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Deciphering the metabolic secret of longevity through the analysis of metabolic response to stress on long-lived species

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A B S T R A C T

Despite intensive research, no satisfactory therapeutic options have been found for aging and age-related diseases. The British scientist Leslie Orgel stated that evolution is cleverer than we are. This assumption seems correct considering that some species are naturally able to resist the age-related diseases that remain unsolved by our modern medicine. Indeed, bowhead whales can live for more than two hundred years and are suspected to possess efficient antitumor mechanisms. Naked mole-rats are exceptionally long-lived compared to similar-sized mammals and are protected from senescence and age-related diseases. Consequently, the characterization of protective molecular mechanisms in long-lived species (i.e. bowhead whale, naked mole-rat, microbat) could be of great interest for therapeutic applications in human. Cellular stress response is considered to be an anti-aging process dedicated to the prevention of damage accumulation and the maintenance of homeostasis. Interestingly, cellular stress response in plants and animals involves the production of health-promoting metabolites such as resveratrol, nicotinamide adenine dinucleotide and spermidine. Do anti-aging metabolites formed during stress exposure differ between human and extreme longevity species in terms of their nature, their quantity or their production? These questions remain unsolved and deserve to be considered. Indeed, the mimicking of anti-aging strategies selected throughout evolution in long-lived species could be of high therapeutic value for humans. This paper suggests that metabolomic studies on extreme longevity species cells exposed to mild stressors may lead to the characterization of health-promoting metabolites. If confirmed, this would provide new avenues of research for the development of innovative anti-aging strategies for humans.

Background

Aging is an endogenous progressive decline of the organism and constitutes the highest risk factor of the most common fatal diseases including cancer, atherosclerosis, diabetes and neurodegenerative disorders. Anti-aging approaches notably involve the inhibition of growth-promoting pathways (growth hormone/insulin-like growth factor 1 axis and mTOR-S6K pathway) and the activation of nutrient sensors (AMPK and sirtuins) that signal nutrient scarcity and stimulate catabolism [1]. Dietary and pharmacological interventions targeting these pathways slow aging in animal models [1–4]. Indeed, numerous publications describe how chronic dietary restriction extends lifespan and delays the onset of age-related diseases that involve the reduction of growth-promoting pathways and the activation of AMPK and sirtuins [1,2,5,6]. Drugs such as the mTor inhibitor rapamycin and other caloric restriction mimetics display anti-aging properties [2,4,7]. However, the beneficial effect of these therapeutic strategies on human longevity remains to be proved, and alternative approaches for the promotion of healthy aging should therefore be investigated. Mutations in nutrient and growth-signaling pathways or pharmacological interventions with drugs such as rapamycin have led to lifespan extension of up to 50% in mice [8]. However, this achievement remains modest in comparison to the wide range of lifespans produced by evolution. This confirms that evolution is better than we are at developing effective strategies to delay aging and age-related diseases, at least for some long-lived species. Consequently, deciphering protective mechanisms in long-lived species should provide clues for the development of innovative anti-aging approaches.

Long-lived species

Humans are considered to be a long-lived species. However, some mammals seem to age more slowly and exhibit a higher level of protection from age-related diseases [9–11]. For example, bowhead whales (*Balaena mysticetus*) live for over 200 years. The extreme longevity of this species strongly suggests the existence of effective mechanisms that confer resistance to age-related diseases [12,13]. Considering their large size and their exceptional longevity, it is highly probable that bowhead whales possess potent antitumor mechanisms. Although a positive linear correlation between body size and maximal lifespan has already been established [11,14], some species such as the naked mole-rat (*Heterocephalus glaber*) and microbats are exceptions to this rule and are therefore considered as long-lived species [11,14]. Indeed, the lifespan of naked mole-rats is approximately eight times longer than similarly sized small rodents. This species exhibits negligible senescence and a high resistance to cancer [15–17]. Moreover, unlike other mammals, naked mole-rat mortality rates did not increase with age, thus establishing naked mole-rats as non-aging mammals [10]. Bats of the genus *Myotis* (known as *little brown bats*) also display an exceptional longevity, and particularly Brandt's bat (*Myotis brandti*), which can live for more than 40 years [18].

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Long-lived species and the hallmarks of aging

Genomic instability

Several excellent reviews have described some molecular mechanisms that may explain how long-lived species delay aging and resist age-related diseases, notably cancer [12,15,19]. Genome sequencing and transcriptomic, metabolomic and lipidomic analysis were performed on long-lived species and compared with other mammalian species with shorter lifespans [12,13,21–25]. Genomic analysis revealed positive selection for genes related to DNA repair as well as upregulation of the expression of DNA repair associated genes in long-lived species [13]. Interestingly, changes in amino acids that are specific to the bowhead whale and the naked mole-rat have been described for proteins involved in DNA integrity [20]. In addition, higher activity of the nuclear factor erythroid 2-related factor 2 regulating antioxidant defense was reported in the naked mole-rat compared to mice [26,27]. These observations support the hypothesis that long-lived species have an intrinsic ability to cope with genomic instability, a hallmark of aging.

Deregulated nutrient sensing

The genetic and pharmacological inhibition of the growth hormone/IGF1 axis is widely associated with lifespan extension in mice [8,32]. This axis is also altered in long-lived species. In the naked mole-rat, a sequence change was observed in the insulin beta-chain and expression of insulin/IGF1 related genes was lower than that reported in mice [23,33]. Interestingly, IGF2 functionally replaces insulin and IGF1 in this species. Indeed, high levels of IGF2 are found in the naked mole-rat and do not decrease after birth, contrary to other rodents [33]. Unique amino acid changes in IGFR and GHR have been characterized in microbats [22]. Moreover, Brandt's bats display similarities with long-lived mice (i.e. GHR−/− mice) insofar as levels of gene expression changes are concerned [12,22].

Loss of proteostasis

Proteostasis involves several processes (i.e. proteasome, heat shock proteins and autophagy) dedicated to the maintenance of proteome integrity [34]. The deregulation of proteostasis is a hallmark of aging, and its improvement is therefore expected to delay aging and age-related diseases [5]. Several reports strongly suggest that proteostasis is more efficient in long-lived species [25,31,33,35]. Translational fidelity is up to ten-fold higher in naked mole-rat cells than in those of mice [36]. This may be explained by a particular ribosomal structure characterized by a 28S ribosomal RNA cleaved into two smaller fragments [33]. Proteins from liver extracts of bats and long-lived rodents are less sensitive to urea-induced unfolding compared to mice [37]. Proteasome, heat shock proteins and autophagy are major players in protein quality control. These processes are more enhanced in long-lived rodents, marsupials and bats than in phylogenetically related shorter-lived species, with the exception of proteasome activity in bats [31].

Altogether, these studies strongly suggest that long-lived species have developed protective mechanisms linked to previously described hallmarks of aging including DNA repair, nutrients sensing and proteostasis. These observations are further confirmed by the fact that fibroblasts from long-lived species are more resistant to a number of stress-inducing agents [28–31].

Long-lived species and cancer

Several studies showed that long-lived species have developed effective antitumor mechanisms [21,38,39]. Indeed, long-lived rodents (i.e. naked mole-rats and blind mole-rat) are resistant to both spontaneous and chemically induced carcinogenesis [40,41]. The African elephant has a low cancer mortality rate (4.81%) [42] compared to mice (50–90%) [43–45] and even humans (23%) [46]. Interestingly, the antitumor mechanisms developed by evolution differ among long-lived species [38]. For example, naked mole-rat fibroblasts undergo cell division arrest at a lower density than that observed in mice fibroblasts due to the secretion of a high molecular mass hyaluronan that triggers early contact inhibition [47]. A study of aging blind mole-rat cells cultured *in vitro* [48] shows that this species, a subterranean long-lived rodent, possesses remarkable cancer resistance that differs from that of the naked mole-rat at the mechanistic level with a "concerted cell death" process arising from IFN-β secretion. Genomic analysis in the African elephant revealed 19 additional copies of the tumor suppressor gene TP53 that may emanate from retro-transposition [42,49]. Consistent with these observations, other studies found that elephant cells are more sensitive to DNA damage-induced apoptosis than human cells [42,49]. This phenomenon probably plays a role in the elephant's greater ability to eliminate mutant cells and the emergence of cancer. Considering that long-lived species evolved diverse and species-specific antitumor mechanisms, it is of interest to study several long-lived species to identify innovative anti-aging strategies.

Cellular stress response and aging

Why we age remains an unresolved issue and is an intense subject of debate [50–52]. Despite this uncertainty about the causes of aging, research in this domain tends to focus on stress exposure, cellular stress response and the time-dependent accumulation of cellular damage [5,53–55]. Indeed, damage accumulation and the stress response machinery are linked to many hallmarks of aging including genomic instability, loss of proteostasis, mitochondrial dysfunction and cellular senescence [5]. Damage accumulation is prone to arise from chronic endogenous and environmental mild stress exposure during life, including but not limited to oxidative stress, heat stress, cold stress, hypoxic or anoxic stress [55]. Consequently, the ability of cells to mount an effective stress response should delay aging and age-related diseases. Cellular stress response involves the activation of defense mechanisms (i.e. unfolded protein response, autophagy, DNA repair and mitochondrial quality control) for the restoration of homeostasis after injuries and/or for the elimination of damage [5,56–58]. It is noteworthy that the anti-aging properties of cellular defense mechanisms induced during stress exposure have been extensively described [5]. Indeed, DNA repair deficiencies accelerate aging in mice and are observed in several human progeroid syndromes [59,60]. Proteostasis is altered in aging and in age-related diseases, whereas the improvement of the proteostasis network extends lifespan [5]. Since energy production is required for cellular stress response [61], mitochondrial biogenesis and mitochondrial quality control are associated with a beneficial impact on health [62–64].

Cellular stress response and protective metabolites

Interestingly, some studies strongly suggest that the production of health-promoting metabolites plays a role in stress response. This process is well described in the plant kingdom [65,66]. For example, the mitochondrial unfolded protein response induced by mitochondrial proteotoxic stress involves the production of phytohormones (i.e. ethylene and auxin) in Arabidopsis [67]. Other stressors including ultraviolet irradiation and bacterial infection trigger the formation of protective phytochemicals such as glucosinolates, resveratrol and curcumin [68,69]. The involvement of protective metabolites during cellular stress response is also reported in mammals. Some studies strongly suggest that mitochondrial stress leads to the production of protective metabolites (e.g. mitokines) that have health-promoting properties in mammals [61,70,72]. For example, fibroblast growth factor 21 (FGF21) is formed through the mitochondrial dysfunction arising from autophagy deficiency or via the inhibition of mitochondrial complex I activity with the antidiabetic drug metformin [72,73]. *In vivo* studies have

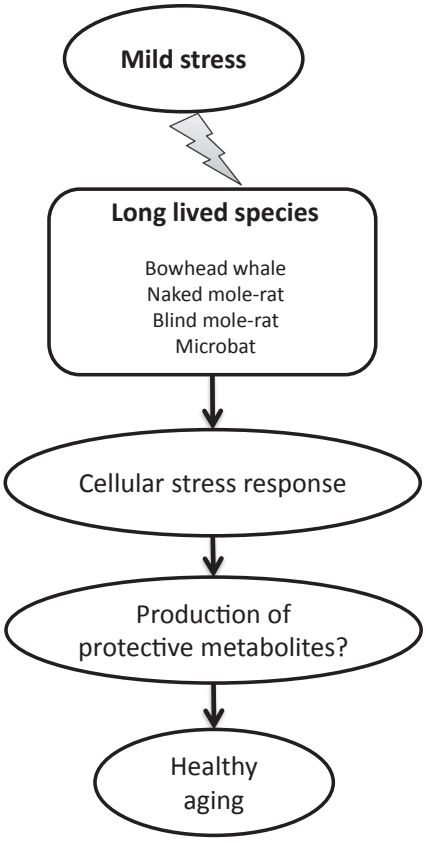

Fig. 1. Stress response in long-lived species. Mild stress exposure could trigger a protective cellular stress response in long-lived species that involves the production of health-promoting metabolites. Internal and environmental stressors include, but are not limited to, heat stress, cold stress, exercise, oxidative stress, food deprivation, hypoxic or anoxic stress, chemical toxins, heavy metals, mechanical stress, salt, alcohol, osmolarity, and even emotional and psychological stresses. The perturbation of homeostasis through non-damaging mild stressors triggers adaptative homeostatic response dedicated to the maintenance of a "normal" homeostatic range. Mild stressors can also stimulate a hormetic response that allows damage repair and a higher resistance to future challenges. Both adaptative homeostatic response and hormetic response involve the activation of cytoprotective mechanisms such as unfolded protein response, heat shock response and antioxidant response. The production of protective metabolites is also stimulated during stress exposure. The elucidation of cellular stress response at the metabolic level in long-lived species should provide innovative anti-aging strategies.

shown that overexpression of FGF21 extends lifespan in mice [74,75]. FGF21 also exhibits a beneficial impact on glucose and lipid metabolism, thus highlighting its potential for the treatment of metabolic syndrome [75–77]. Besides FGF21, mitokines include growth differentiation factor 15, the neurotransmitter serotonin and the mitochondria associated peptide humanin [78,79]. Levels of adenosine increase during cellular stress, particularly in anoxic insults and seizure [80,81]. This metabolite is cytoprotective in neurons exposed to anoxia [82,83]. The polyamine spermidine has been widely reported for its beneficial impact, which includes neuroprotective and cardioprotective effects [82,83]. Spermidine is formed in cells exposed to stress, suggesting that this polyamine is likely to be a metabolic mediator of the stress response [84]. Itaconate is another example of protective metabolite formed under stress exposure [85]. As mentioned above, long-lived species have better resistance to various stressors than short lived species. Consequently, it is highly probable that stress response including the production of protective metabolites is more efficient in long-lived species (Fig. 1). However, the evaluation of metabolite production under stress exposure in long-lived species remains to be addressed.

Hypothesis

In view of the fact that first, lifelong damage accumulation is an important player in aging and age-related diseases [5]; second, an effective cellular stress response involving the production of protective metabolites tends to promote healthy aging (Fig. 1) [53–55,69–84]; third, the elucidation of anti-aging mechanisms from long-lived species offers promising opportunities for the discovery of innovative anti-aging interventions in humans [9,11,12,15,21]; fourth, some mammalian species developed efficient protective mechanisms that are not present in humans [12,15] and fifth, the characterization of metabolic modification during stress exposure in long-lived species has not been addressed yet, I postulate that examining the metabolic profiles of long-lived species cells exposed to stressors should provide innovative strategies to delay aging and age-related diseases in humans. Metabolic response to stress (MRS) will be determined on long-lived species (naked mole-rat, microbats, bowhead whale and human) and compared with phylogenetically related shorter-lived species (mouse, evening bat, chimpanzee).

Evaluation of the hypothesis

The evaluation of the hypothesis involves the following steps (Fig. 2):

Long-lived species cells

Long-lived species will include rodents (naked mole-rat, blind mole-rat), microbats (Brandt's bat, little brown bat) and humans. For the proposed study, phylogenetically-related shorter-lived species such as mice for rodents, evening bats for bats and chimpanzees for primates will be considered to compare their MRS with those of the long-lived species. Fibroblast cells from the skin of long-lived rodents and bats have already been used in numerous studies [29–31], therefore the proposed study is perfectly feasible.

Bowhead whales are of unique interest for biomedical research, notably in the field of aging. Unfortunately, it is obvious that the obtaining of biological materials from bowhead whales for research purposes is highly challenging. However, lung fibroblasts from the bowhead whale have been successfully cultured *in vitro* [86]. Consequently, the study of MRS in bowhead whale cells seems possible and deserves to be considered. Besides *in vitro* studies, the determination of MRS should also be performed *in vivo*. Indeed, an *in vivo* study has already reported the circulating metabolomic signature of the naked mole-rat [24]. Similar experiments should be carried out on long-lived species exposed to stressors.

Stress exposure

Mild stress has been reported to exert beneficial effect through the induction of a protective response known as hormesis, whereas severe stress is deleterious and induces premature senescence [87]. Consequently, mild stress exposure should be favored rather than severe stress. Besides the nature and the intensity of the stressors, kinetics will be also considered for the MRS. Cells will be exposed to various stressors to characterize the metabolic profiles (Fig. 2).

Metabolic profile

The following approaches should be used to investigate MRS:

Radioactive tracers

The use of radioactive tracers should be useful for the

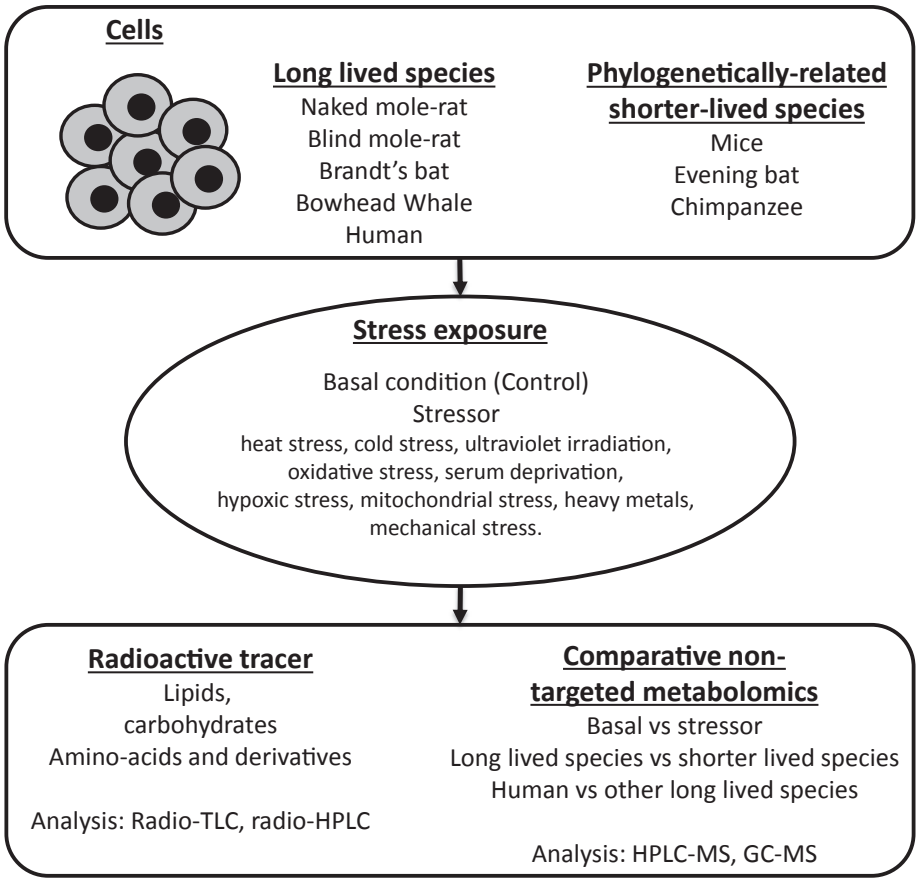

Fig. 2. Evaluation of the metabolic response to stress on long-lived species. Cells from long-lived species and phylogenetically related shorter-lived species will be exposed to increasing intensities of various stressors (i.e. heat stress, cold stress, ultraviolet irradiation, oxidative stress, serum deprivation, hypoxic stress, mitochondrial stress, heavy metals, mechanical stress). Kinetic studies will be performed for the MRS profiles characterization. Radioactive tracers will be used in conjunction with radio-TLC and HPLC coupled to mass spectrometry to investigate the impact of stress exposure on various metabolic pathways in long-lived species compared to shorter-lived species. Comparative non-targeted metabolomic analysis will be performed to identify metabolites and compare data between basal and stressed conditions and between long-lived species and phylogenetically-related shorter-lived species.

characterization of metabolic profiles in cells exposed to stressors. Indeed, various commercially available radioactive tracers are radiolabeled metabolites including lipids, carbohydrates, amino-acids and derivatives, thus allowing the investigation of several metabolic pathways.

Non-targeted metabolomics

For the proposed hypothesis, metabolomic studies aim to determinate a non-targeted metabolic profile of cells exposed to stressors. These profiles will be compared between long-lived species and phylogenetically-related shorter-lived species but also between cells that have been exposed or unexposed to the stressor. For this purpose, GC–MS and LC–MS analysis will be performed on cellular extracts. Non-targeted metabolomics is challenging. However, several studies have reported valuable results using non-targeted metabolomics, indicating the feasibility of this method to evaluate the proposed hypothesis [24,88].

Discussion

Stress resistance and the genes, molecular pathways and biological processes involved in the stress response have already been studied in long-lived species [12,15,19,28–31]. Interestingly, it has been suggested that a link between *in vitro* cell resilience and species lifespan may involve an evolutionary selected resistance to inflammatory events [89]. However, no attention has been paid to the metabolic profiles of stressed long-lived species. The proposed hypothesis should provide an innovative anti-aging strategy involving the use of protective metabolites produced in long-lived species exposed to stressors. Indeed, protective metabolites from stressed long-lived species have a strong potential to delay aging and age-related disease, considering that stress resistance is a pivotal process for the prevention of damage accumulation and the maintenance of homeostasis [53–55,70–84]. A number of differences may occur at the metabolic level between stressed long-lived species cells and phylogenetically related shorter-lived species: first, kinetic differences with a sustained production of protective metabolites in long-lived species; second, a higher level of protective metabolites formed in stressed long-lived species cells and third, the formation of original protective metabolites in long-lived species cells that are not detected in phylogenetically-related shorter-lived species. Of course, metabolic differences are also expected among long-lived species, indicating that protective metabolites that are not produced in humans could be identified. Metabolites formed in long-lived species exposed to stressors will then be tested for their abilities to extend lifespan in mice and to protect against age-related diseases in animal models. It is noteworthy that translational medicine involving a small molecule drug including metabolites is less challenging than genetic therapy. The proposed study should lead to the identification of metabolites from long-lived species that are not produced in humans. Whether a metabolite from one species can be recognized and biologically active in another species is difficult to predict without prior knowledge about its mechanism of action. However, the cross-species recognition of metabolites is likely, as some examples have been reported in the literature. These include the phytochemicals resveratrol or curcumin [90] and the shark metabolite squalamine [91], which all display beneficial effect on mice and human. In summary, the evaluation of this hypothesis is likely to provide new knowledge concerning the protective mechanism of long-lived species at the metabolic level and potentially innovative approaches for the promotion of healthy aging in humans.

Conflicts of interest statement

None.

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