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Spaceflight and Ageing: Reflecting on *Caenorhabditis elegans* in Space

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The prospect of space travel continues to capture the imagination. Several competing companies are now promising flights for the general population. Previously, it was recognized that many of the physiological changes that occur with spaceflight are similar to those seen with normal ageing. This led to the notion that spaceflight can be used as a model of accelerated ageing and raised concerns about the safety of individuals engaging in space travel. Paradoxically, however, space travel has been recently shown to be beneficial to some aspects of muscle health in the tiny worm *Caenorhabditis elegans*. *C. elegans* is a commonly used laboratory animal for studying ageing. *C. elegans* displays age-related decline of some biological processes observed in ageing humans, and about 35% of *C. elegans*' genes have human homologs. Space flown worms were found to have decreased expression of a number of genes that increase lifespan when expressed at lower levels. These changes were accompanied by decreased accumulation of toxic protein aggregates in ageing worms' muscles. Thus, in addition to spaceflight producing physiological changes that are similar to accelerated ageing, it also appears to produce some changes similar to delayed ageing. Here, we put forward the hypothesis that in addition to the previously well-appreciat-

ed mechanotransduction changes, neural and endocrine signals are altered in response to spaceflight and that these may have both negative (e.g. less muscle protein) and some positive consequences (e.g. healthier muscles), at least for invertebrates, with respect to health in space. Given that changes in circulating hormones are well documented with age and in astronauts, our view is that further research into the relationship between metabolic control, ageing, and adaptation to the environment should be productive in advancing our understanding of the physiology of both spaceflight and ageing.

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Introduction

Man has long shown a fascination for the stars and contrived to reach them since early history. This drive culminated in Yuri Gagarin's demonstration that man can survive in space and Neil Armstrong and 'Buzz' Aldrin's demonstration that man can survive travel to, work upon, and return from the Moon. Currently, we live in an age when routinely living and working in space is a reality. A select few have continuously manned our International Space Station (ISS) for more than 10 years, and a handful of individuals have purchased access to the ISS from companies. On the near horizon, several companies are promising cheaper widespread 'space tourism', which

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has been suggested to be a new consideration for doctors in a recent feature in the *British Medical Journal*.

Spaceflight is both a risky and stressful endeavour. The risk is highlighted by the increased incidence of accidental death in American astronauts [1] and Russian cosmonauts; the most commonly considered stressors of flight are altered gravity and increased chance of irradiation. The increased G forces associated with launch and landing have long been known, from studies of fighter pilots, to pose potential operational problems. Intuitively, we also realize that the 'micro-gravity' that arises on orbital missions as the result of being in a state of constant free fall around the Earth is also a physiological stress (when is falling not stressful?). Similarly, we know that exposure to increased radiation can lead to cancer. However, to date, cataracts and not cancer have been documented to correlate with the increased radiation some astronauts have received during spaceflight [1]. In contrast to these well-appreciated risks and stresses, we often forget that in the process of identifying and militating against the physical risks of spaceflight, via spacecraft and subsystem design, that iatrogenic problems can arise. For example, the American use of iodine in water purification systems leading to thyroid problems [1].

Historically, space life sciences and space medicine research have focused on documenting the changes observed in response to spaceflight and militating against undesirable physiological changes in space travellers. Consequently, there is a vast body of data describing the biological response of a variety of organisms to spaceflight [2] and a general consensus that short-term orbital flight is safe for man, but that we lack the evidence base to comment on the safety of human space travel beyond low Earth orbit [3]. However, it is widely acknowledged that a key barrier to travel beyond low Earth orbit is increased exposure to radiation [3].

In cataloguing the biological effects of spaceflight, 2 main themes have emerged. First, in man, spaceflight produces a host of changes that induce a state of frailty akin to ageing [4]; notably, most of these changes are quickly reversed upon re-adaptation to life on Earth. Second, in all organisms yet studied, growth and metabolism are altered in flight. This latter point may not be so surprising if one considers that spacecraft are closed ecological systems and that adaptation to the environment requires energy. Here, we briefly recap past notions of spaceflight as a model for accelerated ageing, the health concerns expressed for individuals engaging in spaceflight activities and the alterations in metabolism in response to spaceflight, and examine some recent data

which suggest that space travel may cause some physiological changes akin to delayed ageing. We close by re-proposing an idea from the dawn of the space age: altered metabolism underlies the physiological alterations observed during spaceflight.

Spaceflight as a Model of 'Accelerated Ageing'

The notion that spaceflight may be a model for accelerated ageing has recently been reviewed [4]. During both spaceflight and ageing, muscle and bone are lost, balance and coordination problems occur, and cardiovascular capacity is reduced. With spaceflight and bed rest, these changes are observed roughly 10-fold faster than with ageing. Additionally, unlike ageing, the physiological changes observed with spaceflight and bed rest are largely, if not completely, reversed upon re-adaptation to life on Earth or the non-bedridden state. Thus, it has been postulated that the lack of mechanical load upon the mechanotransduction-mechanochemical transduction systems underlies many of the changes seen with spaceflight, bed rest, sedentary lifestyle, and ageing. In support of this theory is the observation that mechanosensitive enzymes, such as focal adhesion kinase, are present in lower amounts and with lower activity in human muscle that has atrophied as the result of immobilization [5], while they are present in higher amounts and with higher activity in human muscle that has hypertrophied in response to exercise [6].

Concern for Individuals Engaged in Space Travel

Despite the available evidence suggesting that most of the physiological changes experienced during spaceflight are reversed upon re-adaptation to life on Earth and the lack of evidence of long-term negative consequences of spaceflight [1], a cautionary principle still tends to be employed in discussion of the health risks of spaceflight. For example, an international committee has produced a set of medical standards for certification of non-professional space travellers to be 'space flight participants' onboard the ISS by 'relaxing' the criteria used for professional astronauts and cosmonauts [7]. Included within the criteria that can disqualify prospective participants are many conditions that commonly present in ageing individuals. For example, glaucoma, chronic obstructive pulmonary disease, malignant tumours, hypertension, hypotension, coronary heart disease, arrhythmia, pacemaker, peripheral vascular

disease, diabetes, history of cerebrovascular accident, and neurodegenerative diseases. From an operational perspective, this caution makes sense. The ISS was expensive to build and remains expensive to operate. Flying individuals who could compromise this international investment as the result of exacerbation of an underlying condition would certainly lead to an international uproar and legal actions. From a scientific perspective, this list of disqualifying conditions suggests that adaptation to spaceflight results from more than a simple lack of mechanical load.

Spaceflight Alters Metabolism

The 1960s was a decade of change. Not only did the first men set foot on the Moon, but also the molecular biology revolution began. Prior to the molecular biology revolution, much of biology was devoted to understanding how metabolism controlled biology. Unsurprisingly, older studies of organisms in space document that growth and metabolism are altered, while newer studies document changes in gene expression and suggest molecular pathways that regulate such changes [1]. In astronauts, metabolic effects of spaceflight include loss of body weight and negative metabolic balances of nitrogen, phosphorus, and calcium [8]. Some of these changes are thought to be due to changes in fluid homeostasis [8], some due to decreased energy intake which occurs for incompletely understood reasons that may include sensory and/or neuronal alterations affecting palatability and/or satiety [9], and some for still unknown reasons which might include altered protein homeostasis in muscle which may occur due to altered mechanical load. If one assumes that decreased energy production results in a necessary decline in energy available to combat stress or infection and also for running maintenance and/or repair processes, the impact of spaceflight upon metabolism is sufficient to account for increased frailty. This suggestion is similar to some theories of ageing and/or age-related decline that postulate decreased energy production from the mitochondria occurs with age and contributes to increased frailty.

C. elegans as a Model for Studies of Spaceflight and Ageing

The tiny worm *C. elegans* is a common laboratory animal. Prior to the initial studies of *C. elegans* in space, which revealed that worms are susceptible to the mutagenic effects of increased radiation in space independent-

ly of ‘microgravity’ [10], it was proposed that this worm could be used for studies involving spaceflight and ageing [11].

C. elegans was the first multicellular animal to have its genome sequenced, which gave us the tools and experience needed to sequence the human genome. These efforts inform us that roughly 35% of *C. elegans*’ genes have identified human homologs. Consequently, *C. elegans* remains at the forefront of animals used in experiments to understand how the genome controls health. Other experiments with this worm have led to the discovery of programmed cell death, the phenomena of gene silencing by RNA interference, the discovery of microRNAs, evolutionarily conserved genes that contribute to maximal lifespan [12], and a reproducible genomic response to spaceflight [13] (and subsequent flights).

C. elegans has a short lifespan and rapid generation time, which make it an ideal animal for prospective studies of ageing and also evolution. As with other poikilotherms, *C. elegans* displays an inverse relationship between temperature of cultivation and lifespan. While the mechanism(s) underlying this relationship remain to be established, the observation suggests that *C. elegans*’ lifespan is responsive to the environment, possibly via effects upon metabolism. Like many other animals, including homeotherms, *C. elegans* also displays lifespan extension when grown on any one of several restricted diets, again possibly via effects upon energy metabolism or resulting from altered substrate utilization. In the case of growth in a chemically defined diet versus the standard laboratory diet of *Escherichia coli*, the effects of temperature and diet are independent of each other, and various parameters of *C. elegans*’ life history scale identically as a percentage of maximal lifespan in response to temperature on the 2 diets [14]. Thus, there appear to be at least 2 mechanisms by which environmental factors (e.g. temperature and diet) impact upon *C. elegans*’ lifespan.

In contrast to the incomplete molecular mechanistic understanding that underlies the clearly documented impact of environmental factors upon *C. elegans*’ lifespan, several genes and putative molecular regulatory pathways have been identified. One of the earliest discovered and arguably best-studied pathways is the *daf-2*, *age-1*, *daf-16* pathway. Mutations in these genes, and others, have been shown to act in a common signalling pathway to control lifespan [15]. These genes encode an insulin/insulin-like growth factor receptor, its downstream signalling kinase phosphoinositide-3-kinase, and the DAF-16/FOXO (Forkhead BoX O) transcription factor. At least part of the effect of the protein products of these genes upon

lifespan is achieved via DAF-2 and AGE-1 signalling altering the activity of DAF-16/FOXO. As DAF-16/FOXO is a transcription factor, these alterations result in changes in transcription of genes controlled by DAF-16/FOXO. The transcription of several hundred genes is affected in *daf-2* mutants in a DAF-16-dependent fashion. This finding suggests that insulin/insulin-like signalling control of lifespan is complex. Given that DAF-2 is an insulin/insulin-like growth factor receptor that is well known to control energy metabolism in mammals, it is unsurprising that many of the genes displaying altered expression in long-lived *daf-2* mutants are genes involved in energy metabolism. To date, the precise relationship between DAF-16-controlled alteration of energy metabolism and lifespan remains incompletely defined in *C. elegans*.

C. elegans is used not only to understand what environmental and genetic factors control lifespan and how they do so, but also to understand age-related diseases and changes in tissues and biological processes with age. Intriguingly, expressions of mutant human proteins that cause neurodegeneration with age in man also do so in *C. elegans* (for example: β -amyloid, tau, and α -synuclein). Similarly, both worm and man show an age-related decline in mobility that is an accurate predictor of death, sarcopenia (the decline in muscle size and function with age), and a decline in expression of mitochondrial enzymes required for production of energy. The fact that there is a decline in mitochondrial enzymes required for production of energy with age may be a potential explanation for the decline of tissues with age and also the appearance of age-related diseases such as the neurodegeneration disorders. While the evidence for a causal link between mitochondrial decline, tissue decline, and ageing disorders is currently lacking, mutations in *daf-2* [16] or *age-1* [17] are sufficient to delay the onset of movement decline in *C. elegans*, perhaps again suggesting a link between energy metabolism and ageing.

Could Spaceflight Increase *C. elegans*' Lifespan?

In contrast to the concerns with spaceflight producing physiological changes akin to accelerated ageing and/or exacerbating common conditions associated with ageing, recent data suggest that spaceflight may have some positive consequences for the ageing process. Well, at least in worms.

A series of flights examining alterations in gene expression in space flown worms all found decreases in mRNA levels for genes whose expression is known to be

controlled by DAF-16/FOXO [13] (and subsequent flights). These results suggest both that insulin-like signalling may influence the gene expression changes in response to spaceflight to produce the subsequent biological alterations, and that, perhaps, worms grown in space live longer than their Earthbound counterparts.

To directly test if depressed expression of some identified genes can lead to increased lifespan, 11 genes that displayed large depressions in mRNA levels in response to spaceflight were selected for evaluation. All 11 selected genes were previously known to be involved in neuronal or endocrine signalling but not regulation of lifespan. The inactivation, by loss- or reduction-of-function mutation and/or RNAi, of 7 of the 11 selected genes resulted in increased lifespan [18]. Thus, at least some of the gene expression changes observed in spaceflight can increase lifespan (when knockdown occurs independently of additional induced depressions in gene expression). This finding raises the questions of whether spaceflight can directly increase lifespan, at least in a worm, and how can spaceflight induce both frailty and longevity? Clearly, further experiments are required to answer both questions, and direct measurement of *C. elegans*' lifespan on board the ISS is possible, resources permitting.

Reconciling Increased Frailty against Increased Longevity

With regards to spaceflight inducing both frailty and longevity, one possibility is that, as posed in the 1960's, altered energy metabolism is induced by spaceflight and this accounts for the physiological changes observed [19]. It is important to remember that what we may label as 'accelerated ageing' or frailty is context dependent. That is, most of the physiological changes observed in spaceflight are quickly reversed upon return to Earth and therefore are not really accelerated ageing or a long-term state of frailty, but rather physiological adaptation to spaceflight (including the closed ecosystem of the spacecraft). Various types of diet restriction are also known to induce altered metabolism, frailty, and longevity. This is true of *C. elegans*, where DAF-16/FOXO appears to control altered metabolism, increased risk of death during reproduction, and longevity in response to growth in a fully chemical diet [14]. The diet restriction data demonstrate that it is possible to have increased frailty and longevity. However, the frailty with diet restriction is context dependent. That is, in the absence of reproduction or other stressors such as hypoxia or temperature, frailty would

not be noted in worms grown in a chemically defined diet. Similarly, changes in muscle in response to spaceflight are largely thought to be adaptive to the spaceflight environment, with frailty noted upon return to Earth [3]. In this context, it is particularly interesting to note that not only do space flown worms experience patterns of gene expression in muscle, as experienced by astronauts as well (for example less myosin and less MyoD transcription factor), but also worms with a mutation that induces dystrophy appear less dystrophic in space [20], and worms expressing a 35-glutamine repeat protein in muscle display less protein aggregation than Earthbound counterparts [18]. Thus, changes observed in muscle in space could be labelled as increased frailty (in the context of the ability to deal with a mechanical stress), but by other measures (e.g. less likely to develop myopathies) they are 'healthier' than on Earth.

In conclusion, alterations in energy metabolism occur with both spaceflight and ageing. While not yet proven via interventional studies, in some cases the alterations in energy metabolism are theoretically sufficient to account for the physiological changes observed, particularly increased frailty. Thus, it is plausible that neuroendocrine control of energy metabolism may be a key determinant and potential point of therapeutic intervention for the 'frailty' associated with both spaceflight and ageing. However, a potential key challenge is that as with endocrine disorders in the clinic, where it is frequently the case that balance is key and 'too little' or 'too much' signal is problematic, with both spaceflight and ageing the 'frailty' may be adaptive and intervention may impair future adaptations that may be required.

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