2009). These systems may work to secure the metabolic integrity of the organismal tissues until a reproductive age. We propose that these same systems also contribute to the metabolic quality that provides longevity assurance, which influence the aging process by sharing, at least, maintenance and repair processes, supporting organ reserve.

Organ reserve declines with age (Bortz and Bortz, 1996, Sehl and Yates, 2001). Preventing or delaying cell senescence could help remedy the impact of the aging on organs functions. Anti-senescence agents or regimen that enhance excess metabolic capacity could also enhance organ reserve. We have demonstrated that the redox agent methylene blue (MB) increases the reserve capacity of complex IV as well as induces mitochondrial biogenesis (Tchkonia *et al.*, 2013, Atamna *et al.*, 2015), thus, MB enhance bioenergetics excess capacity. MB also slows the attrition rate of telomeres, which is consistent with its ability to delay cell senescence (Atamna *et al.*, 2015). Interestingly, MB is very effective in delaying cell senescence, increasing cell resistance to oxidative stress and toxic agents (Atamna *et al.*, 2015). However, a single dose of MB (based on data from *in vitro* experiments) was applied to mice for three years led to a small trend of lifespan extension in females and no effect on males (Harrison *et al.*, 2014). The authors concluded given the promising findings from studies on MB, the optimal dose for longevity studies needs to be established.

Caloric restriction (CR), the only regimen that extends the maximum lifespan and improves the health across the species including mammals (Taormina and Mirisola, 2014). CR affects multiple metabolic pathways including bioenergetics, AMPK, cell defense systems (lowering entropy), genome stability, and epigenetics (Ungvari *et al.*, 2008). CR enhances

excess metabolic capacity of complex IV, mtDNA, and mitochondrial oxidative capacity and efficiency (Lanza *et al.*, 2012).

One proposed benefit of excess capacities or redundancies is providing the potential of resisting and recovering from a stressor injury (such as the cancer studies we cited in this paper). Variations in the excess capacity (e.g., due to polymorphism, environment, or life style) may increase the risk of early onset of a specific disease or alter recovery from stressful episodes. Excess capacity may also be viewed as a method of avoiding wastefulness as we discussed in bioenergetic excess capacity. Thus, excess capacities may provide a platform to identify individuals with limited excess capacity and propose a method to enhance this capacity to reduce the risk of a specific age-related disorder or suggest a treatment plan.

Aging could be further understood and managed when its elements are clearly identified and their relations are thoroughly defined (Rattan, 2015, Gladyshev, 2016). Identifying additional excess metabolic capacities and structural reserve capacities beyond what we discussed here could expand our understanding for the molecular basis of organ reserve and the aging process.

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Abbreviations

mtDNA	mitochondrial DNA
Complex IV	cytochrome c oxidase
HMS	Hexose Monophosphate Shunt
TCA	Tricarboxylic Acids Cycle
ETC	Electron Transport Chain

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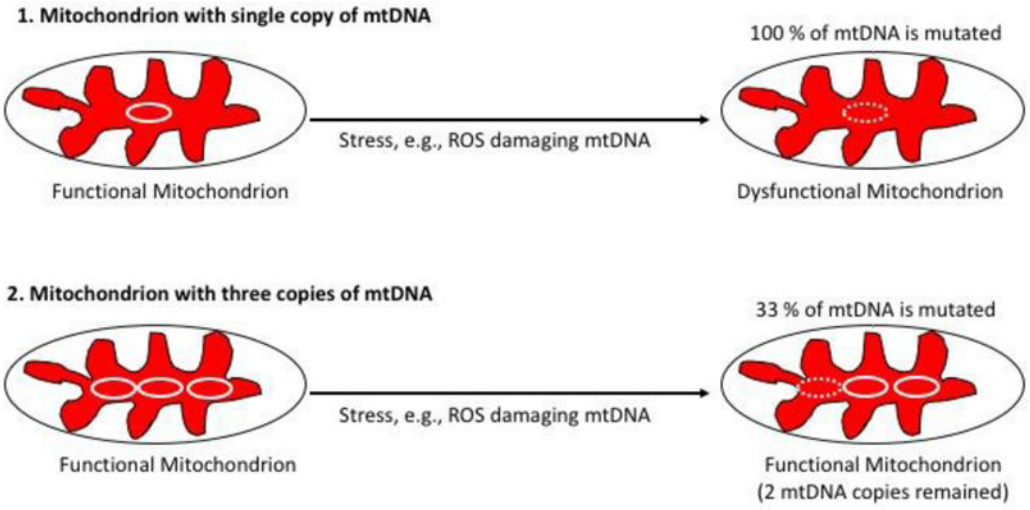
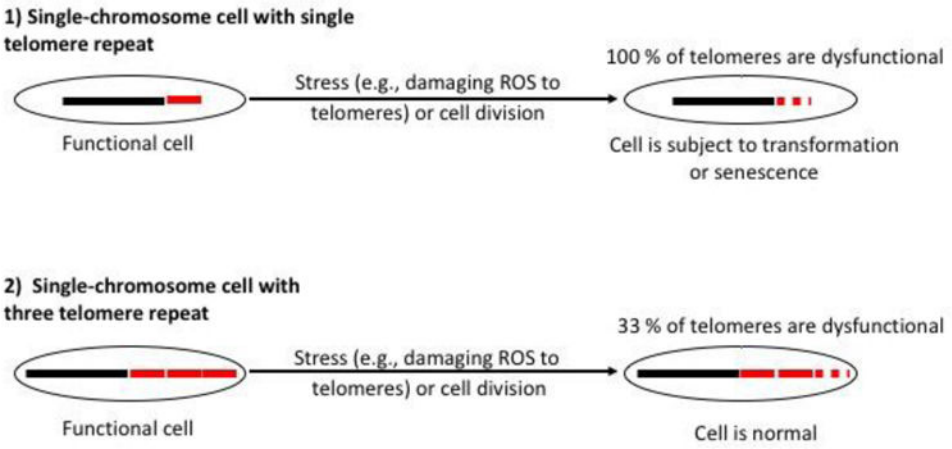


Scheme 1. mtDNA excess capacity

1) A hypothetical case of a mitochondrion with one copy of mtDNA (i.e., 37 genes). When one or more of the 37 genes is mutated (e.g., due to conditions that mutate DNA) a loss of function occurs and the mitochondrion is impaired. Thus, the lack of a backup to the 37 genes increases the risk of compromising the mitochondrial function, energy metabolism, and the cell.

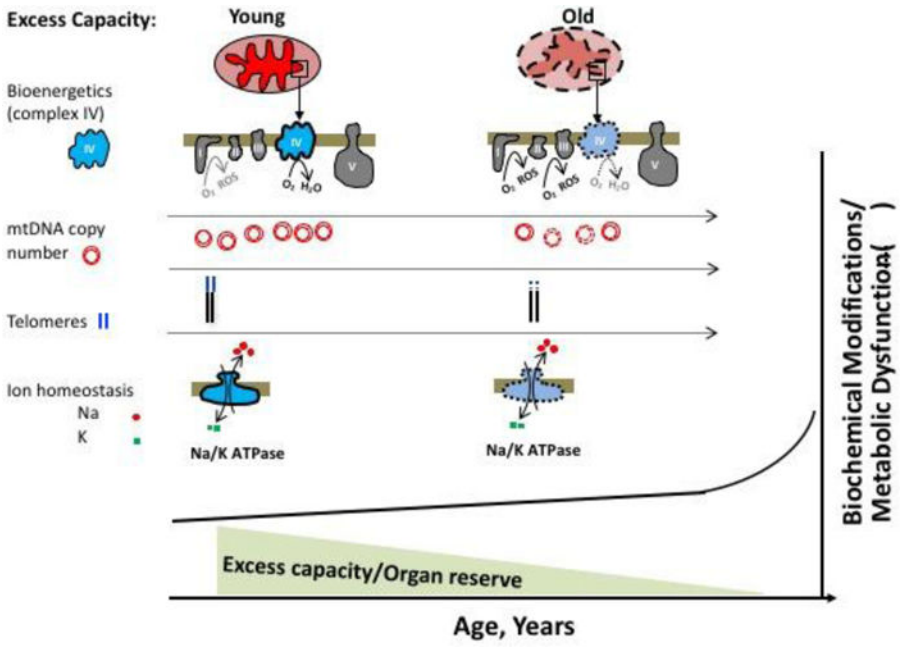
2) A hypothetical case of a mitochondrion with three copies of mtDNA, (i.e., each of the 37 genes is represented three times in three mtDNA copies). The risk of a mutation that compromise the function of this mitochondrion is much lower when the mitochondrion is exposed to the same conditions as in (1). The backup of three copies for each of the 37 gene sets represents excess structural capacity of mtDNA.



Scheme 2. Telomeres excess capacity

1) A model of a hypothetical cell with a single chromosome that has single copy of a telomere (red bar). When the cell is exposed to conditions that compromise the integrity of the telomere (oxidative damage or after one cycle of cell division) the telomere becomes dysfunctional or shorter, thus compromising the chromosome stability risking the cell normal function through senescence or transformation.

2) A model of a hypothetical cell with a single chromosome that has three copies of telomere repeats. The risk of cell senescence or transformation is much lower when the cell is exposed to the same conditions as in (1). The backup of three telomere repeats represents the excess structural capacity of telomeres.



Scheme 3. The proposed change to excess metabolic capacity, metabolic function, and organ reserve with age

Excess metabolic capacities could contribute to organ reserve and the aging process. Excess metabolic capacity and organ reserve also provide the opportunity of integrating many of the factors that were shown to contribute to the aging process. Reduction in excess metabolic and structural capacities could result in an increase in cell entropy and oxidation; resulting in cell senescence, transformation, or death, thus compromising organ reserve. The proposed relations of age, excess capacities, and organ reserve are schematically depicted. A hypothetical plot of the age-related molecular modifications and metabolic dysfunctions are also presented (——) line. Excess metabolic capacities presented in this scheme include enzymes (e.g., Na/K ATPase), mtNDA copy numbers, and repeats in telomeres. The line (·····) indicate the age-related decline in excess capacity. Telomeres erosion or dysfunction are presented with a decrease in the length of the blue lines.