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Review

Long-term human spaceflight and inflammaging: Does it promote aging?

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ABSTRACT

Spaceflight and its associated stressors, such as microgravity, radiation exposure, confinement, circadian derailment and disruptive workloads represent an unprecedented type of exposome that is entirely novel from an evolutionary stand point. Within this perspective, we aimed to review the effects of prolonged spaceflight on immune-neuroendocrine systems, brain and brain-gut axis, cardiovascular system and musculoskeletal apparatus, highlighting in particular the similarities with an accelerated aging process. In particular, spaceflight-induced muscle atrophy/sarcopenia and bone loss, vascular and metabolic changes, hyper and hypo reaction of innate and adaptive immune system appear to be modifications shared with the aging process. Most of these modifications are mediated by molecular events that include oxidative and mitochondrial stress, autophagy, DNA damage repair and telomere length alteration, among others, which directly or indirectly converge on the activation of an inflammatory response. According to the inflammaging theory of aging, such an inflammatory response could be a driver of an acceleration of the normal, physiological rate of aging and it is likely that all the systemic modifications in turn lead to an increase of inflammaging in a sort of vicious cycle. The most updated countermeasures to fight these modifications will be also discussed in the light of their possible application not only for astronauts' benefit, but also for older adults on the ground.

1. Introduction

On Earth, the human body is permanently exposed to various combinations of external or internal, general and specific environmental influences, collectively indicated as exposomes, which sometimes represent a threat to our health status (Wild, 2012). In fact, these exposomes may also include stressors such as mental and social stress, sleep deprivation or impaired sleep, environmental pollutants, climate changes, bad habits, and bacterial, viral or parasite infections, among others. The acute exposure to a stressor induces a response of the immune-neuroendocrine system aimed at counteracting the stress and restoring homeostasis. A chronic or even lifelong exposure to stressors leads to adaptation and remodeling processes that include a subclinical increase in the inflammatory tone, a phenomenon indicated as inflammaging (Franceschi et al., 2000, 2007). Such an increase of the inflammatory tone represents a risk factor for the onset of many (if not all)

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age-related diseases. Inflammation is indeed currently considered one out of seven different molecular pillars underpinning both aging and age-related diseases, according to the Geroscience concept (Kennedy et al., 2014). In this perspective, inefficient bodily adaptation to exposomes may promote inflammation and likely accelerate the aging process and disease onset (Franceschi et al., 2018a, 2018b).

Year-long missions aboard the International Space Station (ISS) are now regularly performed, and deep space missions, e.g., to Moon or Mars seem within reach to humankind in the near future (Schwendner et al., 2017). Therefore, a brand new exposome created by the harsh conditions of spaceflights is emerging. In particular, this "Space" exposome includes microgravity, exposure to radiations, harsh workload, disruption of circadian rhythms, isolation and confinement, and potentially others (Cucinotta, 2014), as listed in Fig. 1. For the forthcoming deep space exploration missions, challenges will be even greater than for Low Earth Orbit (LEO) missions on the ISS. We hypothesize that prolonged exposure to this Space exposome may chronically trigger adaptation (or maladaptation) and repair responses that may trigger the production of molecular "garbage" such as misplaced or unfolded molecules (Franceschi et al., 2017) and prompt many other age-related mechanisms, as previously suggested (see Box 1: age-related molecular/cellular mechanisms modified by microgravity/spaceflight). All these mechanisms may, in an iterative process, further promote chronic inflammation and stress responses thus affecting various organ systems and exacerbating inflammaging. Since inflammaging, as mentioned, is considered a driver of the aging process, it is therefore plausible that the Space exposome may cause an increase in the rate of aging. This possibility represents a great concern for future spaceflights. With this in mind, we have reviewed the most recent literature on how spaceflight may affect the immune-neuroendocrine system, brain, brain-gut axis and metabolism, cardiovascular system and the musculoskeletal system. In particular, we will discuss astronauts' in-flight and post-flight data, with the aim of identifying reversable and eventually non-reversable spaceflight-mediated changes, being the latter a potential driver for an accelerated aging. Potential countermeasures will be also reported in the final section. (Box 1)

2. Effects on immune-neuroendocrine system

Spaceflight affects the human immune-neuroendocrine system (Sonnenfeld, 1999), critical for the best adaptation of the body to the new exposome. In fact, astronauts exhibited significantly increased salivary cortisol concentrations during spaceflight (Mehta et al., 2017) and cortisol spikes in plasma and urinary after return to Earth. This response was more pronounced after long-term missions as compared to short-term missions (Stowe et al., 2011). A recent study also demonstrated an increased in-flight endocannabinoid blood levels as biological stress response (Buchheim et al., 2019). Thus, various immune system components are modified secondary to prolonged psychological and physiological stress which in turn generates effects on the immune system.

As far as innate immune activity is concerned, several studies assessed blood cytokines levels. One exemplary study revealed significant in-flight increases in IL-8, IL-1ra and CXCL5 which recovered after landing (Crucian et al., 2014). IL-1ra has been implicated in chronic elevations of body core temperature during long duration space missions

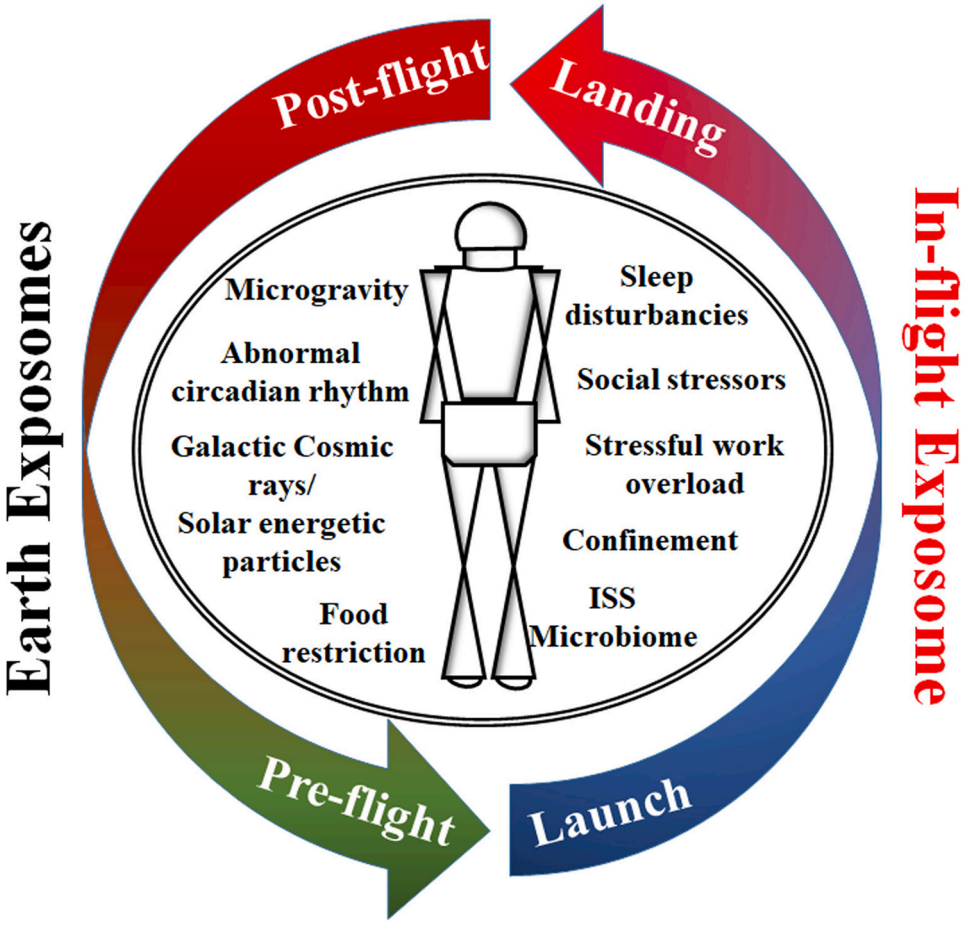

Fig. 1. Human spaceflight exposome and its main interacting variables. Pre-flight, Launch, Landing and post-flight recovery are all phases interacting with Earth exposomes. Astronauts are often exposed to alternate exposomes between ground and orbital in-flight.

Box 1
Age-related molecular/cellular mechanisms modified by microgravity/spaceflight.

A recent literature, based on in vitro models, animal models and astronauts, has highlighted some molecular/cellular mechanisms activated during microgravity/spaceflight that are typically observed during aging. Thus, it seems that the effects of spaceflight can somehow recapitulate at least in part the normal aging process, and therefore spaceflight may represent a driver of accelerated aging and a risk factor for age-related diseases.

- **Oxidative stress, mitochondria dysregulation and autophagy**. Oxidative stress arises when the production of free radicals exceeds the natural antioxidant capacities of the cell. In fact, the predominant mechanism of ROS generation in microgravity conditions seems to be the upregulation of oxidative enzymes and downregulation of anti-oxidative enzymes leading as a consequence to an increase of the inflammatory process (Vitale et al., 2013). In mice model, a decrease in hepatic oxidative defense, measured as glutathione levels, is associated with aberrant tRNA post-translational processing, induction of degradation programs and senescence-associated mitochondrial dysfunction in response to spaceflight (Blaber et al., 2017).
  The increase in oxidative stress has been observed in 59 astronauts by measuring the levels of mitochondrial oxidative metabolite 8-hydroxy-2-deoxyguanosine in urine (da Silveira et al., 2020). It is well known that NF-κB is sensitive to oxidative stress and is a key driver of the inflammatory response. In this perspective, NF-κB may connect an increase in oxidative stress and an increased inflammation during spaceflight. Accordingly, in mice exposed to spaceflight for 15 days , a downregulation of NRF2 and PTGS2, and an upregulation of NOX1 in cardiac tissue was observed, suggesting a persistent increase in oxidative stress-related target genes (Kumar et al., 2021) and confirming previous data and reviews (Takahashi et al., 2017; Goodwin and Christofidou-Solomidou, 2018).
- **DNA damage, telomere length and cell senescence**. DNA damage has been recently demonstrated in astronauts during and after a spaceflight, in particular a directional genomic hybridization analysis has detected an increase of intra-chromosomal inversions, a finding potentially related to stem-cell damage, clonal hematopoiesis, and/or instability. In addition, telomere length seems to be affected, being increased during LEO and then shortened after landing and recovery (Garrett-Bakelman et al., 2019; Luxton et al., 2020; Mencia-Trinchant et al., 2020). Moreover, results obtained on HUVEC cell line suggest that some ultrastructural changes may occur, including cytoskeletal disruption and premature senescence (Kapitonova et al., 2012; Afshinnekoo et al., 2021). Accordingly, recent results from in vitro studies suggested that space radiation stimulates endothelial activation, through mechanisms such as hypoxia and inflammation, DNA repair and apoptosis, inhibition of autophagic flux and promotion of an aged-like phenotype. Conversely, microgravity activates pathways for metabolism and a pro-proliferative phenotype, thus revealing possible opposite effects (Barravecchia et al., 2022). Overall, microgravity and exposure to radiations seem to be apparently divergent mechanisms but actually they could converge in promoting neoplastic transformation, and their synergistic effects should further be investigated in this regard.

As a whole, the above-mentioned mechanisms converge on the induction or regulation of an inflammation process and represent the basis of possible chronic modifications leading to systemic alterations involving immune-neuroendocrine system, brain-gut axis, cardiovascular system, skeletal muscle and not lastly inflammaging.

(Stahn et al., 2017). The idea may be consistent with the cytokine response adaptation, being IL-1ra the antagonist inhibitor of IL-1, but its increase seems not sufficient to avoid the rise of body temperature, that is also regulated by IL-6 and TNF-alpha and likely increased by physical exercise training.

The cytokine network is a crucial component of inflammaging, which is characterized by unbalance between pro- and anti-inflammatory molecules/cytokines and chronicity favors age-related disease onset. In this respect, the improvement of ISS environment condition in the last decade seems to suggest also an improvement in terms of decreased levels of specific cytokines, such as IL-1RA and IL-8 (Crucian et al., 2020), but cytokine network dysregulation is still an ongoing issue. The recent NASA Twin study reported altered cytokine profiles in homozygous twin astronauts on a one-year-spaceflight mission on the ISS, but not in his twin brother who remained on Earth. Results on 50 cytokines measurements suggested that in-flight and post-flight effects are much more severe than previously observed (Garrett-Bakelman et al., 2019). For example, IL-6 increased in space, but decreased after landing. Leptin, by contrast was increased after landing. These results differ from those obtained by our team, showing similar trends for both cytokines (increase after landing and decrease after recovery) with different levels comparing two astronauts, thus suggesting an inter- individual variability (Capri et al., 2019b). Furthermore, a recent work showed a significant alteration of regulatory/inhibitory cytokines i.e., TGF-β, IL-10 and IL-1ra, all of which dropped rapidly after return to Earth (Buchheim et al., 2019) and results suggest a systemic pro-inflammatory status after landing. In this respect, our team observed again a strong inter-individual/astronaut variability, in particular for TGF-β (Capri et al., 2019b). The role of stress and the cytokine profile was also investigated not only in plasma, but also in astronauts' saliva. Significant decreases in saliva of GM-CSF, IL-12p70, IL-10 and IL-13 were observed during spaceflight as compared to baseline concentrations. These data have also been related with different types of plasma cytokines, suggesting an alteration of cytokine homeostasis during flight in two different compartments, both oral cavity and systemic level (Krieger et al., 2021).

A compromised innate immune cell capacity during and after spaceflight is also observed for NK function, particularly in astronauts embarking on their first spaceflight mission (Bigley et al., 2019). Recent studies, applying simulated microgravity in *in vitro* cell models are consistent with dampening of CD56dimCD16 +NK cells under stimulation, thus confirming the inhibition effects of NK (Spatz et al., 2021). The decrease of NK in-flight function may be associated with virus reactivation. In fact, reactivation of various viruses, such as Cytomegalovirus (CMV), Epstein Barr virus (EBV) and varicella-zoster virus (VZV), during long-term (6 months) ISS flight in terms of frequency, duration, and viral copy numbers, has been observed at individual level (Mehta et al., 2017). Chronic virus exposure elicits NK phenotype modifications, e.g., the lacking of CD56 expression and a concomitant reduced functional capacity (Björkström et al., 2010). Despite an elevated neutrophil and monocyte counts, markedly reduced NK cell numbers have been observed after spaceflight (Buchheim et al., 2019), thus suggesting persistent NK function impairments after flight (Bigley et al., 2019). We speculate that prolonged impairments in immune surveillance could pose health risks for astronauts.

During aging process, NK cells lose their proliferative capacity and cytotoxic potential (Witkowski et al., 2020), thus virus reactivation (Stowe et al., 2012) is also observed as people age on Earth. The

Table 1
Inflammaging sources in- and post-flight periods. The reason(s) why these parameters are important for inflammaging (and relative references) are reported in the right columns.

In-flight Inflammaging Sources	References	Knowledge on Inflammaging	References
Pro-anti- inflammatory cytokine unbalance towards a pro-inflammatory status	Crucian et al. (2014); Stahn et al. (2017); Buchheim et al. (2019); Garrett-Bakelman et al. (2019); Capri et al. (2019b); Krieger et al. (2021).	Various pro-inflammatory cytokines/molecules increase and anti-inflammatory cytokine decrease/increase with age	Franceschi et al. (2019); Capri et al. (2019a); Ferrucci and Fabbri (2018); Sayed et al. (2021).
Virus reactivation	Mehta et al. (2017);	Elderly people may suffer of virus reactivation, such as Herpes virus, Cytomegalovirus among others	Thomasini et al. (2017); Palacios-Pedrero et al. (2021).
Salivary/plasma/urinary cortisol increase	Mehta et al. (2017).	Centenarians have a higher plasma level of cortisol than young individuals. Urinary cortisol level increase after 60 years of age	Genedani et al. (2008); Ferrari et al. (2008); Moffat et al. (2020).
NK function decrease	Bigley et al. (2019); Spatz et al. (2021)	A recent literature highlights the decreased function of NK with aging, even if appear to be membrane receptor-dependent.	Pinti et al. (2016); Brauning et al. (2022).
Plasma sIgA increase	Spielmann et al. (2019).	Soluble IgA1 and IgA2 plasma levels increase with aging	Blanco et al. (2018).
Gut microbiome (GM) changes have been identified, but the field is largely unexplored	Voorhies et al. (2019).	Elders show a modified, dysbiosis-like GM. Centenarians show a remodeled GM with the increase of Christensenellaceae and Akkermansia among others. Longevity is associated with xenobiotic degradation and a rearrangement in metabolic pathways related to carbohydrate, amino acid, and lipid metabolism.	Biagi et al., (2010, 2016); Rampelli et al. (2020); Santoro et al., (2018, 2020); Bulut et al. (2021).
Sleep deprivation/Circadian rhythm deregulation	Barger et al. (2014); Flynn-Evans et al. (2016).	Sleep deprivation/circadian rhythm disruption led to an increase of pro-inflammatory status/inflammaging. Centenarians seem to preserve a regular circadian rhythm.	Franceschi et al. (2018c); Irwin and Opp (2017); Martucci et al. (2020); Ragonnaud and Biragyn (2021); Xiao et al. (2022); Xu et al. (2022).
Metabolic changes	Rittwerger et al. (2018); Garrett-Bakelman et al. (2019).	Plasma/urinary metabolite signature may characterize different ages and longevity	Collino et al. (2013); Montoliou et al. (2014); Franceschi et al. (2018b); Salminen (2022); Li et al. (2022).
Post-flight Inflammaging Sources	**References**	**Knowledge on Inflammaging**	**References**
Thymopoiesis decrease; Memory T cell increase	Benjamin et al. (2016); Buchheim et al. (2019).	Thymopoiesis decreases starting at teenage. Cross sectional data including centenarians suggest that thymic remnants are still functioning at extreme ages and memory T lymphocytes increase with age.	Nasi et al. (2006); Ostan et al. (2008).
inflamma-microRNAs -(miRs) increase/ modifications in comparison with baseline	Capri et al. (2019b).	Modification of miRs-21–5p; miR-126 and miR-146 (inflammamiRs) appear to be associated with ageing and with age-related disease	Olivieri et al. (2013a), (2013b); Olivieri et al. (2014).
NK number and function decrease	Buchheim et al. (2019).	A recent literature highlights the decreased function of NK with aging, even if appear to be membrane receptor-dependent.	Pinti et al. (2016).
Plasma/urinary cortisol increase	Benjamin et al. (2016).	Soluble IgA1 and IgA2 plasma levels increase with aging.	Blanco et al. (2018).
Skeletal-Muscle atrophy and proteomics changes	Rittweger et al. (2018); Burkhart et al. (2019); Bailey et al. (2018).	A tight relationship between sarcopenia, frailty and age-related diseases is recognized. An impressive number of studies are going to clarify the molecular aspects.	Kalyani et al. (2014); Gonzalez-Freire et al. (2017); Franceschi et al. (2018c)
Increase expression of TLR-2, TLR4 and circulating self-DAMP molecules	Ponomarev et al. (2016).	DAMPs receptors, such as TLR-2 and − 4, are mediator of inflammatory response. Aging leads to an increase of DAMPs and recent data suggest a dysfunctional innate immune response to TLR-2 and TLR-4 agonists	Feldman et al. (2015); Franceschi et al. (2017); Bailey et al. (2019).
Circulating (c)-mtDNA increases after landing	Capri et al. (2019b).	Plasma c-mtDNA fragments increase with age and associate with pro-inflammatory status. A portion of c-mtDNA is present on extracellular vesicle.	Pinti et al. (2014); Lazo et al. (2021); Fan et al. (2022).

phenomenon has been attributed to immunosenescence, likely involving genomic transposomes/retrotranspons activity (Hurme, 2019) and cell senescence phenotype (De Cecco et al., 2019). These effects reveal an interesting parallelism between some spaceflight mission effects and some characteristics of immunosenescence (see Table 1).

As far as adaptive immune system is concerned, Buchheim et al. (2019) observed 50 % increased B lymphocyte counts in-flight, though unchanged pre- and post-flight. Overall, the B cell compartment appeared preserved during long-term spaceflight, even if plasma immunoglobulins A (sIgA) were increased (Spielmann et al., 2019). Moreover, a recent study showed significant changes in the IgM repertoire during the mission in some crew members (Buchheim et al., 2020). In addition, in vitro post-flight stimulation of whole blood samples with fungal antigen revealed amplified TNF-α and IL-1β responses together

with reductions in CD4 +CD25 +CD27^{low} regulatory T cells (Tregs). The response recovered one month after return from space (Buchheim et al., 2019). Conversely, simulated microgravity enhanced STAT5 signaling in immunosuppressive Tregs (Spatz et al., 2021). Further experiments are necessary to reconcile at least partly contradictory findings, regarding Treg number and function in microgravity. In fact, reduced Treg numbers could shift the balance between protective and pathogenic immunity towards chronic, and perhaps tissue-damaging inflammation (Fulop et al., 2020). On the other hand, increased Treg activity could compensate for reduced Treg numbers.

In vitro studies on T cell activation onboard ISS revealed an inhibition of early genes including Rel/NF-κB, CREB (Chang et al., 2012) and NFK1A (Hughes-Fulford et al., 2015). Benjamin et al. (2016) also reported attenuated thymopoiesis after spaceflight, measured as circulating T cell Receptor Excision Circles (δ-deletion, TRECs) in peripheral blood mononuclear cells together with increase plasma/urinary cortisol. However, the percentage of T lymphocytes appears to be preserved after landing, even though the percentage of memory CD8 + T lymphocytes is increased (Buchheim et al., 2019). Conversely, simulated microgravity impaired multiple aspects of CD8 + T cell function, including CD25, CD69, and JAK/STAT1 and STAT5 signaling responses (Spatz et al., 2021). Suppressed CD8 + T cell function could conceivably translate to impairment in pathogen defense. Decreased thymopoiesis, increased memory T cells, and ineffective CD8 + T cells also mirror the immunosenescence observed at old age (Nasi et al., 2006; see also Table 1).

In contrast, the recent NASA Twin study reported telomere lengthening in peripheral blood mononuclear cells as well as in sorted CD4, CD8, and lymphocytes depleted cells, but not in CD19 cells (Garrett--Bakelman et al., 2019). However, telomeres recovered their pre-flight length after one month on Earth. These data have been confirmed later on (Luxton et al., 2020) highlighting that telomere length tended to be shorter after spaceflight than before spaceflight. Signatures consistent with persistent DNA damage responses were also detected, including mitochondrial and oxidative stress, inflammation, and telomeric and chromosomal aberrations. The findings provide an impetus to further investigate DNA damage, DNA damage response, and cell senescence during spaceflight as these mechanisms drive aging and age-related diseases (Kennedy et al., 2014; Franceschi et al., 2017), as also mentioned in Box 1. In addition, telomere elongation during spaceflight deserve attention, since the phenomenon characteristically occurs in malignant cells.

Importantly, the sleep deficiency that commonly affects astronauts (Barger et al., 2014), partially due to circadian misalignment in space (Flynn-Evans et al., 2016), may activate the Hypothalamic-Pituitary-Adrenal (HPA) axis and modulate autonomic nerve system responses with pervasive effects on the immune system. For example, sleep disturbances may promote norepinephrine release from sympathetic terminals in primary and secondary lymphoid organs and adrenal epinephrine release into the systemic circulation. Both neuromediators stimulate leukocyte adrenergic receptors (e.g., ADRB2 or beta-2 adrenergic receptor) and activate NF-κB-mediated inflammatory programs (Irwin and Opp, 2017). Persistent sleep deprivation may chronically activate the inflammatory response, which could further exacerbate inflammaging. In this direction, some PAMP/DAMP receptors, such as Toll-Like Receptors, TLR-2 and TLR-4, were increased in peripheral blood granulocytes/monocytes of astronauts after long-term spaceflight exposure. In parallel, serum concentrations of self-molecules which are ligands of TLR-2 and TLR-4, such as HSP60 and HSP70/HMGB1, respectively, were also increased post-flight (Pono-marev et al., 2016), with recovery after seven days. These results may sustain the hypothesis that spaceflight increases "blood circulating self-molecules/garbage", as fuel for inflammaging and inflammatory tone. These molecules through various DAMPs receptors converge on NF-κB activation pathway and likely inflammaging propagation, as proposed previously (Franceschi et al., 2017).

Taken together, these findings are consistent with a dysregulated immune system, in particular during spaceflight, with hyporeactive/exhausted T and NK cells and hyperreactive innate responses thus resembling some aspects of immunosenescence in older people (Fulop et al., 2020, 2022; Santoro et al., 2021). In Table 1 inflammaging sources in-flight and post-flight are provided.

3. Effects on brain, brain-gut axis, and metabolism

Literature on spaceflight effects on brain structure and function is rapidly surging (Van Ombergen et al., 2017a, 2017b; Pechenkova et al., 2019). Central Nervous System (CNS) changes during and after spaceflight in term of neurovestibular problems, alterations in cognitive function and sensory perception, complications with motor function, cephalic fluid shift and psychological disturbances are in the focus. The spaceflight-associated neuro-ocular syndrome (SANS), which includes optic-disk edema, hyperopic shifts and possibly elevated intracranial pressure receives much attention (Mader et al., 2011, 2013; Garrett-Bakelman et al., 2019). SANS is likely associated with cephalad fluid shift in space (Marshall-Goebel et al., 2019) and can be reproduced in strict head-down tilt studies (Marshall-Goebel et al., 2016). Furthermore, 61 % of astronauts analyzed by magnetic resonance imaging reported some brain structure changes such as stretching of the pituitary stalk (Roberts et al., 2017). It is tempting to speculate that these findings could affect brain and pituitary function. The latter could elicit hormonal changes, however, data on hormonal regulation in male and female astronauts is scarce.

In this perspective, another player with possible influence on the brain is the gut microbiota (GM), thus becoming relevant for long term human space missions (Turroni et al., 2020). Importantly, interactions between microbiota metabolites and host receptors supporting the gut-brain axis have been highlighted (Cerdó et al., 2019), but studies on brain-gut axis in human spaceflight are scarce. The ground-based Mars500 project investigated long-duration health in six probands isolated for 520 days. Confinement per se did not strongly affect GM (Turroni et al., 2017), but a recent deep reanalysis with advanced technology identified 408 exact sequence variants (ESV, or operational taxonomic units), including 213 shared by all probands. In particular, 32 ESVs were significantly differentially abundant over time, including depletion of keystone resistant starch degrading, anti-inflammatory and insulin sensitivity-associated species (Brereton et al., 2021).

Importantly, in-flight effects have been reported on GM biodiversity, measuring both alpha and beta diversity. While alpha-diversity represents the diversity within an ecosystem or a sample, beta-diversity represents the difference between two ecosystems/samples. In other words, beta-diversity estimates how much two ecosystems or samples resemble or diverge from each other. Voorhies et al. (2019) showed that alpha and beta diversity were increased and decreased, respectively in 9 astronauts over the course of a 6–12-month mission to the ISS. Interestingly, GM composition became more similar across astronauts in spaceflight primarily through reduction in few bacterial taxa. Among taxonomic groups, a more than five-fold in-flight reduction in *Akkermansia* and *Ruminococcus* was observed, and about 3-fold reductions in *Pseudobutyrivibrio* and *Fusicatenibacter*. Most of these changes reverted to preflight levels after recovery, with some exception of genera belonging to the phylum Firmicutes (Voorhies et al., 2019). We have recently observed that *Akkermansia* abundance, which is crucial for gut immune system homeostasis (Hand et al., 2016), relates to longevity (Biagi et al., 2016). Possibly, GM dysbiosis during long term space missions could contribute to an inflammaging phenotype, which could provide a rational for countermeasures, as described below. As far as beta diversity is concerned, Voorhies et al. (2019) revealed in-flight qualitative and quantitative changes in the microbial composition of gastro-intestinal and skin microbiomes that persisted in post-flight samples. These findings are noteworthy and deserve additional investigation to understand the possible impact on brain functions/metabolism and health status in long-term missions.

On the other hand, brain can affect intestinal functions via hormones, neuropeptides, and neurotransmitters such as substance P, neurotensin, corticotropin releasing hormone, acetylcholine and 5-hydroxytryptamine, derived from tryptophan (Petra et al., 2015; Schroeder and Bäckhed, 2016). In this regard, the NASA Twin study speculated that post-flight cognitive impairments could relate to microbiome modification; the response persisted up to 6 months after landing (Garrett-Bakelman et al., 2019). Yet, another study showed that spaceflight affected sensorimotor performance that recovered within 30 days, while cognitive performance was preserved (Tays et al., 2021).

As far as tryptophan is concerned, evidence in mice and in *in vitro* systems exposed for a relatively short time to spaceflight suggest a possible microgravity effect of tryptophan deficiency and alteration of key pathway enzymes, respectively (Chakraborty et al., 2018; Popova et al., 2015). To our knowledge the tryptophan system has not been investigated in astronauts, even if circulating tryptophan may affect cognitive function in human beings (Santoro et al., 2018). Thus, we propose that tryptophan metabolism should be studied in astronauts since its possible alteration could be attenuate by nutritional countermeasures (Sorgdrager et al., 2019).

Several studies have shown that GM composition changes have striking association with metabolism, energy balance, and immune-metabolism. Recent reviews highlight the impact of microbiota metabolites on the differentiation of immune system cells involving also Treg and their activity beyond the intestine up to the CNS in both health and disease (Nguyen and Palm, 2022; Choi et al., 2022). In particular, specific GM taxa are associated with a reduced visceral adipose tissue and healthier metabolic profile in old people (Tavella et al., 2021). In this perspective, GM changes appear extremely relevant for health status and brain-gut axis. As reported by the NASA Twin study several small-molecule markers of microbial metabolism, including phenyls, secondary bile acid metabolites, and indole containing compounds, were changed. In particular, 3-indole propionic acid, which has anti-inflammatory effects, was reduced in-flight (Garrett-Bakelman et al., 2019). Increased lysophosphatidylcholine and decreased lysophosphatidylethanolamine during, both, in- and post- spaceflights could promote a pro-inflammatory state. Our study on metabolomics suggests individual metabolic adaptations after flight, in particular an increased pyruvate and lactate, possibly the adherence to exercise countermeasures modulated the response (Rittweger et al., 2018).

4Effects on cardiovascular system

In most countries, cardiovascular disease is a leading cause of morbidity and mortality and age is the prime cardiovascular risk factor. Because spaceflight affects many of the pathways contributing to aging-associated vascular disease as outlined in this review, potential risks for cardiovascular health in astronauts are a matter of concern (Shen and Frishman, 2019; Vernice et al., 2020; Baran et al., 2021; Jordan et al., 2022, Jirak et al., 2022). The progression of cardiovascular disease can be conceptualized as sequence starting with functional changes followed by subclinical changes in cardiovascular structure and ultimately overt cardiovascular disease. Functional cardiovascular changes in real and simulated space conditions have been intensely investigated. There is less data on preclinical changes in vascular structure. Sufficient data on cardiovascular morbidity and mortality does not exist given the low number of people exposed to space conditions.

Exposure to microgravity affects cardiovascular regulation in a time-dependent fashion. Reduced gravity decreases the hydrostatic pressure, and body fluids are redistributed toward the upper body and head. The upward fluid shift acutely increases central vascular volume with a paradoxic reduction in central venous pressure (Buckey et al., 1993; Baran et al., 2021). Yet, neck veins are grossly distended, which may predispose to neck vein thrombosis in space (Marshall-Goebel K et al., 2019; Limper et al., 2021). Central hypervolemia early into spaceflight appears to engage counter-regulatory mechanisms through carotid, aortic, and perhaps, cardiac receptors (Iwase et al., 2020). In head-down bedrest studies, cardiac stretch promotes atrial natriuretic peptide (ANP) release while baroreceptor mechanisms attenuate renin–angiotensin–aldosterone system activity (Pavy-Le Traon et al., 2007). Natriuretic responses while responding to changes in sodium ingestion are rest to lower levels in space (Frings-Meuthen et al., 2020). Together, these counterregulatory responses result in a 10–15 % reduction in blood plasma volume (Vernice et al., 2020). Bioimpedance measurements suggest that thoracic blood volume decreases during long duration space missions (Frings-Meuthen et al., 2020). ANP has also been implicated in vasodilatation and changes in vascular permeability during shorter-term microgravity exposure (up to 10 days), which could also decrease plasma volume and lower atrial pressure (Aubert et al., 2005). In fact, plasma volume reduction results at least in part from transient fluid shift from intravascular to interstitial and intracellular spaces (Watenpaugh, 2001).

The hemodynamic responses to space conditions are complex and not fully understood. Cardiac output increases initially and tend to be increased with different effects depending on the time of the missions. The response is mainly mediated though increased stroke volume rather than a change in heart rate. Yet, systemic vascular resistance appears to be substantially reduced in space (Norsk et al., 2015). These rapidly reversible responses may be considered a specific response to space-conditions. Resting blood pressure changes little in space and may even decrease (Baevsky et al., 2007). Heart rate seems to be stable or decreases in the different types of missions (Baran et al., 2021; Baevsky et al., 2007). These space-related features do not characterize aging phenotype. However, the associated reduction in cardiopulmonary fitness and propensity to experience orthostatic intolerance occurs in astronauts and in older people alike.

Several non-invasive measurements have been utilized in the past to identify early vascular aging in patients on Earth. However, these measurements may also be affected by functional cardiovascular changes and cannot be equated with hard clinical endpoints. Following long-term space missions, increases in carotid intima media thickness as well as in femoral intima media have been reported. Overall arterial stiffness may also increase (Hughson et al., 2016). Arterial stiffness can be observed in early stages of artery aging even before overt atherosclerosis or clinical symptoms occur. Various traditional cardiovascular risk factors, such as arterial hypertension, dyslipidemia, smoking, and type 2 diabetes mellitus contribute to vascular stiffening, however, a wide spectrum of molecules such as cytokines, chemokines and microRNAs among others, also contribute to vascular aging (Collura et al., 2020). Chronic inflammation and cardiovascular diseases are closely interrelated through molecular pathways such as NF-κB (Fiordelisi et al., 2019). However, it cannot be excluded that changes in vascular measurements in space result from volume shifts or changes in vascular filling.

Post-flight orthostatic intolerance is commonly observed in astronauts and could pose major risks when landing on another planet. The phenomenon likely results from changes in volume status as described above and adaptation of the autonomic nervous system to weightlessness (Jordan et al., 2022). This condition needs the adoption of specific countermeasures. In fact, over the years, various non-pharmacological and pharmacological countermeasures have been investigated and some of them currently adopted at the ISS (see below). When considering to land on another celestial body, the specific gravity conditions may have to be taken into account when dosing such countermeasures (Beck et al., 2018).

Since the space-exposome comprises risk factors that are known to affect cardiovascular disease and appear to set off an inflammaging phenotype, cardiovascular disease progression in space and after return to Earth requires attention. Perusal of the existing epidemiological literature on standardized mortality risk in astronaut cohorts since 1960 s reveals decreased all causes mortality risk (Reynolds and Day, 2010). Differences between American astronauts and Russian

cosmonauts for cardiovascular diseases and all cause of mortality (Reynolds et al., 2014) should be interpreted with caution given the small sample size and unaccounted confounding variables. In fact, a more recent Russian analysis did not confirm the results (Ushakov et al., 2017).

5Effects on skeletal-muscle system

Spaceflight effects on skeletal-muscle have been investigated since many years, and central spaceflight data have been published in humans (Tschan et al., 1993; Fitts et al., 2010; Rittweger et al., 2018), in non-human primates (Bodine-Fowler et al., 1992), in rodents (Sandonà et al., 2012) and in other species. Even more extensive studies on skeletal muscle have been performed with ground-based models, such as − 6° head-down tilt bed rest (Kakurin et al., 1976), dry immersion (Tomilovskaya et al., 2019), unilateral limb suspension (Berg et al., 1991), or orthotic devices (Zange et al., 2017). Logically, these ground-based models only replicate the immobilization and disuse effects in the lower extremity, and not all variables associated with the in-flight exposome. However, they affect the human body in a remarkably similar way as genuine spaceflight, which highlights the view that lower extremity disuse is a very important element in the adaptation to the space environment.

Long-term spaceflight, as well as ground-based analog models, induce significant muscle wasting and weakness. In particular, lower limb muscles undergo rapid wasting and loss of function as shown in a 17-day of spaceflight (Narici et al., 2003), with an even more pronounced response after 45 days of spaceflight, at which time 20 % fiber atrophy has been reported (Fitts et al., 2010). At least in bed rest, different muscles depict different atrophy rates, with the soleus muscle typically being most affected, and the anterior tibial group being almost spared from shrinkage (Belavý et al., 2009). In the plantar flexor musculature, our team has shown individual-specific decrease of volume, angle pennation, fascicle length, and physiological cross-sectional area (CSA) on both medial gastrocnemius and soleus muscles. The soleus volume reached the 21.1 % of decrease after 6 months at the ISS in one astronaut after landing with minor recovery after 15 days. Data have also been corroborated by an individual-related effect in terms of soleus muscle proteomics and in costamere proteins along with the disruption of muscle's oxidative metabolism (Rittweger et al., 2018). Another study reported both CSA reduction and weakening of paraspinal muscles after long-duration spaceflight, but while CSA returns to preflight values within 1 year of recovery, psoas and quadratus lumborum muscle attenuation remain reduced even 2–4 years post-flight (Burkhart et al., 2019). Additionally, six-months spaceflight affect also other muscles of spine. In particular, *multifidus* muscle atrophy was strongly associated with lumbar flattening and increased stiffness (Bailey et al., 2018).

Similarly, in ground-based models (e.g. limb suspension and bed rest), muscle atrophy is associated with decreases in fascicle pennation angle and length (de Boer et al., 2007, 2008). Alterations of muscle architecture are expected to affect the mechanical output, thereby contributing to muscle weakness (Wilson and Lichtwark, 2011). Moreover, muscle unloading also reduces fibers' specific force and power and myosin heavy chain concentration (Hvid et al., 2017). Slow and fast fiber types undergo partially different changes, unloading alone upregulated markers of neuromuscular damage and the pathway controlling EIF5A hypusination (Murgia et al., 2022).

All these factors can independently alter the mechanical capabilities of muscles and data obtained by the above-mentioned models represent the best experimental design on Earth to disentangle microgravity effects on skeletal muscle. Since in-flight exposome, as depicted Fig. 1, represents a unique condition where synergistic or additive effects of all variables can occur, only in-flight data may identify the accurate true health risk for astronauts, even if also the variable "time" is likewise relevant.

The muscle atrophy observed in response to spaceflight has some analogy with the age-associated loss of muscle mass or sarcopenia (Biolo et al., 2003; Narici and de Boer, 2011). In fact, emerging molecular studies indicate that immunosenescence and inflammaging strongly contribute to the pathophysiology of sarcopenia (Wilson et al., 2017; Baylis et al., 2013). The age-related changes in the cells of the innate immune system indirectly contribute to sarcopenia by an increase of systemic inflammation. Under physiological conditions on Earth, neutrophils migrate in response to damage into skeletal muscle, followed by M1 macrophages that instigates muscle inflammation. This early phase is followed by infiltration of M2 macrophages that produce soluble factors to orchestrate repair the muscle injury and promote regeneration (Tidball, 2005). With aging, neutrophil function decreases including migration capacity (Zhang et al., 2015). It has been hypothesized that, once migrated into the muscle, neutrophils with impaired migration capacity can contribute to increased inflammation (Wilson et al., 2017). Interestingly, the experiment of ground-based confinement has also revealed an impairment of granulocytes in migration capacity (Strewe et al., 2015). Thus, the possible involvement of the immune system in spaceflight muscle atrophy as well as in sarcopenia has an increased number of evidences. Further, incomplete muscle recovery is associated with an increase of pro-inflammatory cytokines and a prolonged inflammatory response to muscle injury causing muscle atrophy and weakness on Earth (van der Poel et al., 2011; Costamagna et al., 2015). This condition may also slow-down muscle recovery in post-flight period or after several spaceflights of the same crewmembers.

Muscle atrophy emerges when protein degradation exceeds protein synthesis rate be it during spaceflight (Rittweger et al., 2018) or during aging (Schiaffino et al., 2013; Cohen et al., 2015). Increased mitochondrial ROS production, as well as endoplasmic reticulum stress, protein catabolism, and decreased antioxidant capacity play key roles in triggering sarcopenia and inflammation with aging (Drew et al., 2003; Short et al., 2005; Narici and Maffulli, 2010; Pellegrino et al., 2011; Vitale et al., 2013). Importantly, our results on muscle proteomics suggest an aerobic/anaerobic metabolism unbalance after 6-months of spaceflight with a decrease of many proteins related to aerobic metabolism. Further, the costameric-phosphorylated protein FAK-pY397 dramatically decreased in the crewmember who did not exercise intensively (Rittweger et al., 2018). The costameres also accommodate a signalling hub containing desmosomal components and the insulin receptor, which activates the PI3K-FOXO signalling preventing muscle atrophy (Cohen et al., 2014). Decreases demosomal component expression and other interactors of this molecular complex (Eid Mutlak et al., 2020) has been shown both in bed rest and spaceflight (Rittweger et al., 2018; Murgia et al., 2022).

Overall, two major protein degradation pathways, i.e., the proteasomal and the autophagic-lysosomal pathways, are activated during muscle atrophy and differently contribute to the loss of muscle mass. Accordingly, the same pathways were also activated in mice liver after 13.5 days of spaceflight (Blaber et al., 2017) suggesting a common metabolic-related effect of spaceflight exposome. In particular, these pathways involve a variety of atrophy-related genes or atrogenes, which are controlled by specific transcription factors, such as FOXO3, which is negatively regulated by AKT, and NF-κB. The latter is activated not only by inflammatory cytokines, but also by a variety of non-self, quasi self-molecules (GM and related metabolites), and self-molecules such as nuclear and mitochondrial DNA (mtDNA) (Franceschi et al., 2017, 2018a) that are able to activate the cytosolic cGAS-STING pathway and in turn it activates NF-κB (Chen et al., 2016). Circulating (c)-mtDNA has recently received the attention for its systemic role on inflammation (Zhang et al., 2010) and muscle wasting disorders (Picca et al., 2018). In this regard, our team has found an increase of (c)-mtDNA in one astronaut out of two both after landing and recovery time (Capri et al., 2019b), thus highlighting that many receptors (PRRs) of immune system may be involved in the activation of NF-κB.

Moreover, cells exposed to simulated microgravity in in vitro model have confirmed the increased expression of several atrophy markers as

well as in in vivo models (Harding and Vargis, 2019), but peculiar characteristics of spaceflight effects on muscle atrophy have recently been raised up in MuRF1 null (KO) mice model. In fact, MuRF1 KO mice are protected from muscle atrophy in ground-based models unlike those subjected to 21 days of microgravity on the ISS (Cadena et al., 2019), likely suggesting the role of other interacting variables on muscle wasting.

In this perspective, we have observed individual effects, likely related to the physical exercise-based countermeasure, in terms of circulating pro-anti-inflammatory molecules in astronauts after recovery from six-months of spaceflights. In particular, blood circulating inflamma-microRNAs (miRs)− 21–5p, − 126–3p, and − 146a-5p which are related to stress-inflammatory responses and aging process (Olivieri et al., 2012, 2013a) and circulating myo-miRs-206, primarily expressed in skeletal muscle, did not recovered after landing. An individual-related effect was observed, in particular myo-miRs-206 seemed to be a promising biomarker to monitor skeletal-muscle effects (Capri et al., 2019b). Accordingly, in a mouse model the muscle expression of miR-206 decreased after spaceflight (Allen et al., 2009) thus underpinning the crucial role of miRs/myo-miRs in regulating muscle wasting during catabolic conditions (Soares et al., 2014). Attention currently focusses on c-miRs and spaceflight for their role as potential biomarkers/predictors to monitoring astronaut health along with space missions and countermeasure development (Malkani et al., 2020; Goukassian et al., 2022).

Mechanical inputs greatly influence muscle and bone strength (Hart et al., 2017). During space missions, astronauts are no longer statically loaded by gravity, similar to the ground-based disuse models. Because skeletal remodeling is dependent on the level of strain within the bone, this absence of loading is significant (Buckey, 2006). Spaceflight-related unloading promotes biochemical and structural changes in bone tissue which directly correlate to bone fragility and compromised bone strength. Bone loss during spaceflight and during bed rest is occurring in the legs, but not in the upper extremity (Vico et al., 2000; Rittweger et al., 2005). However, bone losses in space seem to be affected by exaggerated osteoclastic resorption and hampered osteoblastic formation (Collet et al., 1997; Caillot-Augusseau et al., 2000), whereas bed rest-induced bone loss seems mostly (Rittweger et al., 2005) or even solely, (Rittweger, 2010) dependent of increased osteoclastic bone resorption. Notably, muscle loss is recovered about six months faster than bone loss in astronauts (Keyak et al., 2009) and similarly after bed rest (Rittweger and Felsenberg, 2009). Altered gravity conditions therefore entail extensive effects on bone formation and resorption as well as bone metabolism, recently detailed reviewed (Grimm et al., 2016; Vico and Hargens, 2018). Muscle and bone are inextricably linked genetically, molecularly and mechanically whereas the intertwining of the connection at the different organizational levels (subcellular, cellular, and supracellular) makes it difficult to tease out the relative contribution of each connection (Avin et al., 2015). In this regard, adaptation of muscle and bone are interdependent; such that alterations in muscle size, density and strength are temporally linked and positively correlated with alterations in bone size, density and strength (Cianferotti and Brandi, 2014; Ireland et al., 2014; Kaji, 2014). Focusing on the mechanism of bone loss, osteoclast-mediated bone resorption increases during aging and in particular during osteoporosis in such a way that the ratio between bone formation and bone resorption becomes unbalanced, since the amount of bone forms falls below the amount of bone resorbed. During spaceflight scenarios, bone loss begins immediately on arrival in space. During the first days of a mission, a 60–70 % increase in urinary and fecal calcium is noted which continues throughout the mission (Buckey, 2006; Clement, 2003). Bone resorption markers are increased in urine and the blood levels of parathyroid hormone and 1,25-dihydroxyvitamin D are reduced (Cann, 1997). Classically, age-related bone loss is the primary cause of osteoporotic fractures in the elderly population, characterized predominantly by reduced bone formation in the setting of persistent bone resorption (Rachner et al., 2011; Khosla, 2013). Age-related osteogenic cellular dysfunction is thought to be a major cause of age-related bone loss. However, the cellular and molecular mechanisms underlying changes in osteoblast function with aging are poorly understood (Duque and Troen, 2008; Kassem and Marie, 2011).

Furthermore, the muscle atrophy and its structural reorganization both during spaceflight and aging could also contribute to the modification of circulating molecules/myokines (Pedersen and Febbraio, 2012; Bucci et al., 2013; Capri et al., 2019b; Buchheim et al., 2019) and of their networking with the stress response and chronic low-grade pro-inflammatory status, even if the time has different magnitude in spaceflight and aging. In fact, some phenomena appear accelerated by spaceflight exposome including muscle wasting, which has systemic effects. Thus, major concerns exist for long-term crewed missions, such as those that would be required on a voyage to Mars. When comparing the loss in plantar flexor volume seen after 6-month missions to ISS (typically 10–15 %) with the age-related wasting in the same muscle group (around 5 % per decade) it is evident that space can take its toll at much faster pace than natural aging, perhaps not only in muscle, but also at the heart, blood vessels, bones and other organs (Ireland et al., 2020).

6Progress in countermeasure development

Since the emergence of human spaceflight, provision and effectiveness of countermeasures have steadily improved (Crucian et al., 2020). However, current countermeasures are still not fully effective (Scott et al., 2020), further scientific advancements are therefore required to implement new and more effective ways to mitigate the space-exposome effects, especially as far as long-term deep-space missions are concerned. We have proposed in this paper that inflammaging, a crucial driver of aging, could be accelerated in astronauts, thus, new-generation countermeasures could be focused on this phenomenon, which, as discussed is very pervasive and accounts for different pathological processes such as muscle wasting/bone loss (Lang et al., 2017; Lau et al., 2022; Rittweger et al., 2018; Capri et al., 2019b), sleep disturbances, brain-gut axis adaptation and cardiovascular system adaptation/remodeling that all share an inflammatory pathogenesis (Fig. 2). In particular, here we surmise that NF-κB serves as a signaling hub, as already indicated (Zhang et al., 2017). In fact, NF-κB is central to aging process/inflammaging, and its dynamics is crucial for the regulation of downstream target genes at systemic level (Tieri et al., 2012; Haga and Okada, 2022). However, the possibility to implement therapies or treatments that may modulate NF-κB seems at the moment unlikely, due to the wide pleiotropy of this transcription factor. On the other hand, a recent work appears to pave the way for the decrease of molecular inflammatory profile at systemic level, thus likely counteracting inflammaging and reducing human biological age (Kim et al., 2022).

As a further layer of complication, it is likely that all the spaceflight exposome-related modifications in turn lead to an increase of inflammaging in a sort of vicious cycle (Fig. 2), eventually leading to the development of overt diseases. Thus, effective countermeasures should take into consideration all the molecular mechanisms that end up in triggering inflammatory responses. In this regard, careful human physiology investigations coupled with omics characterizations not only of cell systems and animal, but foremost from human samples could pave the way for more targeted and individualized countermeasures for human spaceflight. Omics approaches involving different molecular levels and their inter-relationships, such as transcriptomics, epigenomics, glycomics, metabolomics, proteomics, metagenomics/metatranscriptomics hold promise in that regard, in particular when performed in time series experimental design (Monti et al., 2017; Cohen et al., 2022) as well as the precision medicine indicates.

Countermeasures, including physical and drug/nutrient provisions, should be focused on the different organ systems, always considering the multitude of impacts they have on astronauts. Three main approaches

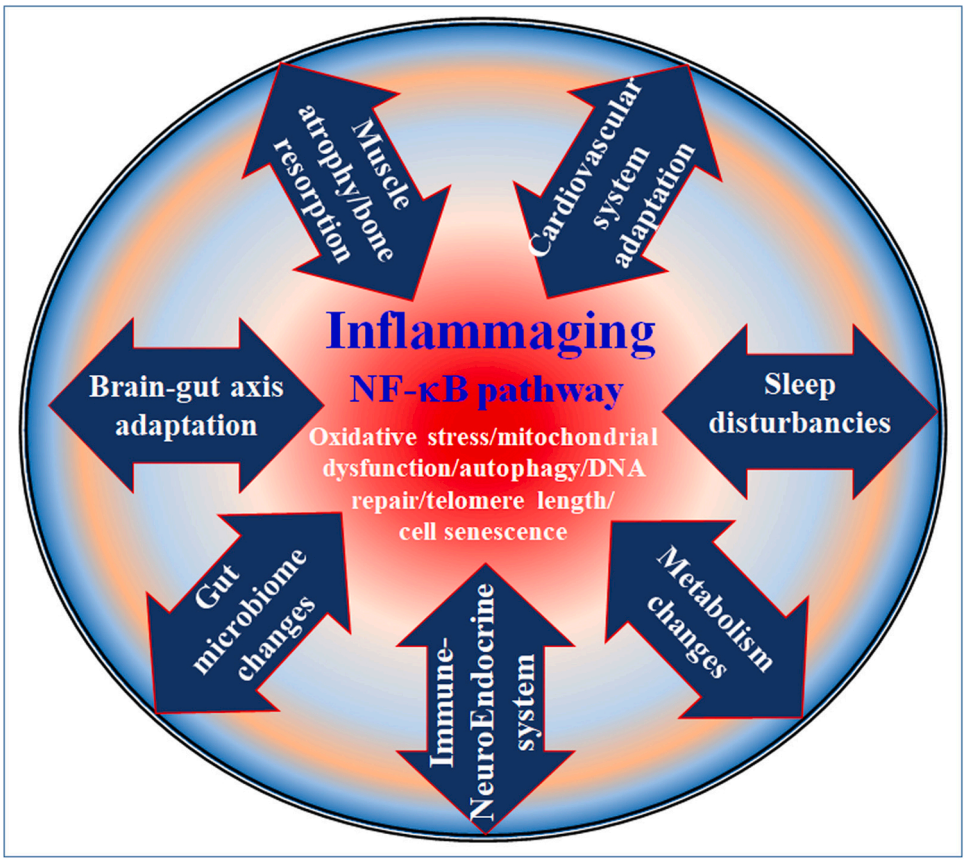

Fig. 2. Emerging spaceflight exposome effects on human body. The in-flight and post-flight effects converge on activating NF-kB pathway and may sustain inflammaging if chronically persisting. All the systemic modifications in turn may lead to an increase of inflammaging in a sort of vicious cycle.

are pursued, in particular:

i. anti-stress strategies with specific attention to circadian rhythm and interventions for the mitigation of its disruption such as melatonin supplementation, with positive effects on psycho-neuro-immune-endocrine system. Different pharmacological treatments to counteract fatigue should be also considered. In this perspective, the realization or optimization of wearable sensors for monitoring the cross-talk among organs through the real-time measurement of blood circulating markers, e.g. stress hormones, myokines, mitokines, immunological parameters, should be promoted and implemented;
ii. countermeasures to counteract muscle mass waste and metabolism alteration should be further improved. At present, these include a personalized physical exercise training based not only on resistance and aerobic exercises, but also involving elements of plyometric and high-intensity interval training (Gruber et al., 2019), together with a careful control of the energetic balance and the intake of macro/micronutrient. In this direction, all the progresses in nutraceutical and intake optimization of vitamins (e.g. vitamin D, omega 3/6) and different types of integrators should be pursued. Finally, pre/probiotic/post-biotic intake for the best modulation of GM should be also implemented, as described below. Some of these interventions have been recently reviewed (Crucian et al., 2018; Agha et al., 2020);
iii. Drug-based therapies in case of acute adverse effects, treatments for autonomous nerve system, or the use of artificial gravity to decrease the effects on cardiovascular and muscle-skeletal systems should be strongly considered (Evans et al., 2018; Lecheler et al., 2021). Concomitantly, the modelling of the estimation of medical risk will likely play an essential role for future deep space missions (), but a sufficiently large evidence-based data set is still missing on this regard. Fig. 3 shows a summary of the most important countermeasures to date.

As above described, the gastrointestinal microbiota plays an important role in astronauts health by interacting with host immune, metabolic, and neurological functions. The space environment imposes many challenges to human physiology, including functions interacting with the GM. Spaceflight conditions such as microgravity, confinement, isolation, limited nutrition as well as high radiation exposure can be identified to alter the GM and herewith representing risks for astronaut health, especially during long-term spaceflight missions. Jiang and colleagues speculated that microgravity leads to significant changes in the gastrointestinal tract via fluid shifts altering the metabolic environment for the GM causing alteration in the community structure, microbial activities and consequently influencing digesta movement leading to changes in the physiological and behavioral responses of the astronauts (Jiang et al., 2019). The GM and the brain 'communicate' with each other via various routes including the immune system involving microbial metabolites such as short-chain fatty acids or branched chain amino acids. Many factors can influence microbiota composition, including infection, use of antibiotic medications, the nature of nutritional provision, environmental stressors, and individual genetics. Stress, in particular, has to been determined to have a major impact the microbiota-gut-brain axis (Cryan et al., 2019).

The central role of the brain-gut-axis for the investigation of the long-term spaceflight effects should be explored with more effort than previously done and countermeasure should be identified with personalized approach as well as new advanced techniques for engineered gut microorganisms as therapy for GM improvements (Huang et al., 2022). A possible adoption of countermeasures by means of specific

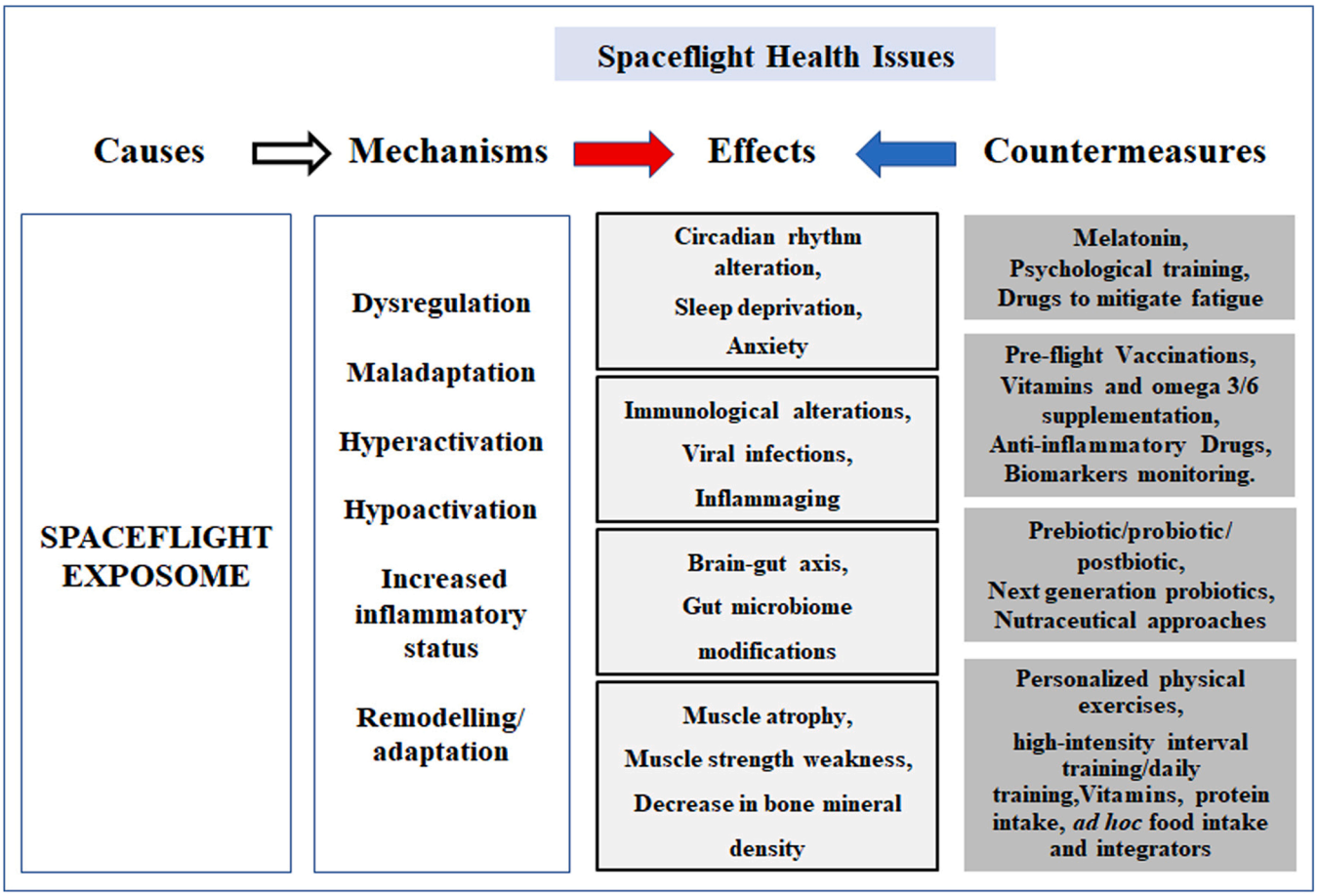

Fig. 3. Effective and in progress countermeasures. Different types of countermeasures are mentioned, some of them are still under clinical trial such as next generation probiotics and other are currently adopted (e.g. Vitamin D supplementation, diet and nutrition warnings, ad hoc physical exercise, pre-flight vaccination).

pre-/probiotic cocktails (Turroni et al., 2020) will be expected in the next years due to the deep knowledge that will be achieved on human GM, multiomics, and xeno-metabolites affecting brain-gut axis. On the other hands, the emerging next -generation probiotics (NGPs) focuses on the identification of each strain and its role within the complex ecosystem of the human gastrointestinal tract. Thus, NGPs pave the way for the application of novel preventive and therapeutic tools in influencing host and validated results will allow the treatment for health improving both for spaceflight and ground. In fact, recent performed clinical trials seem to confirm benefit with specific *Bifidobacterium* longum 1714 strain in terms of reduced stress and improved memory in healthy volunteers (Allen et al., 2016). One of the most promising NGPs, not yet translated into clinical trials, is *Faecalibacterium prausnitzii*, due to its well characterized anti-inflammatory activity, but others strains are already under clinical trial (Miquel et al., 2015; Martín et al., 2018; Barone et al., 2021).

In this perspective, the study of microbiome of ISS confined environment is a crucial issue. First data obtained by comparative analysis of the microbial compositions of ISS with Earth analogs revealed that the ISS environmental surfaces were different in microbial composition and an increase in anti-microbial resistance and virulence gene factors persisted over time in different subsequent spaceflights (Singh et al., 2018), highlighting the key issue of microbiome monitoring both for ISS environment and humans.

Overall, the possibility of measuring advanced blood biomarkers, such as miRs, and pro- and anti-inflammatory molecules offer the intriguing opportunity of easily monitoring crewmember health for the application of in-flight countermeasures. Some Authors suggest also the possibility to treat astronauts with anti-miRs (Malkani et al., 2020), but this hypothesis requires further investigation.

7. Conclusion

The complex scenario of a multitude of spaceflight-exposome effectors constitutes not only challenges to human body in deep space missions, but it also raises many questions that are still unanswered, such as all the possible effects of the various interacting variables after long term period. In fact, the new spaceflight exposome contains many, probably interacting variables as summarized in Fig. 1. In particular, microgravity per se represents an unpredicted condition since our body and cells have been adapted to gravity over millions of years in their evolution. Fascinatingly, both spaceflight and aging share the same feature i.e., neither microgravity effects nor human aging process have been shaped by evolution force. In this perspective, an important hallmark of microgravity's side effects is the dramatic disruption of muscle function and loss of muscle mass. Similarly, immune cell activity, based on cell mobility and movements with chemotaxis or along extracellular matrix (Moreau et al., 2017), is another system that can be critically impaired by spaceflight exposome. A chronic exposure to such environment, with many variables that cannot be disentangled and conditions not foreseen by evolution, may result in a strong personalized effect, as the most recent literature seems to suggest. Thus, it is time to understand that aggregated data, described by mean or median, plus standard deviation and absolute median deviation, respectively, may be not the most appropriate methods for statistical evaluation of spaceflight exposome effects and only longitudinal personalized analysis (N-of-1 studies) may let emerge the large heterogeneity that exists among individuals and crewmembers (Schork, 2015). On the other hand, additional data are

necessary to draw conclusion on gender effects and shared effects among crew members.

Many effects induced by the space-exposome, such as those on skeletal muscle and brain appear to be particularly relevant in terms of possible health risks, acceleration of aging process and difficulty to be reverted after landing (Vico and Hargens, 2018), and, as discussed, most of them and in particular those related to the immune-neuroendocrine system seem to converge in inflammation, thus in the end promoting and sustaining inflammaging. Since inflammaging is considered a driver of aging, the current question if spaceflight exposome can accelerate aging can be answered "yes" and the reason why could be indeed a premature inflammaging accelerated by the spaceflight-exposome, as described in Table 1. This hypothesis is supported by the data and findings discussed so far that identified many molecular mechanisms that converge directly or indirectly on the activation of NF-kB signaling (Fig. 2). Further evidences are however needed to formally prove this hypothesis.

On the other side, other data from NASA twin study focused on genome-wide DNA methylation surprisingly are suggestive of a "rejuvenation" effect, at least in specific genome loci/genes, but these data are still in their infancy and new analyses in larger cohort of astronauts and time series are needed. Similarly, telomere length increase could let hypothesize "in-flight rejuvenation phenomena or potentially cancerogenic mechanisms", but these data are not firm enough to draw definitive conclusions.

Overall, our current knowledge about long-term human spaceflight effects should induce the scientific community to exert all the possible caution principles and all possible ad hoc countermeasures as described above. In this perspective, the research fields of anti-aging and long-term human spaceflight could mutually fertilize each other, thereby achieving the best possible health protection for astronauts (Vernikos and Schneider, 2010). Accordingly, most of the bed rest studies are in the light of their possible application not only for astronauts' benefit, but also for older adults on the ground. In fact, these studies have highly improved the knowledge on age-related muscle atrophy (Buehlmeier et al., 2017; Floreani et al., 2018) and accordingly, have proposed how to counteract muscle waste on ground, identifying possible critical issues and new protocols for older adults (Hedge et al., 2022). On the other hands, current anti-aging strategies and therapies on ground could be a valuable translational research field also for spaceflight countermeasures.

Author contributions

All authors contributed to the manuscript on the basis of their expertise. Original proposal and writing: **MCa, CF, MG, MMV, AB, MaC, PL, JR**; text improvement: **JJ, SS**; special expertise: **EC, AS, CP, PG, FL, RM, TI**.

Declaration of conflicts of interest

The authors declare no conflicts of interest.

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