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# Trends in Endocrinology and Metabolism

## Are your mitochondria ready for a space odyssey?

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<b>Abstract:</b>	Anticipating very long space trips, NASA has performed pan-OMIC analyses on in-flight samples from astronauts, mice and cells. Results revealed major mitochondrial dysfunctions responsible for alterations in metabolism, immunity and circadian rhythm, which should prompt the evaluation of countermeasures to reduce the risks of future space odyssey, especially towards Mars.

## Spotlight

# Are your mitochondria ready for a space odyssey?

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Keywords: space odyssey, OMICS, mitochondria, genome.

### Abstract (53 words)

Anticipating very long space trips, the NASA has performed pan-OMIC analyses on in-flight samples from astronauts, mice and cells. Results revealed major mitochondrial dysfunctions responsible for alterations in metabolism, immunity and circadian rhythm, which should prompt the evaluation of countermeasures to reduce the risks of future space odyssey, especially towards the planet Mars.

20 **Core text** (800 words)

21

22 Over the next decades, space flight will increase dramatically, including for recreational  
23 purposes. The duration of space cruises will also increase, since it will take at least 400 to 500  
24 days to make a round-trip flight to the planet Mars [1].

25 This odyssey will undoubtedly induce physiological changes on the passengers that must be  
26 anticipated to reduce health problems. In a surprising study, entitled “*Comprehensive multi-*  
27 *OMICs analysis reveals mitochondrial stress as a central biological hub for spaceflight*  
28 *impact*”, by Da Silveira *et al.* published in November 2020 in Cell, NASA and associated  
29 teams addressed the molecular and biochemical consequences of space flights on cellular,  
30 animal and human samples collected during previous missions. Their study revealed drastic  
31 alterations of mitochondrial physiology as the main origin of most secondary metabolic and  
32 physiological manifestations occurring during space flights.

33 The multi-OMICS approach including epigenomic, transcriptomic, proteomic and  
34 metabolomic analyses were performed on cultured (fibroblasts and endothelial) and primary  
35 (T cells and hair follicles) human cells, on multiple organs from the C57BL/6 and BALB/c  
36 inbred mouse strains, as well as on urine and blood samples from 59 astronauts, the latter  
37 including the NASA *twin study* data [2].

38 The main results emerging from the study of this remarkable collection of data concerned  
39 changes in mitochondrial physiology occurring during space flights.

40 Indeed, OMIC signatures revealed a drastic uncoupling of the nuclear and mitochondrial  
41 genome cross-talk, with a systemic down-regulation expression of nuclear genes linked to  
42 energy production (i.e. electron transport, oxidative phosphorylation (OXPHOS) and ATP  
43 synthesis), while a progressive 2 to 9 fold longitudinal overexpression of mitochondrial genes,

44 paralleling increased mtDNA copy number, was observed, in particular in the blood cell  
45 fraction of astronauts, proportional to the time spent in space.

46 This nucleo-mitochondrial genome uncoupling is responsible for misassembly of respiratory  
47 chain complexes, decreased mitochondrial oxidative metabolism and increased production of  
48 reactive oxygen species (ROS). In parallel, a metabolic shift from glycolysis to OXPHOS  
49 respiration, as well as increased beta-oxidation of long-chain fatty acids and Krebs cycle were  
50 observed in mouse skeletal muscle, but not in liver. In addition, the imbalance of the  
51 OXPHOS complex subunits led to proteostasis failures triggering the mitochondrial unfolded  
52 protein response (UPR<sup>mt</sup>), and eventually the activation of Gadd34 and of the integrated stress  
53 response (ISR) in glycolytic muscle, while ISR biomarkers were downregulated in oxidative  
54 muscles together with a downregulation of the FGF21 and GDF15 mitokines. Alterations of  
55 mitochondrial physiology were further associated to the enrichment of genes associated to  
56 DNA repair as well as excretion of 8OH-dG in urine, witnessing possible alterations of the  
57 mitochondrial genome, and resulting in increased secretion of damage-associated molecular  
58 patterns (DAMPs) and VEGF, IGF1, IL1 $\alpha$ , IL1 $\beta$  and IL-1ra in blood, and up-regulation of  
59 IFN-dependent innate immune pathways in internal organs. In addition, genes involved in cell  
60 cycle were upregulated in all mouse tissues except T-cells, most likely to compensate for a  
61 higher level of apoptosis, as were genes involved in circadian rhythm in all internal organs,  
62 except liver, although animals were maintained in 12h/12h-light/dark cycle. Finally, the  
63 decreased in the synthesis of 1.25 vitamin D and the increase in the metabolism of NAD are  
64 further associated to the worsening of mitochondrial functions and alterations of DNA  
65 integrity, respectively. Notably, epigenomic methylation signatures reflected the major  
66 transcriptomic modifications induced by space flight. Ultimately, most of these deleterious  
67 changes reverted to normal in the weeks following the end of flight.

68 Altogether, these cellular modifications are witnessing processes related to premature aging,  
69 which could originate from major alterations of the mitochondrial genome, as loss of mtDNA  
70 integrity is clearly responsible for aging in mice [3,4] and humans [5]. In this regard, future  
71 assessments of mtDNA integrity in space-exposed samples are warranted to further reveal the  
72 initial mechanism responsible for the molecular changes reported in the Da Silveira paper, as  
73 mtDNA instability could be triggered both by the exposure to low doses of irradiation [6] and  
74 by the consequences of microgravity [7].

75 The effects of accelerated aging of space flight further result in somatic changes, including  
76 loss of bone density, reduction in muscle mass and strength. Stiffening of the arteries,  
77 overactivation of the immune response, increased cardiovascular risks and possibly thrombo-  
78 vascular events were also observed. Alopecia, a marker of premature aging in animal models,  
79 is also affecting astronauts. Therefore, if astronauts (or future space tourists) do not wish to  
80 land on Mars as “centenarians”, countermeasures are needed to minimize the consequences of  
81 long-duration space flights. In addition to daily muscular exercise, nutritional and  
82 pharmacological supplementation targeting mitochondrial physiology are mandatory. The  
83 “Mitochondrial Space Odyssey Cocktail” should be composed of anti-oxidants such as  
84 CoQ10, to counteract the oxidative stress and promote mitochondrial electron transfer,  
85 vitamin B3 to sustain NAD-related mitochondrial activity and DNA repair, and vitamin D to  
86 maintain bone mineral density and arteries plasticity. And why not a bottle of red wine to  
87 promote mitochondrial turnover and rejuvenation [8]?

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109 extends lifespan of a Drosophila model of Parkinson's disease through activation of  
110 mitophagy. Exp Gerontol. 2018 Nov;113:10-17.

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112

## 113 **Figure Legend**

### 114 **Synopsis of the molecular processes affecting mitochondrial physiology and the related** 115 **somatic consequences on health.**

116 Exposure to low doses radiation and microgravity most probably induces mitochondrial  
117 genome alterations that are responsible for the uncoupling of the nuclear and mitochondrial  
118 genome cross-talk, the overproduction of DAMPs and changes in NAD metabolism, resulting  
119 in downstream somatic effects reflecting a transient premature systemic aging process.

120

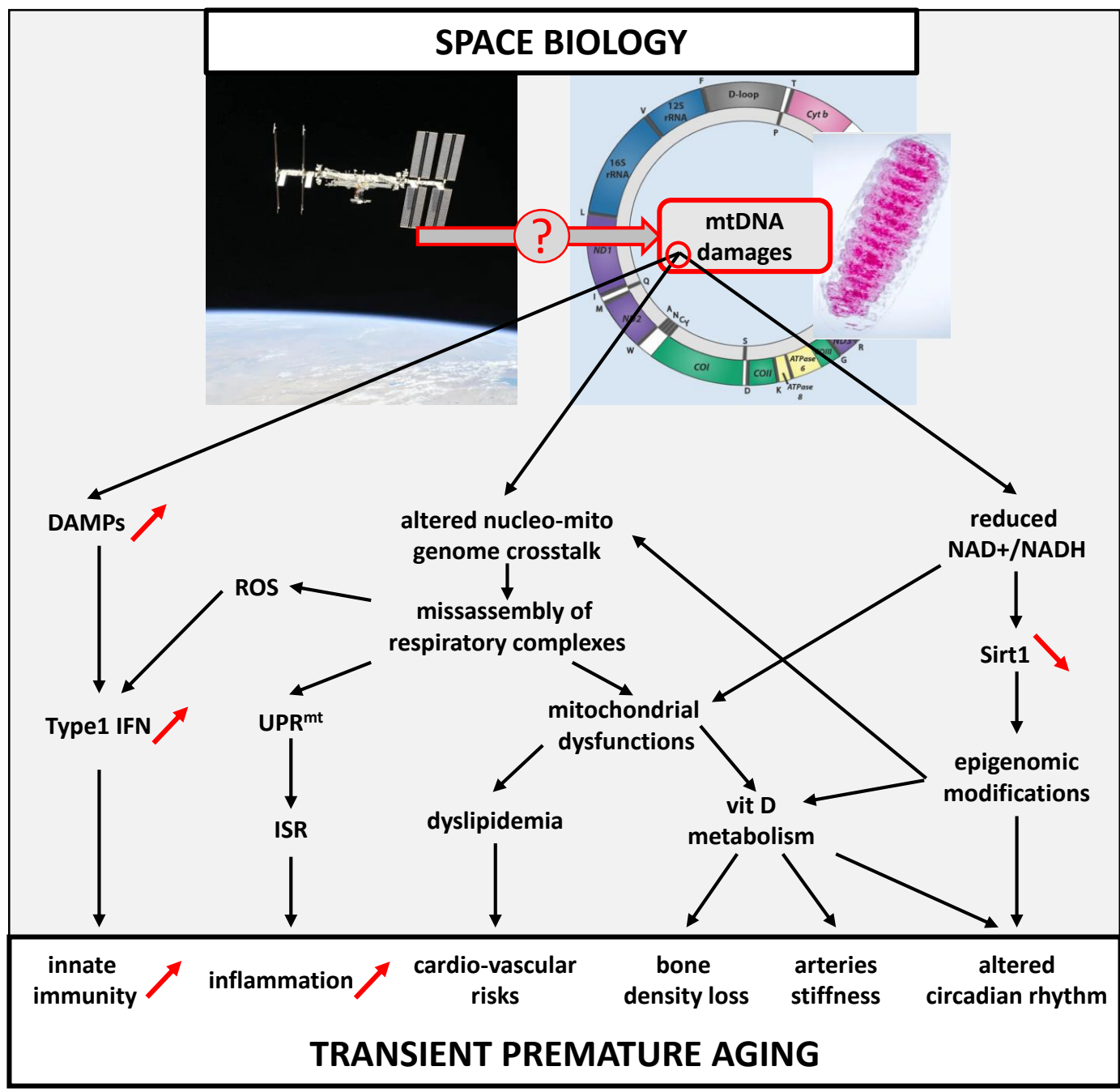
121

### 122 **Abbreviations:**

123 DAMP: damage-associated molecular patterns; IFN: interferon; ISR: integrated stress  
124 response; mtDNA: mitochondrial DNA; NAD: nicotinamide adenine dinucleotide; OXPHOS:  
125 oxidative phosphorylation; ROS: reactive oxygen species; UPR<sup>mt</sup>: mitochondrial unfolded  
126 protein response; vit D: vitamin D.



Figure



## Spotlight

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### 3 **Are your mitochondria ready for a space odyssey?**

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9 **Anticipating very long space trips, the NASA has performed pan-OMIC analyses on in-**

10 **flight samples from astronauts, mice and cells. Results revealed major mitochondrial**

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12 **which should prompt the evaluation of countermeasures to reduce the risks of future**

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