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Do Mitochondrial DNA and Metabolic Rate Complement Each Other in Determination of the Mammalian Maximum Longevity?

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ABSTRACT

In animal cells, mitochondria are semiautonomous organelles of virtually "hostile" (bacterial) origin, with their own code and genome (mtDNA). The semiautonomy and restricted resources could result in occasional "conflicts of interests" with other cellular components, in which mitochondria have greater chances to be "the weakest link," thus limiting longevity. Two principal questions are addressed: (1) to what extent the mammalian maximum life span (MLS) is associated with mtDNA base composition? (2) Does mtDNA base composition correlate with another important mitochondria-associated variable—resting metabolic rate (RMR)—and whether they complement each other in determination of MLS? Analysis of 140 mammalian species revealed significant correlations between MLS and the content of the four mtDNA nucleotides, especially noted for GC pairs ($r^2 = 0.42$; $p < 10^{-17}$). The most remarkable finding of this study is that multivariate stepwise analysis selected only the GC content and RMR, which together explained 77% of variation in MLS ($p < 10^{-25}$). To the authors' knowledge, it is the highest coefficient of MLS determination that has ever been reported for a comparable sample size. Taking into account substantial errors in estimation of MLS and RMR, it could mean that the GC and RMR explain most of the MLS biological variation. Other putative players in MLS determination should have relatively small contribution or their effects should be realized via the same channels. Although further research is clearly warranted, the extraordinary high correlation of mtDNA GC and RMR with MLS suggests a "direct hitting" of the core longevity targets, inferring mitochondria as a primary object for longevity-promoting interventions.

INTRODUCTION

> The reasons for some animals being long-lived and others short-lived, and, in a word, causes of the length and brevity of life call for investigation.
>
> —Aristotle
> *On Longevity and Shortness of Life* (350 B.C.)

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Mitochondria are semiautonomous organelles metabolizing over 90% of consumed oxygen and producing most amounts of reactive oxygen species (ROS).[1,2] Mitochondria are supposed to be offspring of α-proteobacteria[3,4] that, once invading and "conquering" eukaryotic cells, could at least for a while be used to the parasitic behavior. Although modern mitochondria are apparently fully paying their toll, they still could preserve some of the "old habits," for example, receiving practically all necessary substances ready-made from the cell. Moreover, mitochondria preserved their own genetic code and tiny part of the genome (mtDNA)—a small, poorly protected, intronless, double-stranded, supercoiled circular molecule (the "magic circle").[5–8] The semiautonomous life style and complete reliance on the cellular supplies could, however, provoke occasional "conflicts of interests" between the mitochondria and other cellular components. The conflicting events could be aggravated in stress and aging. In such situations mitochondria have higher chances to be "the weakest link," thus limiting the cell life span and ultimately the organism longevity. The assumption is supported by the fact that mitochondria-associated parameters (e.g., the resting metabolic rate and body temperature, the rates of ROS generation and scavenging, mtDNA damage and repair, etc.) often exhibit correlation with life span in various experimental and evolutionary models.[9–20] Recently, strong correlations between mammalian MLS and mtDNA base composition were found by the authors[21] and others.[22]

In this paper, the authors further address the following, still unexplored, questions: (1) To what extent could the mtDNA base composition and RMR explain the differences in mammalian MLS? (2) Is there any relationship between mtDNA base composition and RMR? (3) Do mtDNA and RMR complement each other in determination of mammalian MLS?

MATERIALS AND METHODS

Data sources

To ensure maximal randomization, the data matrix included all reported cases of completely or near-completely sequenced mtDNA and MLS, totaling 140 species from 22 mammalian orders. Of them, 88 species had established RMR. Complete mtDNA sequences were collected from the NCBI database (<www.ncbi.nlm.nih.gov>). Base content was calculated for the heavy strand (H-strand) of mtDNAs using the Genomatix tools (<www.genomatix.de/cgi-bin/tools/tools.pl>) and expressed as the number of bases per 1 kbp of total mtDNA. Records on MLS and resting (basal) metabolic rate (RMR) of species with established mtDNA sequences were collected from HAGR (Human Ageing Genomic Resources, AnAge database[23]; <http://genomics.senescence.info/species>). For several species, the data on RMR, lacking in AnAge, were collected from the literature.[24,25] All data on the mtDNA and RMR represent typical values for a given species. For comparative purposes, human MLS of 90 years was used, as argued elsewhere (HAGR, AnAge, 2007, <http://genomics.senescence.info/species>).

Statistical evaluation

Statistical evaluation of the links between MLS and other variables under study was carried out using the well-known methods of basic statistics, pair-wise and partial correlations, three-dimensional non-linear regression (quadratic response surface), and stepwise multivariate (forward) regression analyses. The coefficient of determination (r^2) was applied as a primary index of data fitting. Its significance was assessed by the corresponding coefficients of correlation (simple regressions) or F-criteria (multivariate analyses). To ensure linear relationships, MLS and RMR were ln-transformed, where necessary. Because the null-hypothesis of distribution normality could be rejected for most of the variables, both parametric (Pearson) and non-parametric (Spearman) coefficients of correlation were estimated. In all cases analyzed, the parametric and non-parametric estimates were in good agreement. Therefore, the results of only parametric analyses were presented. For the sake of avoiding the scale interferences in multivariate analyses, the data matrix was standardized so that all variables had the means equal to zero and standard deviations equal to 1. This transformation allowed a direct comparison of relative input of

the regression variables. All statistical calculations, as well as two- and three-dimensional plotting, were performed using the Statistica 6 (StatSoft, Inc., Tulsa, OK) or the statistical package for the social sciences (SPSS, Inc., Chicago, IL) software.

RESULTS

Coefficient of variation and skewness

The coefficient of variation (CV), estimated as a ratio of standard deviation (SD) and absolute mean value (CV = SD/mean), is a simple and suitable measure for the assessment of variability. Because CV is scaleless, it allows comparing variables of different nature. Among the parameters under present analysis, the variability was the highest for RMR and MLS (CV $\pm$ SE_{CV}, 98.8 $\pm$ 10.5% and 69.7 $\pm$ 5.1%, respectively). The CVs for mtDNA base contents were much lower and ranged from 3.6 $\pm$ 0.2% to 8.7 $\pm$ 0.5%, in a decreasing order of the CV value: G > A > C > T.

Skewness is another simple and scaleless index that could be useful for estimation of a distribution asymmetry and, hence, an assessment of its possible deviation from the normal (Gaussian) distribution. Most of the variables studied were characterized by either significant positive (RMR, MLS, A, and C) or practically zero skewness (T and G).

Base content of mtDNA correlates with MLS

Despite a relatively low variability, the mtDNA base contents displayed significant correlations with mammalian MLS. Several remarkable features of these correlations were revealed. First, the bases that determine the total number of GC pairs in mtDNA—that is, G and C contents on the heavy strand (H-strand)—correlated positively, whereas A and T correlated negatively with MLS (Table 1). Second, the purines (A and G) were superior in determination of MLS to that of the pyrimidines (C and T). As indicated by the r^2 values, the contents of G and A explained a considerable part of variation in the MLS across mammals (37.2%, $p < 10^{-15}$; and 29.9%, $p < 10^{-11}$, respectively), whereas the analogous effects of the pyrimidines T (12.5%, $p < 0.00005$) and especially C (3.2%, $p = 0.034$) were much lower. However, the highest coefficient of MLS determination was found for the sum of G and C (GC) contents ($r^2 = 41.7$ %, $p < 10^{-17}$).

Guanine dominates over other bases in correlative links with MLS

The correlations between MLS and mtDNA base composition could be masked by co-variations of two or more bases. Partial correlation analysis, which removes the co-variation effects, revealed a leading role of G in correlative links between MLS and mtDNA base contents. As seen in Table 1, removing the effect of A, T, or C did not considerably alter the correlation of MLS with G. In striking contrast, controlling for the G dramatically decline the correlations of MLS with other bases.

Guanine content and metabolic rate correlate independently with MLS

Maximum life span, in both the absolute and ln-transformed (lnMLS) forms, exhibited very similar correlations with the mtDNA base composition (Fig. 1B and Table 1). However, the de-

Table 1. Pearson and Partial Correlation[a] Coefficients of Base Contents on mtDNA Heavy Strand with MLS in Mammals

	Guanine (p)	*Adenine* (p)	*Thymine* (p)	*Cytosine* (p)
r	0.61 ($<10^{-15}$)	−0.55 ($<10^{-11}$)	−0.35 ($<10^{-3}$)	0.18 (<0.04)
r_G	—	0.02 (>0.8)	−0.08 (>0.3)	0.10 (>0.2)
r_A	0.32 ($<10^{-4}$)	—	−0.29 ($<10^{-3}$)	0.05 (>0.5)
r_T	0.54 ($<10^{-11}$)	−0.52 ($<10^{-10}$)	—	−0.04 (>0.6)
r_C	0.60 ($<10^{-14}$)	−0.53 ($<10^{-10}$)	−0.31 ($<10^{-3}$)	—

[a]Correlation between two variables when the effect of one or more related variable is removed (held constant or controlled). r, Pearson correlation coefficient with MLS, r_G, r_A, r_T, and r_C, partial correlation coefficients (r_P) with MLS upon removing the effect of guanine (G), adenine (A), thymine (T), and cytosine (C), respectively.

pendence of MLS on RMR or lnRMR was far from linearity. Therefore, ln-transformation of MLS and RMR data were performed before including them in the analysis.

As expected, a strong negative correlation between lnMLS and lnRMR was observed (Fig. 1A). When two variables correlated with a third one, they usually exhibited certain correlation with one another. Although G and lnRMR highly correlated with lnMLS, nevertheless, there was no significant correlation between G content and lnRMR (Fig. 1C). The partial correlation analysis further confirmed a very low interaction, if any, between them in determination of MLS. Removing the effect of RMR did not significantly alter the correlation of MLS with G (as well as with other bases) and vice versa.

Joint effect of G or GC content and metabolic rate in determination of MLS

The weak interaction between G and RMR, as well as a minor input of their non-linear components in determination of MLS, definitely follows from the dependence of the lnMLS on the lnRMR and G content, described by the quadratic response surface (Eq. 1):

$$\ln\text{MLS} = -0.1 - 0.6\ln\text{RMR} + 0.5\text{G} - 0.03\text{G} \times \ln\text{RMR} - 0.05(\ln\text{RMR})^2 + 0.03\text{G}^2 \quad \text{(Eq. 1)}$$

The model (Eq. 1) explains over 75% of the MLS variation and had an extraordinary significant F-criteria ($r^2 = 0.757$; $F = 51.0$; $p < 10^{-25}$). Of note, due to the standardized matrix, the input of any member of regression was proportional to the corresponding coefficient of regression (see the section on Methods). The coefficient of interaction between G and lnRMR (0.03) and the coefficients for the quadratic components of the $(\ln\text{RMR})^2$ (0.05) and G^2 (0.03) were an order of magnitude lower compared with the linear ones. It is also worth mentioning that the linear coefficients at lnRMR (0.6) and G (0.5) were comparable, suggesting an almost identical impact of these two independent variables on MLS (Eq. 1).

In this research, the highest coefficient of determination was found when describing the lnMLS dependence on lnRMR and GC by the quadratic response surface (Eq. 2):

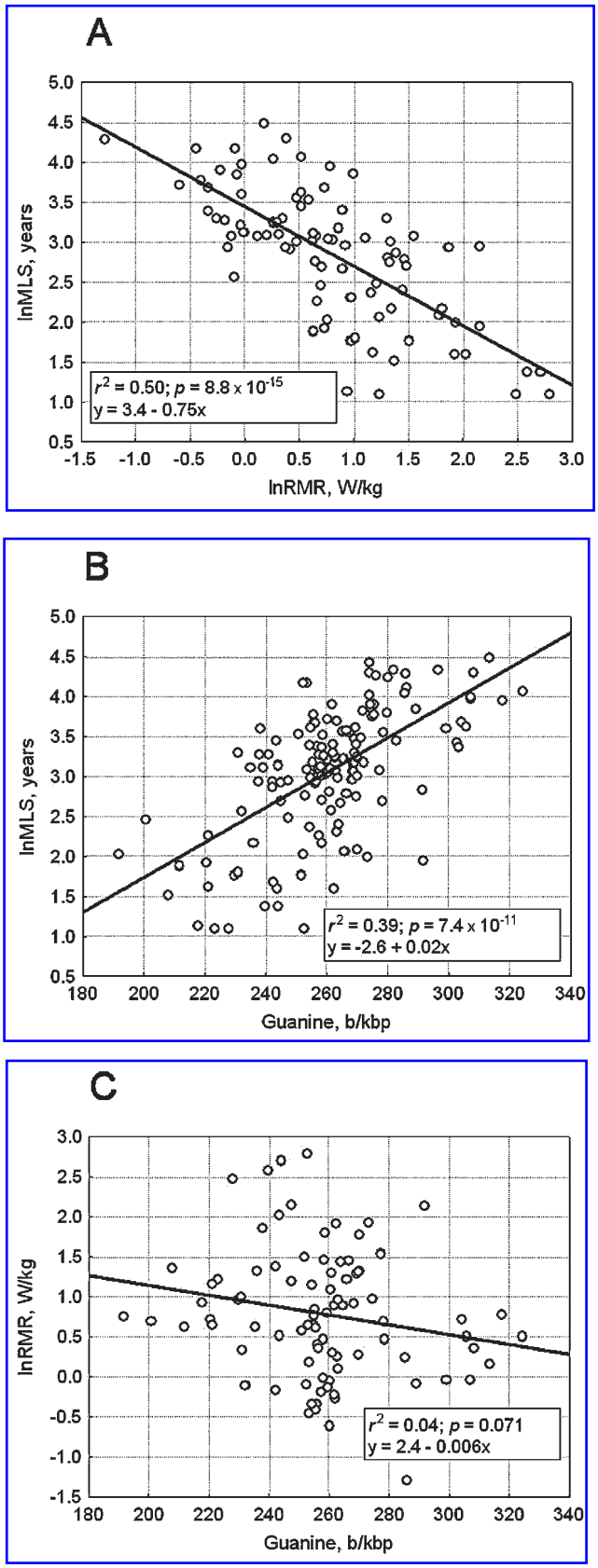

FIG. 1. Relationships between lnMLS and lnRMR (**A**), lnMLS and G content on the mtDNA heavy strand (**B**), and lnRMR and G content across mammals (**C**).

$$\ln\text{MLS} = -0.16 - 0.62\ln\text{RMR} + 0.49\text{GC} - 0.042\text{GC} \times \ln\text{RMR} - 0.067(\ln\text{RMR})^2 + 0.005\text{GC}^2 \quad \text{(Eq. 2)}$$

The model (Eq. 2) explains over 77% of the lnMLS variation ($r^2 = 0.774$; $F = 56.3$; $p < 10^{-25}$). As in Eq. 1, the quadratic components and interaction between lnRMR and GC displayed surprisingly modest input into the MLS determination.

The statement could be more comprehensibly demonstrated by the three-dimensional (3D) quadratic response surface (Fig. 2). The surface demonstrates an excellent data fitting. Its contours are close to a plane, meaning that the non-linear components of the lnRMR and GC content have a small impact on lnMLS determination.

GC content and lnRMR are the main determinants of MLS

When all variables under study were included in the stepwise multivariate regression analysis, only the GC content and lnRMR were left. Other variables were rejected by the analysis, apparently because they had insignificant additional input in determination of MLS (Eq. 3):

$$\ln\text{MLS} = 0.53\text{GC} - 0.59\ln\text{RMR} - 0.22; \; r^2 = 0.769; \; F = 141.6; \; p < 10^{-25} \quad \text{(Eq. 3)}$$

Thus, even within a simple linear model, as described in Eq. 3, GC and RMR explain almost 77% of the MLS variation and had a very high F value.

Summary of the results

Collectively, the results clearly demonstrate that the RMR and mtDNA G or GC content are powerful determinants of mammalian longevity. Their combinations (RMR and G, or RMR and GC) could explain over three fourths of variation in MLS across mammals.

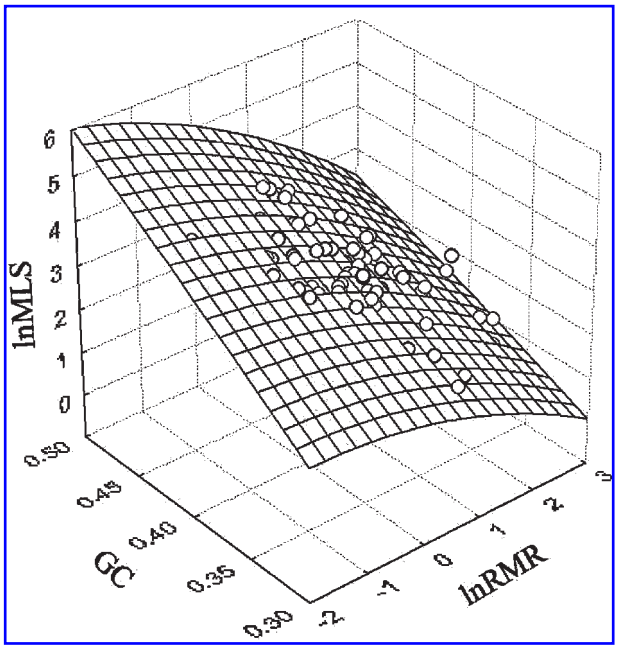

FIG. 2. The 3D quadratic response surface of the lnMLS dependence on GC content and lnRMR across mammals ($r^2 = 0.774$; $F = 56.3$; $p < 10^{-25}$). MLS in years, RMR in W/kg.

DISCUSSION

In animal cells, there are two physically separated centers of storing and expression of the genetic information—nuclear and mitochondrial. Because of the virtually "hostile" (bacterial) origin and relatively small resources, aggravated by a certain degree of autonomy, mitochondria could be a limiting subsystem among those ensuring cellular viability and ultimately the longevity of an organism. Based on this general paradigm, the authors analyzed the relationships between the mammalian maximum longevity and the variables directly related to mitochondria—mtDNA composition and metabolic rate.

In mammals, strong correlations of MLS with metabolic rate have been long established and intensively discussed.[10,13,14,26,27] Herein, a particular emphasis was placed on relationships between the mtDNA base composition and RMR, primarily to answer the principal question whether they complement each other in determination of the mammalian MLS. Also, the authors tried to receive further insight into possible links between MLS and mtDNA composition. The compositional characteristics of the H-strand were mostly considered, because the H-strand represents a primary target for

the directional mutation pressure, whereas changes in the L-strand are suggested to be secondary, reflecting mostly the alterations in base composition on the H-strand.[28]

RMR and mtDNA GC or G contents are the main determinants of longevity and explain over three fourths of variation in mammalian MLS

The most remarkable finding of this study is that the two mitochondria-associated parameters, the GC content and RMR, explain more than 77% of variation in mammalian MLS ($r^2 = 0.774$, $p < 10^{-25}$). To the authors' knowledge, it is the highest coefficient of MLS determination that has ever been reported for a comparable sample size. Because estimations of the MLS and RMR are inevitably associated with certain errors (technical component of variation), the remaining "free pool" of variation could be restricted by some 5–15%. It could mean that the GC and RMR explain most of the MLS biological variation. If so, other putative players in MLS determination should have relatively small contribution or their effects should be realized via the same "channels" as RMR or GC (or G).

Co-evolution of the metabolic rate and directional mtDNA nucleotide substitution in animals,[29,30] but not in mammals,[31] has been reported. In this study, no significant correlation between RMR and mtDNA base composition was found. Moreover, as was evident from the multivariate analyses, there was a negligible interaction between RMR and mtDNA base composition in determination of mammalian MLS. Altogether, this indicates that RMR and mtDNA are the two independent predictors of MLS and could complement each other in MLS determination. The multivariate analyses also showed the almost equal input of RMR and GC (or G) as predictors of MLS.

How could the mtDNA base composition matter to mammalian longevity?

Although we cannot rule out other targets involved in MLS determination, the results obtained suggest that the mitochondria could be a challenging object for exploration of longevity-associated mechanisms. To receive further insight into possible links between MLS and mtDNA, the authors first re-evaluated to what extent the mtDNA base composition matter to mammalian MLS, using a substantially enlarged dataset than that used in the previous study.[21] The results definitely confirmed strong correlations between mtDNA base composition and MLS in mammals. The correlations between mtDNA base contents (especially for G and A) and MLS are so strong and of such unbelievably high significance that "cause-and-effect" relationships between mtDNA and MLS can be suggested. In fact, such values are extremely rare for biological relationships in general, and for longevity in particular. Partial correlation and multivariate analyses might to some extent be considered a step towards illuminating the causative links between co-

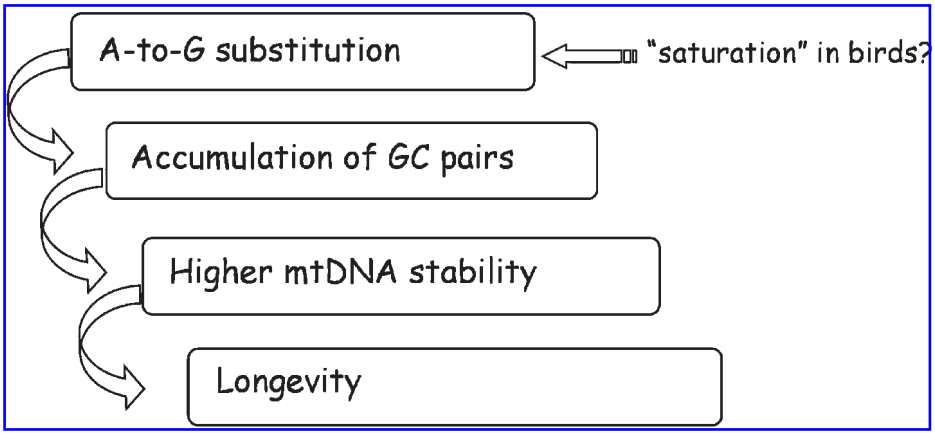

FIG. 3. mtDNA–longevity cascade: a possible scenario in endotherms.

varying variables. Their application highlighted a leading role of G in the MLS–mtDNA base composition relationships. It means that the effect of other bases on MLS could be realized mainly through the G-controlled channels.

How could the mtDNA base composition, G content in particular, matter to mammalian longevity? The simplest but not the only explanation is that an increase in G content and the subsequent accumulation of thermodynamically more stable GC pairs would result in a higher stability of mtDNA, ensuring thus a higher resistance of mtDNA against denaturizing factors, for example, temperature fluctuations (Fig. 3). This could be particularly relevant for endothermic organisms. Indeed, the authors found a significant positive correlation between the GC content and typical body temperature in mammals ($n = 79$; $r = 0.31$; $p = 0.006$), which was even more evident when birds were also included in the analysis (data not shown). A clear trend in A-to-G substitution on H-strand (and, accordingly, T-to-C substitution on L-strand) was observed from short-lived to long-lived mammals.[21] These processes seem to reach "saturation" in birds, with their higher body temperature and metabolic rate, presumably explaining the lack of correlation between MLS and mtDNA base composition in birds.[32] Alternative explanations for the links between mammalian MLS and mtDNA may suggest some specific, yet unknown function(s) for G or its possible relation to some longevity-associated mtDNA sequences.

In this study, the authors addressed the overall compositional features of the H-strand with respect to MLS. The relations could also be mtDNA region- or sequence-specific. For example, association of the mammalian MLS with mtDNA repeats was shown.[33,34] In another study, co-evolution of longevity and mtDNA protein coding sequences in mammals was proposed.[17,35] In support of the possible role for a non-specific accumulation of G on H-strand in mammalian longevity are our data on mtDNA codon usage in primates.[36] The increase in primate MLS was primarily associated with a substitution of the synonymous codons containing T at the "evolutionary neutral" third codon position (T_3) to the C_3-containing codons (this corresponds to the A-to-G substitution on H-strand). Changes in the non-synonymous codon usage appear to play a much lesser role in determination of the direction and significance of correlations with the MLS. Since the substitution of synonymous codons does not result in a change in the amino acid content, these findings are in favor of the assumption that MLS is primarily attributed to mtDNA base composition *per se*, rather than to the specific changes in mtDNA-encoding proteins.

CONCLUDING REMARKS

The comparative study of longevity is an intriguing area of research where much is known, more remains controversial, and much more remains to be learned. The results of this study led to the inference that the base composition of mtDNA, especially the G or GC content could undergo co-evolution with the mammalian longevity. The lack of correlation between G or GC content and metabolic rate suggests the independence of evolutionary alterations in the mammalian mtDNA nucleotide composition from the system of oxidative phosphorylation, which input in MLS could primarily be associated with the metabolic rate. The recent impressive progress in mtDNA sequencing fuels the authors' ambition to discover the most powerful determinants of longevity and their efficient combinations among the mitochondria-associated indices. Although further research is clearly warranted, the extraordinarily high correlation of the mtDNA GC (or G) and RMR with mammalian MLS suggests a "direct hit" of the core longevity targets, inferring mitochondria as a primary object for longevity-promoting interventions.

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