





Poor mitochondrial health and systemic inflammation? Test of a classic hypothesis in the Baltimore Longitudinal Study of Aging

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Abstract Although a persistent inflammatory state has long been associated with aging and negative health outcomes, the underlying mechanisms remain unclear. Mitochondrial dysfunction has been proposed as a cause of inflammaging, but evidence of an association in humans is lacking. In this study, we analyzed the cross-sectional association between inflammatory biomarkers and mitochondrial oxidative capacity in skeletal muscle, assessed as post-exercise phosphocreatine recovery time constant by phosphorus magnetic resonance spectroscopy, in a population of 669 adults (mean age 67 years) from the Baltimore Longitudinal Study of Aging. We observed that participants with lower mitochondrial oxidative capacity exhibited hallmarks of inflammation, specifically markedly higher levels of interleukin-6 and C-reactive protein, as well as increased erythrocyte sedimentation rate when compared with participants with better oxidative capacity, independent of age and sex. We speculate that this association reflects the observation that products of damaged mitochondria, such as mitochondrial DNA, activate multiple pathways that lead to inflammation. Furthermore, excess production of oxidative species (ROS) by dysfunctional mitochondria could trigger inflammation

either directly via NF- κ B or through oxidative damage to proteins, lipids, and nucleic acids. Longitudinal studies are necessary to ascertain whether and through which mechanisms mitochondrial dysfunction activate inflammation or whether both these phenomena derive from a common root.

Keywords Mitochondria · Inflammaging · Oxidative stress · Phosphorus magnetic resonance spectroscopy

Introduction

A chronic, low-grade inflammatory state, accompanied by high blood levels of pro-inflammatory biomarkers, is often observed with aging and has been associated with a higher risk of sarcopenia, cardiovascular and neurodegenerative diseases, anemia, multimorbidity, disability, frailty, and premature death (Fabbri et al. 2014; Ferrucci and Fabbri 2018; Franceschi et al. 2000; Franceschi and Campisi, 2014; Wang et al. 2017). Despite extensive research and several hypotheses aimed toward explaining the origin of “inflammaging,” causal mechanisms remain unclear. An emerging hypothesis focuses on mitochondrial health and the interrelationship of age-related deterioration in mitochondrial function and generation of reactive oxygen species (ROS) (Conley et al. 2000; Porter et al. 2015; Sun et al. 2016). ROS can upregulate inflammation directly, by triggering the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and indirectly, by inducing macromolecular damage. Such damage can trigger a cascade of

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events that ultimately result in the production of type I interferons (α and β) and other proinflammatory cytokines. If the dysfunctional mitochondria are not removed, the pro-inflammatory state becomes chronic (Green et al. 2011).

The connection between poor mitochondrial health and chronic inflammation is further supported by evidence that diseases characterized by a strong mitochondrial dysfunction, such as type 2 diabetes, Alzheimer's disease, and Parkinson's disease, are associated with systemic inflammation (Beal 2003; De Felice and Ferreira 2014). Whether age-associated mild decline in mitochondrial function explains in part elevated blood levels of pro-inflammatory markers observed in many older persons is unknown.

In this study, we examined whether poorer or sub-optimal mitochondrial oxidative capacity assessed *in vivo* by phosphorus magnetic resonance spectroscopy (^{31}P -MRS) in relatively healthy persons was associated with higher blood levels of interleukin (IL)-6 and C-reactive protein (CRP) and with increased erythrocyte sedimentation rate (ERS), among the most widely used biomarkers of inflammaging.

Methods

Participants

The study population consisted of 669 men and women aged 22 to 97 years from the Baltimore Longitudinal Study of Aging (BLSA), seen between April 2013 and December 2019. The BLSA is a prospective open cohort study of community-dwelling volunteers. Since 1958, the BLSA has been continuously enrolling participants, primarily from the Baltimore, MD, and Washington, DC, area. BLSA participants are free of major chronic conditions and functional impairments at enrollment and are followed for life regardless of changes in health and functional status, as described in detail elsewhere (Kuo et al. 2020; Stone and Norris 1966). Assessments were performed at the Clinical Research Unit of the Intramural Research Program of the National Institute on Aging during an on-unit clinic visit over 2.5 to 3.5 days. Certified nurse practitioners and certified technicians conducted all assessments according to standardized procedures. The study protocol was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences (NIEHS,

NC). All participants consented to participate in the study, after receiving detailed descriptions at every visit.

Demographic and health characteristics were ascertained either through self-report questionnaires or using standard criteria and algorithms (Guralnik et al. 1995). Physical activity was determined through a standardized questionnaire that enquired about different types of activities performed during a typical week. A measure considering all the high intensity activities, including brisk walking, was adopted in our models (Brach et al. 2004).

Body weight was measured in kilograms using a calibrated scale to the nearest 0.1 kg. Body height was measured in centimeters by a stadiometer to the nearest 0.1 cm (Lohman et al. 1988). Body mass index was calculated by dividing body weight by the square of height in meters.

IL-6, CRP, and ESR

IL-6 (pg/mL) and CRP ($\mu\text{g/mL}$) serum concentrations were quantified using enzyme-linked immunosorbent assays (ELISA, R&D Systems, Minneapolis, MN, and Alpha Diagnostic International, San Antonio, TX). ESR (mm/h) is defined as the rate at which erythrocytes (red blood cells) settle at the bottom of a test tube of anticoagulated whole blood in one hour. Higher ESR occurs when acute phase reactant proteins are high, indicating a pro-inflammatory condition. In this study, ESR was measured using a standard BD vacutainer tube (BD, Franklin Lakes, NJ). IL-6, CRP, and ESR values of 0 (non-detectable values) were excluded, and all measures were logarithmically transformed in the analyses to minimize the influence of skewed distribution.

Phosphorus magnetic resonance spectroscopy

Using a 3T MR scanner (Achieva, Philips Healthcare, Andover, MA), *in vivo* ^{31}P -MRS measurements of the concentrations of the phosphorus-containing metabolites phosphocreatine (PCr), inorganic phosphate (Pi), and ATP were obtained from the vastus lateralis muscle of the left thigh, following a standardized protocol described previously (Choi et al. 2016; Coen et al. 2012). Spectra of phosphorus-containing metabolites were acquired before, during, and after a ballistic knee extension exercise performed for an average duration of 30 s. A series of pulse-acquire ^{31}P spectra were obtained before, during, and after the exercise with a repetition

time of 1.5 s, using a 10-cm ^{31}P -tuned surface coil (PulseTeq, Surrey, UK) fastened above the left thigh. Signals were averaged over four successive acquisitions for signal-to-noise ratio enhancement, so that the data consisted of 75 spectra obtained with a temporal resolution of 6 s. The duration of exercise was optimized by consistently requiring a depletion in PCr of 33 to 67% relative to initial baseline values, in order to standardize the measure of oxidative function across different subjects and to provide sufficient dynamic range to fit the PCr recovery curve. If intramuscular acidosis, defined as intracellular pH lower than 6.8, was detected, the test was repeated at a lower intensity (Paganini et al. 1997). The pH was determined according to the chemical shift of Pi relative to PCr (Taylor et al. 1986). Spectra were processed with jMRUI software (MRUI Consortium, version 5.2), and metabolite concentrations were calculated by nonlinear least squares fitting implemented through AMARES (Naressi et al. 2001; Vanhamme et al. 1999).

Post-exercise PCr recovery rates were calculated by fitting time-dependent changes in PCr peak area to the monoexponential recovery function:

$$\text{PCr}(t) = \text{PCr}(0) + \Delta\text{PCr} \times \left(1 - \exp\left(-\frac{t}{\tau_{\text{PCr}}}\right)\right)$$

where PCr(0) is the end-of-exercise PCr signal area (i.e., the PCr signal area at the beginning of the recovery period); ΔPCr is the decrease in signal area from its pre-exercise baseline value, averaged from the multiple baseline scans, to PCr(0) resulting from in-magnet exercise; and τ_{PCr} is the PCr exponential recovery time constant, measured in seconds (Choi et al. 2016). This time constant is inversely proportional to the maximum in vivo oxidative capacity of skeletal muscle, with longer τ_{PCr} reflecting slower recovery and therefore lower oxidative capacity (Prompers et al. 2014). Since the energy demands during post-exercise PCr resynthesis are minimal, $1/\tau_{\text{PCr}}$ reflects the maximum mitochondrial ATP production rate (Arnold et al. 1984; Choi et al. 2016; Conley et al. 2000).

Statistical analysis

Variables were described as mean values and standard deviations or proportions as appropriate. The time constant τ_{PCr} was expressed as an ordinal variable, through

assignment to quintiles. Participants in the first quintile of τ_{PCr} (best mitochondrial function, τ_{PCr} below 39.7 s) were considered the reference group and compared with those in the higher quintiles using dummy variables in a linear regression analysis adjusted for sex (coded as 1 = male, 0 = female) and age. Body mass index (BMI) and physical activity (min/week) were initially considered in the model but later removed as they did not contribute significantly to model fit ($P = 0.22$ and $P = 0.24$, respectively). The analyses were performed using RStudio version 1.2.1335. $P < 0.05$ was considered statistically significant.

Results

Table 1 reports the demographic and health characteristics of the 669 study participants. Most subjects were Caucasian (67%), approximately half women (55%),

Table 1 Demographic and health characteristics of 669 adults from the Baltimore Longitudinal Study of Aging

Characteristic	Mean (SD), median (IQR), or percent
Age (years) ^a	66.9 (15.2)
Race (%)	
White	67.1
Black	23.5
Other	9.4
Sex (% female)	55.3
Education, < 16 years (%)	17.1
Smoking status (%)	
Never	68
Former	30.5
Current	1.5
BMI (kg/m ²) ^a	26.77 (4.49)
Physical activity (min/week) ^a	107.9 (165.3)
τ_{PCr} (s) ^a	49.80 (11.72)
Interleukin 6 (pg/mL) ^b	3.7 (2.9–4.98)
CRP ($\mu\text{g/mL}$) ^b	1.09 (0.57–2.31)
ESR (mm/h) ^b	8 (4–15)
Hypertension (%)	33.6
Myocardial infarction (%)	2.1
Cerebrovascular accident (%)	3.9
Peripheral artery disease (%)	6.7
Diabetes mellitus (%)	13.9
Cancer (%)	26.1

^a Mean (SD)

^b Median (IQR)

and the majority had completed college (82%). The prevalence of chronic diseases was relatively low. The mean (standard deviation) for τ_{PCr} was 49.8 (11.7). Table 2 presents study population characteristics by quintile of mitochondrial oxidative capacity (τ_{PCr}). Age, BMI, physical activity, IL-6, CRP, and ESR differed across quintiles of τ_{PCr} , with participants in the highest quintile of τ_{PCr} (poorer oxidative capacity) being older, having higher BMI, reporting less physical activity, and having higher IL-6 and CRP blood levels and higher ESR.

Table 3 reports results of the linear regression model assessing the relationship between τ_{PCr} and $\log(\text{IL-6})$ within quintiles of τ_{PCr} , using dummy variables and adjusting for age and sex. Participants in the first quintile of τ_{PCr} , those with the best oxidative capacity, served as the reference group. Participants with the lowest oxidative capacity (upper quintile of τ_{PCr} , with $\tau_{\text{PCr}} > 59.5$ s) had significantly higher $\log(\text{IL-6})$ levels than the reference group. None of the other quintiles differed from the reference quintile. Table 4 shows a similar linear regression treating $\log(\text{CRP})$ as the outcome of interest. Participants in the third, fourth, and fifth quintile of τ_{PCr} had significantly and progressively higher $\log(\text{CRP})$ than the reference group, independent of covariates. Finally, Table 5 reports the results of the regression with $\log(\text{ESR})$ as outcome: subjects in the fourth and fifth quintiles of τ_{PCr} had larger $\log(\text{ESR})$ than those in the first quintile, independent of age and sex ($P = 0.06$ and $P = 0.0002$ respectively). Figure 1 represents the relationships between τ_{PCr} and $\log(\text{IL-6})$, $\log(\text{CRP})$, and $\log(\text{ESR})$.

Discussion

The present study found that a greater proportion of persons with very low in vivo skeletal muscle mitochondrial oxidative capacity had higher levels of IL-6 and CRP as compared with subjects with better oxidative capacity.

For decades, IL-6 has been considered the “cytokine for gerontologists,” as high IL-6 levels have been consistently associated with higher prevalence and incidence of multiple chronic diseases and many adverse health outcomes (Ershler 1993; Maggio et al. 2006). For example, elevated IL-6 levels are often found in older patients with severe multimorbidity, disability, and frailty, with additional evidence that high levels of IL-6 predict the development of these outcomes, independent of other established risk factors (Cohen et al. 1997; Harris et al. 1999). IL-6 is widely recognized as a hallmark of inflammaging (Franceschi and Campisi 2014).

CRP is an acute-phase protein produced by hepatocytes in response to IL-6. Its main function is to activate the complement system after binding to dying cells or bacteria. Similar to CRP, ESR is a non-specific and widely used marker of inflammation. ESR is determined by the balance between factors that enhance sedimentation of red blood cells, such as fibrinogen, and factors resisting sedimentation. During an inflammatory process, fibrinogen increases, causing a shift of the balance toward sedimentation.

Several potential mechanisms have been proposed to explain the potential role of mitochondria in the genesis

Table 2 Characteristics of 669 study participants by quintile of mitochondrial oxidative capacity (τ_{PCr} , seconds)

Characteristic	Quintile 1 < 39.7 (<i>n</i> = 134)	Quintile 2 39.7–46.1 (<i>n</i> = 134)	Quintile 3 46.1–52.1 (<i>n</i> = 134)	Quintile 4 52.1–59.5 (<i>n</i> = 134)	Quintile 5 > 59.5 (<i>n</i> = 133)	<i>P</i> value*
Age (years) ^a	56.9 (16)	64.8 (14.7)	66 (15.1)	72.6 (12.6)	74.4 (10.3)	< 0.0001
Female sex (%)	55.2	50	55.2	55.2	60.9	0.52
BMI (kg/m ²) ^a	26 (4.1)	26.6 (4.5)	26.9 (4.5)	27.2 (4.5)	27.1 (4.7)	0.025
Physical activity (min/week) ^a	165.9 (221.4)	131.1 (160)	90.2 (147.8)	87.8 (142.9)	67.4 (124.8)	< 0.0001
IL-6 (pg/mL) ^b	3.24 (2.6–4.15)	3.45 (2.9–4.5)	3.7 (2.9–4.68)	3.8 (3.1–5)	4.1 (3.2–5.5)	0.02
CRP (μg/mL) ^b	0.8 (0.44–1.76)	1.08 (0.48–1.96)	1.06 (0.64–2.55)	1.17 (0.61–2.54)	1.76 (0.73–3.87)	< 0.0001
ESR (mm/h) ^b	6 (2–10)	6 (3–12)	7 (4–12)	8.5 (5–18)	14 (6–24)	< 0.0001

^a Mean (SD)

^b Median (IQR) or percent values

* ANOVA for continuous variables; Pearson chi-square test for categorical variables

Table 3 Linear regression model with dummy variables for quintiles of τ_{PCr} , assessing the relationship between $\log(IL-6)$ and τ_{PCr} , adjusting for covariates

Variable	Beta coefficient	Standard error	<i>P</i> value
Quintile 2	0.03	0.04	0.47
Quintile 3	0.04	0.04	0.38
Quintile 4	0.07	0.04	0.12
Quintile 5	0.10	0.04	0.02
Age	0.004	0.0009	0.0002
Sex	0.05	0.03	0.05

of inflammaging. In healthy mitochondria, the process of oxidative phosphorylation produces small amounts of ROS, which currently are considered important signaling molecules and are easily removed by multiple scavenging systems. However, if mitochondria become dysfunctional, production of ROS exceeds scavenging capacity and thus induces macromolecular damage. Mechanistic work, primarily conducted using model organisms, has shown that through oxidative stress, mitochondrial dysfunction triggers inflammation through multiple pathways (López-Armada et al. 2013). ROS directly activate NF- κ B and other redox-sensitive transcription factors and induce production of cytokines, chemokines, eicosanoids, adhesion molecules, and inducible nitric oxide synthase (Chung et al. 2009; López-Armada et al. 2013). Further, free radicals can damage lipids, proteins, and nucleic acids, causing major structural and functional alterations of membranes, enzymes, signaling molecules, genes, and RNAs. Mitochondrial macromolecules are particularly susceptible to oxidative damage, due to proximity and reduced protective barriers (Sastre et al. 2000). Cardiolipin, a phospholipid specific to mitochondrial membranes and essential to preservation of the

Table 4 Linear regression model with dummy variables for quintiles of τ_{PCr} , assessing the relationship between $\log(CRP)$ and τ_{PCr} , adjusting for covariates

Variable	Beta coefficient	Standard error	<i>P</i> value
Quintile 2	0.08	0.06	0.18
Quintile 3	0.13	0.06	0.03
Quintile 4	0.15	0.06	0.02
Quintile 5	0.24	0.06	0.0002
Age	0.003	0.001	0.05
Sex	−0.07	0.03	0.08

Table 5 Linear regression model with dummy variables for quintiles of τ_{PCr} , assessing the relationship between $\log(ESR)$ and τ_{PCr} , adjusting for covariates

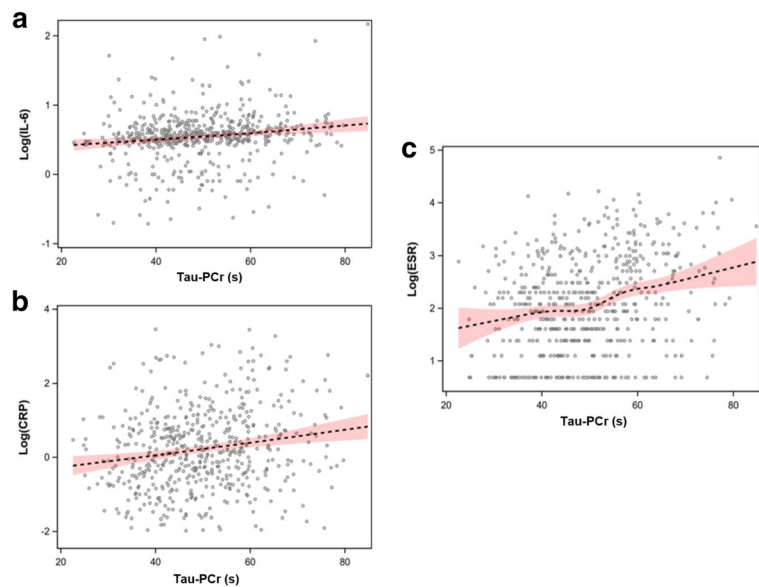
Variable	Beta coefficient	Standard error	<i>P</i> value
Quintile 2	0.01	0.05	0.87
Quintile 3	0.02	0.05	0.67
Quintile 4	0.09	0.05	0.06
Quintile 5	0.19	0.05	0.0002
Age	0.006	0.001	<0.0001
Sex	−0.26	0.03	<0.0001

mitochondrial cristae and correct functioning of the electron transport chain (ETC) complexes, is a main target of free radical attack. Peroxidation of cardiolipin disrupts energy production, regulation of apoptosis, and other mitochondrial functions and has been implicated in the pathogenesis of sarcopenia and frailty (Ferrucci and Zampino 2020; Semba et al. 2019). Through impairment of the ETC, oxidized cardiolipin could induce further generation of ROS, mainly produced by complexes I and III (Murphy 2009).

When mitochondria sustain damage, mitochondrial components are released into the cytoplasm and extracellular space. These components include mtDNA, formyl peptides, and lipids, which can act as damage-associated molecular pattern (DAMP) agents, through a connection that can be traced back to the bacterial origins of the mitochondrion. Since mtDNA is not methylated, it is recognized by the immune system through members of the toll-like receptor family, activating an inflammatory response via stimulation of the NF- κ B pathway (Sun et al. 2016). Formyl peptides can trigger the immune response by interacting with the formyl peptide receptor-1 (Sun et al. 2016).

Furthermore, mtDNA and increased levels of ROS activate the NLR family pyrin domain containing 3 (NLRP3) inflammasome, the major immune sensor for stress signals, which induces a pro-inflammatory response mainly through activation of caspase-1 and subsequent secretion of the cytokines IL-1 β and IL-18 (Tschopp 2011). Notably, inflammasomes are implicated in the pathogenesis of age-related diseases such as metabolic syndrome, atherosclerosis, and Alzheimer's disease (Salminen et al. 2012). mtDNA can also activate cyclic GMP-AMP synthase (cGAS), a cytosolic sensor for genomes of viruses and bacteria. cGAS catalyzes the formation of a messenger that activates the adaptor protein stimulator of interferon genes (STING) with

Fig. 1 Scatterplots of the relationship between τ_{PCR} and $\log(\text{IL-6})$ (a), $\log(\text{CRP})$ (b), and $\log(\text{ESR})$ (c) with loess, or locally weighted, regression lines



consequent stimulation of the transcription factor interferon regulatory factor 3 (IRF3) and expression of innate immune response genes, including type I interferon (IFN) cytokines (Dhanwani et al. 2018; White et al. 2014). Among its functions, type I IFN enhances

production of IL-6 (Zimmermann et al. 2016). An increase in plasma mtDNA concentration with age has been observed in past studies and has been associated with increased concentrations of IL-6 and other pro-inflammatory cytokines (Pinti et al. 2014).

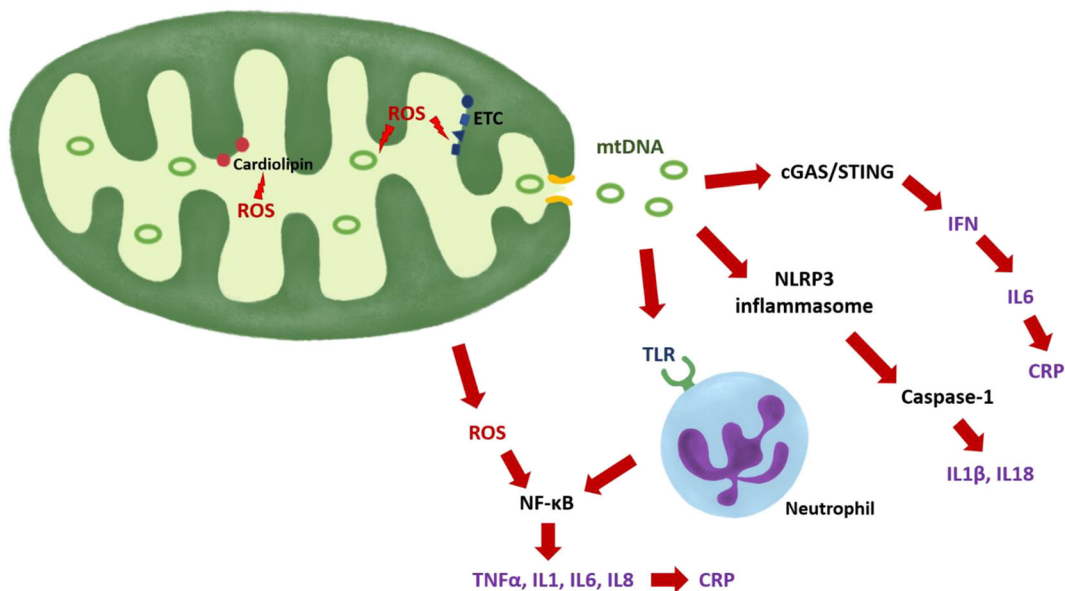


Fig. 2 Mechanisms through which damaged mitochondria may trigger inflammation. ROS can directly activate NF- κ B or oxidize phospholipids (such as cardiolipin), proteins (such as ETC complexes), or mtDNA. Mutated mtDNA can translate into altered ETC protein complexes. Oxidized cardiolipins and altered ETC complexes generate more ROS. mtDNA can be released and activate the cGAS/STING pathway with induction of IFN

production, activate the TLR of the neutrophils, or stimulate the NLRP3 inflammasome. ROS reactive oxygen species, mtDNA mitochondrial DNA, NF κ B nuclear factor κ B, ETC electron transport chain, cGAS cyclic GMP-AMP synthase, STING stimulator of interferon genes, IFN interferon, CRP C-reactive protein, NLRP3 NLR family pyrin domain containing 3, IL interleukin, TNF α tumor necrosis factor α , TLR toll-like receptor

In this study, we demonstrated that poor mitochondrial oxidative capacity is associated with elevated serum levels of IL-6 and CRP and with faster ESR. Because of the cross-sectional, observational nature of this analysis, our data cannot establish whether inflammation is a function of a health condition that also causes mitochondrial damage, or conversely that dysfunctional mitochondria directly cause inflammation through the mechanisms reported above and illustrated in Fig. 2. Nevertheless, our study shows that relatively healthy individuals, mainly those with poor mitochondrial oxidative capacity measured in vivo, show signs of systemic inflammation status. Of note, several subjects with poor oxidative capacity did not show elevated inflammatory markers (Fig. 1), suggesting that mitochondrial energetic dysfunction is not synonymous with systemic inflammation and may reflect non-disease factors such as low physical activity or exercise tolerance (Adelnia et al. 2019). Future studies should test the hypothesis that improving mitochondrial health through exercise and/or pharmacological interventions may reduce inflammation and its consequences on health. Another limitation of this study is that the mitochondrial oxidative capacity was measured exclusively in skeletal muscle, while systemic inflammation was assessed via blood samples.

Strengths of the study include a large and well-characterized cohort with rigorously standardized collection of in vivo ³¹P-MRS measurements, as well as accurate measurements of serum concentrations of IL-6 and CRP, and of ESR. The results of this study may not be generalizable to other populations, as the ethnic composition, exceptional health status, and high educational attainment of this cohort differ from the general population. Moreover, it is worth noting that since this population is healthy, the signals from mitochondrial dysfunction and inflammation observed in this study may be weaker than those that would be detected in the general population. Further longitudinal research is needed to gain insight into the temporal relationship between the occurrence of mitochondrial dysfunction and chronic inflammation. These studies should include older persons who are frail or pre-frail as these are most likely to show substantial impairment of mitochondrial oxidative capacity and oxidative stress.

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Compliance with ethical standards The study protocol was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences (NIEHS, NC). All participants consented to participate in the study, after receiving detailed descriptions at every visit.

Conflict of interest The authors declare that they have no conflict of interest.

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