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Review Article

A biomimetic natural sciences approach to understanding the mechanisms of ageing in burden of lifestyle diseases

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The worldwide landscape of an ageing population and age-related disease brings with it huge socio-economic and public healthcare concerns across nations. Correspondingly, monumental human and financial resources have been invested in biomedical research, with a mission to decode the mechanisms of ageing and how these contribute to age-related disease. Multiple hallmarks of ageing have been identified that are common across taxa, highlighting their fundamental importance. These include dysregulated mitochondrial metabolism and telomeres biology, epigenetic modifications, cell–matrix interactions, proteostasis, dysregulated nutrient sensing, stem cell exhaustion, inflammageing and immuno-senescence. While our understanding of the molecular basis of ageing is improving, it remains a complex and multifactorial process that remains to be fully understood. A key aspect of the shortfall in our understanding of the ageing process lies in translating data from standard animal models to humans. Consequently, we suggest that a 'biomimetic' and comparative approach, integrating knowledge from species in the wild, as opposed to inbred genetically homogenous laboratory animals, can provide powerful insights into human ageing processes. Here we discuss some particularities and comparative patterns among several species from the animal kingdom, endowed with longevity or short lifespans and unique metabolic profiles that could be potentially exploited to the understanding of ageing and age-related diseases. Based upon lessons from nature, we also highlight several avenues for renewed focus in the pathophysiology of ageing and age-related disease (i.e. diet-microbiome-health axis, oxidative protein damage, adaptive homoeostasis and planetary health). We propose that a biomimetic alliance with collaborative research from different disciplines can improve our understanding of ageing and age-related diseases with long-term sustainable utility.

Introduction

Human life expectancy has achieved an unprecedented rise, at a rate of 5 years per decade, since the beginning of the millennium. The population aged 65 years or over is projected to reaching 1.5 billion in 2050 [1]. Despite the improvement of lifespan, health span (years of healthy living) continues to lag behind, as ageing populations are overwhelmed by age-related diseases and multi-morbidities, including chronic kidney disease (CKD), cardiovascular disease (CVD), type 2 diabetes, obesity, cancer, osteoporosis, frailty and neurodegenerative disorders [2,3]. This '*diseasome of ageing*' has a huge socio-economic impact and challenges public healthcare across nations [4]. Conventional strategies, aimed at tackling a single chronic disease/disorder, generally fail to affect other diseases of ageing and result only in a short-term improvement in health span. Clearly, a better understanding of the underlying physiology of ageing is a

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prerequisite for tackling ageing, and therefore promoting healthy normative ageing, by delaying onset of multiple age-related diseases as a '*longevity dividend*'. Thus, multidisciplinary perspectives are crucial to untangling the underpinning mechanisms of ageing, as well as developing effective interventions. Given the restrictions of ethics, long lifespan, social environmental factors and genetic heterogeneity in humans, animal model systems have typically provided the basis for ageing research. Indeed, great strides have been made in exploring the mechanisms and interventions in ageing using an array of experimental model organisms, including yeast (*Saccharomyces cerevisiae*), nematodes (*Caenorhabditis elegans*), fruit flies (*Drosophila melanogaster*) and mice (*Mus musculus*). The relatively short lifespans of these organisms have allowed an extensive examination of their respective ageing processes.

Studies in different model organisms have shown that longevity is controlled by a hub of related mechanisms affecting mitochondrial metabolism, telomere biology, the epigenetic landscape, cell–matrix interactions, proteostasis, nutrient sensing, stem cell biology, inflammageing and immuno-senescence [5–8]. Identification of the common hallmarks of cellular and molecular ageing pathways has provided potential for developing a range of geroscience approaches, to mitigate the effects of ageing, including lifestyle strategies and pharmacological interventions. However, critical questions remain about the use of data from conventional laboratory models and how readily they can be extrapolated to man. Such an issue is amplified in the field of ageing research (in comparison to other research contexts) as ageing processes have been adaptively remodelled during evolution by natural selection [9]. This is particularly pertinent in humans, where post-reproductive lifespan is relatively long and physiological resilience to age-related decline is already substantive. As such, it is possible that the modulation of pathways shown to improve health and life span in standard models, may have limited or no effect in man, as a direct consequence of existing evolutionary selection for optimal performance for a given pathway or process. Consequently, manipulation of any such pathway may prove misleading. Moreover, it must also be viewed through the lens of antagonistic pleiotropy. Thus, stage in the life course must be accounted for. Hence when and where in the life course interventions occur, might have profoundly different consequences. Targeting cellular senescence, for example, early in the life course, might result in loss of physiological capability or induce developmental changes. Targeting it later in the life course may have anti-oncogenic and rejuvenation effects based on the premise that senescent cells contribute to age-related physiological decline and increased cancer risk [10]. As such, it is likely easier to break a biological system than to build a new one. One promising novel approach to tackle this issue is to apply a biomimetic approach; i.e. study how nature has already solved problems over the course of genus and species evolution.

Over the last 540 million years, multicellular animal life has experienced five major mass extinction events caused by extreme environmental conditions, such as flood basalt, sea-level changes, asteroid impacts, global cooling, global warming and anoxic events. The aftermath of these catastrophic extinctions has seen adaptive changes driven to enable species to exploit challenging and changing environments. Species that did not evolve and adapt to these dramatic environmental changes became extinct. The unfolding of deep-time palaeogenomics was recently shown to have a real potential to expand our understanding of long-term adaptive evolution [11]. Emerging evidence from the current Anthropocene era (i.e. the geological epoch dating from the commencement of significant human impact on the planets ecosystem) is experiencing an ongoing sixth mass extinction, as a result of increasingly rapid destruction of ecosystems affected by human activities. The recent observation that the human-made global mass exceeds all living biomass [12] is a painful reminder that *Homo sapiens* in the 21st century has become unsynchronised with the rest of biosphere and the geosphere. Consequently, humans are exposed to a spectrum of societal and public health concerns, including adverse environmental changes, global economic disparity, increasingly sedentary lifestyles, pharmaceutical drugs and imbalanced diets with excessive caloric intake. To survive in a rapidly changing environment, humans rely upon evolutionarily ancient physiological adjustments to adapt to these rapidly occurring challenges. However, the evolution of adaptive homoeostasis to cope with such a rapidly changing anthropocenic environment is too slow to cope. As a result, humans are during the era of Antrophene more exposed to conditions that stimulate a '*diseasome of ageing*' [13].

As many of the approximately 8.7 million eukaryotic species [14] that currently inhabit the planet have successfully survived previous extreme various environmental and internal conditions (e.g. hypoxia, hibernation, food and water shortage, infections, trauma etc.), their adaptive strategies throughout evolution could provide key insights for improving human health. Furthermore, as each species has acquired a unique adaptive system for health and survival acquired through 'trial and error', the potential resulting from exploitation of a biomimetic research approach is huge [15]. While short-lived traditional animal models, such as mice and rats, form the basis of biomedical research into ageing, the efficacy of laboratory studies in inbred mice and rat strains seeking efficient treatment strategies for burden of lifestyle diseases have been doubted [16]. We therefore believe in exploiting a biomimetic approach, based around a better application of the natural sciences, to provide a comprehensive understanding of the physiology of

ageing and ageing-related diseases. A such, this will require a comparative and evolutionary strategy, to identify commonalities and peculiarities across species with unique ageing trajectories (e.g. slow, negligible or accelerated ageing patterns) evolved over the course of evolution by natural selection. CKD can be exemplified as a clinical model to illustrate the pathophysiology of premature ageing [17, 18]. In this in-depth review, we discuss biomimetic insights into the mechanism and physiology of ageing, CKD and other clusters of age-related burden of lifestyle disorders.

CKD – of cats and men

The Felidae family are highly susceptible to CKD, which is the common cause of death affecting up to 80% of domestic felines >5 years of age [19–21]. Free-ranging big cats (e.g. tigers, lions and leopards) also experience kidney disease of various pathologies, they typically die in a natural setting through predation or other natural causes, prior to the onset of disease. This may be the reason why felids during evolution have failed to evolve mechanisms to cope with their high meat intake. While the exact intrinsic causes of kidney diseases in felines remain to be investigated, one potential insight into the high prevalence of CKD in cats comes via their high-protein diet [22]. The cat family are obligate carnivores – domestic and captive felids are fed with a high-protein diet on a daily basis, while wild cats feed naturally on the meat of prey species. Though the mechanisms by which high-protein intake may cause, or accelerate CKD, have not been fully elucidated, preclinical studies in various animal models have implied that a high-protein diet induces glomerular hyperfiltration and causes a deterioration in kidney function [23]. In humans, data from long-term observational studies and clinical trials investigating the association, or cause–effect, between a high-protein diet and decline in kidney function remain inconclusive [23–27]. Nevertheless, a high-protein diet is closely correlated with phosphorus intake, possibly accounting for 84% of the variance in dietary phosphorus intake [28]. During evolution, accumulation of phosphorus, in the form of calcium-phosphate, first occurred in bony fish approx. 400 million years ago, as a prerequisite for the evolution of terrestrial vertebrates. The precipitation of calcium and phosphate during the evolution of the skeleton, has been modulated by the fibroblast growth factor 23 (FGF23)–Klotho endocrine system [29]. Intriguingly, a high serum phosphate level is thought be universally involved in accelerated ageing and shortened lifespan in mammals [30]. In mice lacking FGF23 or Klotho, a low-phosphate diet ameliorates the ageing phenotype [31]. In humans, high serum phosphate levels are associated with poor clinical outcomes both in CKD [32] and non-renal populations [31,33,34]. Taken together, high phosphate intake may partially explain the role of excessive red meat consumption in promoting acceleration of the ageing process and poorer renal function in the general population [35], i.e. high protein and high phosphate intake – two partners in crime [36]. A decrease in the intake of red and processed meat is in accord with recent recommendations for an urgent need to radically transform global food systems by the EAT Lancet commission [37].

We are what we eat

The link between a high-protein diet and CKD, observed in felids and man, implies a role for diet in ageing and age-related diseases. It is likely that a skewing towards a more carnivorous diet in the Western world during the last century have resulted in a dietary association with the '*diseasome of ageing*'. Underpinning this phenomenon are the activities of gut microbial metabolites. Dietary choline [38] and carnitine [39], nutritionally acquired from red meat, are metabolised into trimethylamine (TMA) – the precursor of trimethylamine N-oxide (TMAO), by distinctive microbial choline TMA-lyases, including the proteins encoded by the choline utilisation C/D genes in gut commensals [40]. The gut-derived TMA is then converted into TMAO which is catalysed by the enzyme flavin-containing monooxygenase 3 (FMO3) in the liver [41] (Figure 1). A study on protein source (red meat vs white meat vs non-meat) found that subjects consuming a red meat diet presented with higher levels of TMAO. More importantly, such exposure to a red meat-rich diet (8 oz. of steak/day for 1 month) caused a reduced fractional renal excretion rate of TMAO, despite no functional change in glomerular filtration rate [42]. Recent data from a prospective follow-up study examining the association of meat intake with risk of 25 common diseases, revealed that higher consumption of either separate or combined unprocessed red and processed meat, was associated with increased risk of ischemic heart disease, pneumonia, diverticular disease, colon polyps and diabetes [43]. A randomised controlled trial demonstrated that 14 days of ultraprocessed vs unprocessed food (with diets matched for calories, sugar, fat sodium, fibre and macronutrients) caused weight gain [44]. Multiple evidence have indicated the participation of TMAO in multiple age-related diseases, including CVD, type 2 diabetes, CKD, cancer and metabolic dysfunctions [45]. More recently, TMAO has been recognised as being involved in platelet function and thrombosis [46], which can possibly explain the association between TMAO and cardiovascular events [47–49]. As TMAO crosses the blood–brain barrier [50] high TMAO levels may also promote neuro-inflammation and cognitive dysfunction [51].

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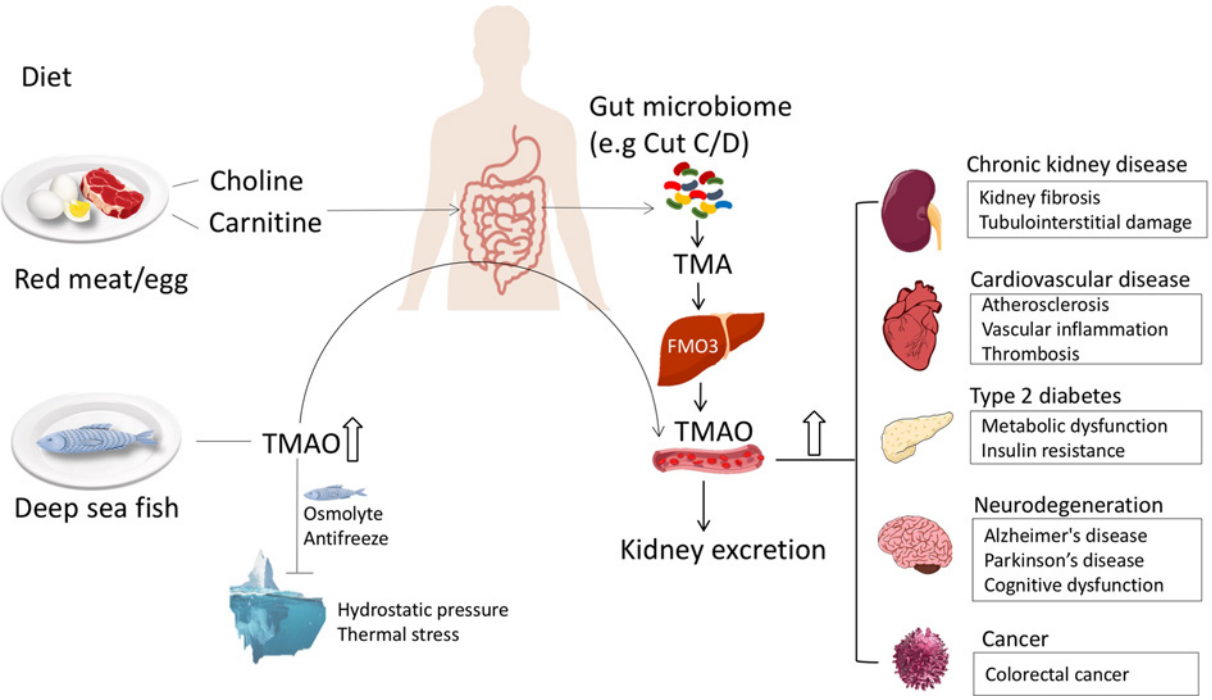

Figure 1. Dietary intake, TMAO metabolism and disease risk

Animal food such as egg and red meat rich in choline and carnitine (dietary precursors of TMAO), and fish naturally abundant in TMAO, are the main dietary source of TMAO. Dietary nutrients choline and carnitine are converted into TMA by distinctive enzymes encoded by gut microbiota. The gut-derived TMA is then oxidised into TMAO by hepatic FMO3, released into blood, taken up by extrahepatic tissues and excreted in urine. Fish-source TMAO can bypass gut and live metabolism and directly be absorbed into blood. High circulating TMAO increase the risk of multiple diseases including CKD, CVD, type 2 diabetes, neurodegenerative disorders and cancer. In deep sea fish (and other marine organisms), high TMAO is evolutionally adapted as an organic osmolyte and antifreeze to maintain cell volume and protein stability against hydrostatic and thermal pressures.

Despite large-scale studies indicating TMAO as a risk factor for adverse human health, results still must be interpreted with caution. Considering that the circulating TMAO level is affected by multiple factors, such as diet pattern, kidney function, gut microbiota composition and FMO3 activity, it is not entirely clear whether TMAO directly causes certain disease phenotypes, or is merely a marker of certain underlying pathogenesis [45]. However, at present, available evidence suggest that TMAO is causally linked to CVD [52]. With respect to diet, aside from the precursor sources of choline and carnitine mainly obtained from eggs and red meat, TMAO also naturally exists in a preformed state in a subset of deep sea or cold climate fish (*vide infra*). In healthy young men, fish consumption rich in preformed TMAO yielded ∼50-times higher post-prandial circulating TMAO level compared with egg or beef consumption [53]. Accordingly, an increased urinary excretion of TMAO and its derivatives was observed after consumption of fish, but not meat, dairy or other food categories [54,55]. Moreover, in contrast with dietary precursor intake (i.e. choline and carnitine), preformed TMAO consumption, is likely to be absorbed independently of the host microbiota, as circulating TMAO was found to be elevated within 15 min after fish intake [53], a time window within which contribution from a microbial or hepatic pathway is unlikely. This intrinsic metabolic profile of TMAO from fish may also explain the discrepancy in circulating TMAO levels observed among populations with different food cultures, such as study populations from Japan and Scandinavia, both with a high seafood consumption and likely to present with a feature of high TMAO levels. Hence, epidemiological data from different population settings and cultural backgrounds must be evaluated cautiously.

From an evolutionary point of view, however, TMAO also exerts a wide range of biological effects across species beneficial to their survival. Acting as an organic osmolyte and antifreeze, TMAO facilitates marine organisms to maintain cell volume and protein stability against hydrostatic and thermal pressures [56–58]. The plasma TMAO level in deep sea fish increases with the depth of their habitat, thus elevating osmolality. A seasonal accumulation of TMAO, for example, occurs in Newfoundland fish to suppress freezing of their body fluids, in response to extreme

seasonal differences in water temperature [57]. In vertebrates, TMAO level in the mouse kidney is higher than that in plasma, possibly acting as an osmotic agent in tubular tissues to regulate water reabsorption and urine concentration [45]. While the role of TMAO in the kidney has not been fully elucidated, it may provide therapeutic opportunities to target TMAO urinary excretion for blood pressure control, with concomitant cardio-renal protective effects. While it is plausible that evolution has enabled development of certain adaptive physiology to produce TMAO to cope with external stressors, this trait may have become a culprit in a modern athropogenic exposome [59], replete with dietary imbalance, sedentary lifestyles, socioeconomic deprivation and psycho-social stressors. The dynamics of exposome factors and their subsequent impact on health, are thought to be mediated by the epigenetic landscape of ageing [59]. Maintenance of a canonical epigenome, in particular the methylome, is affected by inflammation and thus impacted upon by TMAO levels. Additionally, the availability of methyl donor substrates is also influenced by diet and one carbon metabolism [60]. In particular betaine levels, a primary source of methyl donors, is derived via the same biochemical pathway as TMAO, albeit on a different branch. It is therefore of note, that we recently reported that free-ranging brown bears may turn on a metabolic switch that in hibernation shunts choline to generate betaine instead of TMAO [61], thus decreasing inflammatory burden and enabling epigenetic changes in preparation for the metabolic changes occurring on emergence from hibernation. Characterisation and better understanding of such an adaptive switch turning on and off TMAO generation could hold clues for novel treatment options in burden of lifestyle diseases.

An unhealthy diet, with suboptimal intake of fruits, vegetables, whole grains and a high consumption of processed food products high in saturated fat, with added sugar and salt, all major risk factors for poor health outcomes. Processed food (the key hallmark of Western diet) do not only cause excess of calorie intake [44] but also drive intestinal barrier permeability and microvascular disease [62]. Moreover, as it was recently reported that processed red meat, in contrast with unprocessed red meat, was linked to increased risk of incident dementia [63], it seems like the processing of food *per se* drive disease. A recent finding in two large prospective cohorts combined with a meta-analysis of 26 prospective cohort studies has shown that a higher intake of fruit and vegetables was non-linearly associated with low total and cause-specific mortality and the lowest risk was observed for five servings/day for fruit and vegetable intake, providing a succinct evidence and recommendation for healthy eating [64]. The notion of a healthy diet used as a modern reinvention of the Hippocratic '*Food as medicine*' strategy, has also recently been highlighted as a promising strategy to combat CKD and age-related diseases [65]. Indeed, the bioactive compounds found in turmeric, berries, broccoli sprouts, legumes and other whole foods and plant-based diets are natural senotherapeutic medicines that can modulate premature ageing and age-associated complications via multiple pathways [65].

Of microbiome and men

The role of diet in health inevitably suggests that the gut microbiome plays an important role in the ageing processes [66]. The gut microbiota is recognised as a hub for the integration of diet with inherent (epi)genetic and immune signals throughout life. This has been manifested vividly during the current pandemic, where the prevalence and mortality risk of COVID-19 is heightened in the elderly population. Despite the fact that this vulnerability comes, in part, from age-related physiological decline, the gut microbiota *per se* play a role in resistance to viral infection [67]. Indeed, the gut microbiota is involved in the magnitude of COVID-19 severity via modulating the immune responses [68]. Moreover, the role of gut microbiota is mirrored in other ubiquitous chronic disease conditions and physiological decline [69]. Given the abundant evidence for such a key role in metabolic, immune and neuroendocrine pathways, the exploration of the gut microbiota in ageing and ageing-related phenotypes has thrived over the last decade. Population studies from different geographical locations have suggested a structural and functional change in the gut microbiota in the elderly [70–76]. Biagi et al. [77] have reported that the microbiota in centenarians from Northern Italy had a decreased core taxa diversity and an increased prevalence of the taxon *Proteobacteria*, in comparison to younger adults. These findings have since been replicated in other centenarian populations from Sardinia, China and Korea. Some studies, however, have reported a higher core diversity in centenarians compared with younger subjects [75,78–80], suggesting that commensal microbiota continue to be stable within the host. The difficulty remains in defining what actually constitutes a normative gut microbiota with increasing age. Notably, changes in the gut microbiome can be accompanied by elevated levels of circulating inflammatory cytokines, indicating a plausible link between a leaky gut with inflammageing [81]. This has been supported by a study from Buford et al. [82], where the circulating microbial DNA profile in adults (>60 years) differed from young adults (20–35 years), and where the abundance of several phyla, in particular *Bacteriodetes*, were significantly correlated with increased serum inflammatory markers in the elderly. It is also worth mentioning that in order to track the trajectory of human gut microbiome with longevity, Biagi et al. [83] have profiled the microbiota in semi-supercentenarians (105–109 years),

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centenarians (99–104 years), elderly (65–75 years) and young adults (22–48 years). In line with their previous findings, where the ageing-associated microbiota was reshaped with a decrease in core taxa and enriched in subdominant bacteria with pro-inflammatory effects, the present study highlighted that the microbiota profile in extreme longevity (>105 years) was featured with increment of salutogenic bacteria [83].

It is thus tempting to speculate that while changes in the composition of the gut microbiota may drive physiological decline in ageing, it must be also be tempered with an appreciation of the influence of antagonistic pleiotropy, layered across any evolutionary 'longevity adaptation' that the gut microbiota has evolved to maintain a stable commensal status during a healthy life course. Indeed, data from the ELDERMET cohort have shown that clustering of components of microbiota composition differentiates the healthy community-dwelling elderly from those less healthy elderly in long-term residential care and was well correlated with both frailty and parameters of poor health [71]. Moreover, consistent with a reduced microbial diversity among the long-stay elderly, metabolomics analysis of faecal water revealed that levels of short-chain fatty acids (SCFAs), including acetate, propionate and butyrate, were decreased in parallel with a depleted frequency of genes for SCFAs production [71]. Such correlation between deduced metagenome and metabolic change in SCFAs suggest that gut-derived metabolites are mediators between gut microbiome and ageing. Indeed, as a readout of saccharidic metabolism by the microbial community, SCFAs were shown to be involved in modulating blood pressure [84,85], cardiac repair [86] and inflammation [87]. As recently reviewed [52], a wide range of other microbiota-dependent metabolites, including bile acids, phenylacetylglutamine (PAG), *p*-cresyl sulphate, indoxyl sulphate and TMAO can alter host metabolism via specific receptors/pathways linked with cardiometabolic diseases. Bárcena et al. [88] demonstrated that faecal microbiota transplantation from wildtype donors to progeriod recipients, in mice, attenuated the accelerated ageing phenotype and improved survival, whereas faecal microbiota transplantation from progeroid donors to wildtype recipients caused metabolic disorders.

Given its developing importance to health and disease, the gut microbiota represents a new area in healthy ageing and longevity research. Wilmanski et al. [89] have described the dynamics of the gut microbiota across human life course, in a detailed phenotyping of 9000 subjects spanning 18–101 years of age. This investigation has revealed that the gut microbiota tends to become more unique to respective individuals with increasing chronological age, and this 'uniqueness' was characterised by a distinct shift in plasma gut microbial metabolites, with significant changes in phenylalanine and tryptophan pathways. As PAG possesses the strongest correspondence with the uniqueness of gut microbiota, this is consistent with previous reports indicating increased PAG in centenarians compared with younger subjects [90,91]. Interestingly, PAG has recently been identified to play a role in thrombotic cardiovascular events via activating adrenergic receptors [92]. One possible explanation of the rising burden of gut xenobiotic metabolites in the healthy ageing host is that these resilient individuals can adapt or neutralise the toxicity of microbial compounds, whereas those vulnerable to the negative effects of these toxins are predisposed to accelerated ageing and diseases. Furthermore, a unique microbiome profile was associated with better survival over a 4-year follow-up. It is thus conceivable that the increasing uniqueness of the microbiome may not only reflect, but also contribute to healthy ageing with longer health span and lifespan (Figure 2A,B). However, a fundamental question relating to 'cause and effect' between the gut microbiome profile and ageing remains. Interventional clinical trials are needed to address this. In this regard, the New Dietary Strategies Addressing the Specific Needs of the Elderly Population for Healthy Aging in Europe (NU-AGE) project revealed the results from a 12-month Mediterranean diet intervention in the elderly, which was reported to have led to increased richness in specific microbial taxa that were associated with less inflammation, lower frailty and improved cognitive function [93]. As such, it stressed the notion of the diet-microbiome-health axis, and the feasibility of changing the habitual diet to modulate gut microbiota, which has the potential to promote healthy ageing. The finding that naked mole-rats (NMRs) (*Heterocephalus glaber*) display a peculiar gut microbiota composition (with an enrichment of SCFAs and carbohydrate degradation products) shared with human gut microbial ecosystems of Hadza hunter-gatherers and centenarians further support a direct link between the gut microbiome and ageing [94]. As it has been reported that type of digestion (i.e. monogastric species vs hindgut fermenters and ruminants) may be a potential determinant of faecal microbiota diversity [95], it should also be studied if type of digestion could impact longevity via microbiota diversity and composition.

Digging deep into subterranean eusocial colonies

The NMR is a eusocial, subterranean rodent that lives in socially hierarchical groups dominated by a queen. This native inhabitant of Eastern Africa is the longest lived rodent known, with a maximum lifespan of +30 years, exceeding far beyond what would be expected for a rodent of similar size by allometric assessment [96]. Moreover, it shows little signs of age-associated declines in physical function well into its third decade, and it exhibits lifelong reproductive activities with extraordinary resistance to myriad disease, including cancer, CVD and neurodegenerative disorders

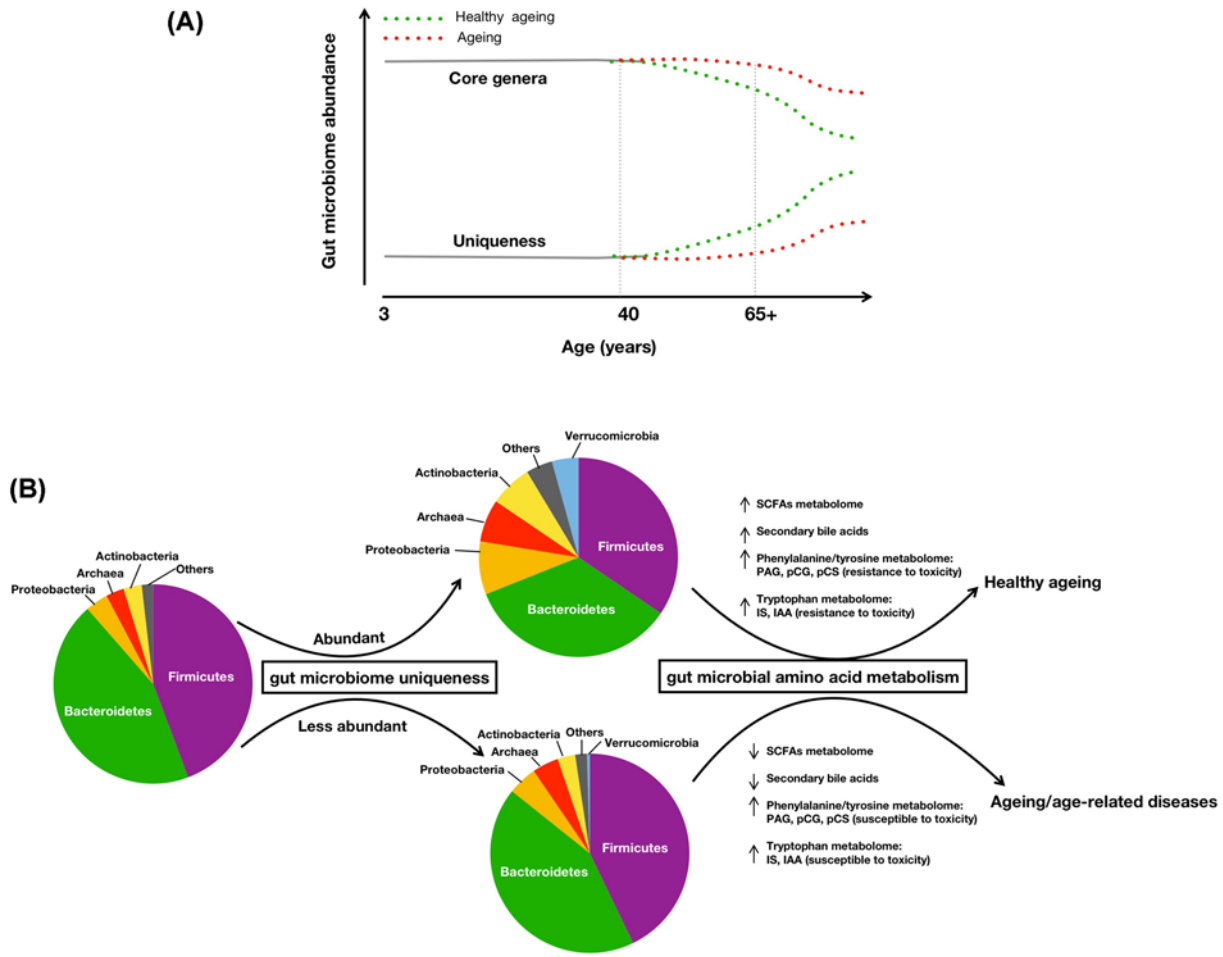

Figure 2. Gut microbiome pattern and ageing

(**A**) **Temporal gut microbiome trajectories across lifespan.** The human gut microbiome establishes a more adult-like composition at approx. the age of 3, followed by a long period of relative stability, ending with temporal changes with advanced age [188]. Starting in mid-to-late adulthood, gut microbiomes exhibit a depletion in core abundant taxa, complemented by an increase in rare taxa. This trajectory may originate early in the 40s and continue to develop in the later decades of human life (>65 years) [89]. A highly developed compositional uniqueness of the gut microbiome is a component of healthy ageing, which is amplified in centenarians [89] and supercentenarians [83]. (**B**) **Gut microbiome uniqueness, metabolites and ageing.** The degree of uniqueness of gut microbiome in the elderly with decline of the core taxa (e.g. *Bacteroidetes* and *Firmicutes*) and increased representation of rare taxa (e.g. *Proteobacteria*, *Archaea*, *Actinobacteria*, *Verrucomicrobia* and others) is critical in human ageing. The high abundance of microbiome uniqueness in normative ageing is characterised by a distinct change in microbial metabolites, including high activation phenylalanine/tyrosine and tryptophan metabolic pathways, and an increased output in secondary bile acids and SCFAs; low abundance of microbiome uniqueness in the elderlies is reflected in microbial metabolite profile with decreased secondary bile acids and SCFAs, as well as increased phenylalanine/tyrosine and tryptophan metabolic pathways [71,89]. The highly activated phenylalanine/tyrosine and tryptophan pathways, with toxic microbial end products, indicates an increasing burden of gut xenobiotic metabolites in an ageing host. Studies have produced inconsistent results regarding the association between these gut-derived toxins and ageing phenotypes in the elderly [89,189,190]. High plasma concentrations of metabolites like PAG, pCG, pCS, IS and IAA observed in healthy older adults and centenarians suggest that these resilient individuals adapt to, or neutralise the toxicity of microbial compounds. In contrast, those vulnerable to the negative effects of these toxins are predisposed to accelerated ageing and diseases. Notably, owing to high variability and discrepancies in the gut microbiota composition pattern reported between studies, the ratio between microbiome core taxa (e.g. *Bacteroidetes* and *Firmicutes*) and rare taxa (e.g. *Proteobacteria*, *Archaea*, *Actinobacteria*, *Verrucomicrobia* and others) and its changing pattern are only conceptual and are not settled to provide a precise representation at an individual level. Abbreviations: IAA, indole-3-acetic acid; IS, indoxyl sulphate; pCG, *p*-cresol glucuronide; pCS, *p*-cresol sulphate.

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[97–100]. In fact, the NMR is the only species that appears to defy Gompertz's law; i.e. the age-specific risk of death does not increase with age [98]. This atypical ageing pattern in the NMR makes it stand out as a quintessential model of successful healthy ageing and provides a proof-of-concept in mammals for the assertion that age-associated decline in health is avoidable. Learning lessons from the resilient physiology of this long-lived rodent may provide powerful insights into healthy normative ageing.

The biological mechanisms that prevent age-associated decline in NMRs are most likely complex, comprising extensive evolutionary adaptation imposed by natural selection and exposome changes. Notably, the adaptation to living in a subterranean habitat predisposes NMRs to a profound tolerance of hypoxia and anoxia [101]. Strikingly, while in this environment they are subjected to higher levels of oxidative damage, these rodents are spared from physical dysfunction despite an insufficient DNA repair system, which undermines the free radical theory of ageing [102]. Studies have explored the intrinsic genomic integrity [103,104], cytoprotective pathways such as increased nuclear factor erythroid 2-related factor 2 (NRF2) signalling [105,106], and proteostatic mechanisms [107,108], as possible agents involved in counteracting reactive oxygen species (ROS)-induced cellular and tissue damage. In addition, it has been suggested that a constitutive nuclear localisation of tumour suppressor protein 53 [109] and abundant extracellular high molecule weight hyaluronan [110], are pivotal for cancer resistance and longevity in NMRs. It should be noted that the role of high-molecular weight hyaluronan in cancer resistance of NMRs was recently refuted [111]. Other eco-physiological adaptive modulations, such as diet restricted in calories and methionine [112], reduced metabolic rate [113], lipid membranes that are particularly resistant to oxidative stress [114] and fructose-driven glycolysis [101] may also facilitate its exceptional disease resistance and longevity. Another unique trait associated with the NMRs longevity lies in the theory of ageing in eusocial organisms. It has recently been reported that the transcriptome pattern in sexually mature NMR breeders was associated with reinforced ageing-related gene networks, including lipid metabolism and oxidative phosphorylation [99]. Moreover, the eusocial traits of the NMR resonate with longevity in man, where centenarians and supercentenarians report social networking as the major factor for their good health in old age [115].

Lessons from animals characterised by negligible senescence

It is indisputable that the compensatory adaptations in NMRs tried and tested through natural selection contain a blueprint for strategies to stave off age-related physiological decline in mammals. While numerous mechanistic insights have been explored, a full understanding of the mechanisms underpinning the NMRs longevity remains to be achieved. One simple thesis, however, might be addressed to explain capabilities of this long-lived mammal – the theory of oxidative protein damage. Protein susceptibility to oxidation is the leading common causal root of ageing and physical degeneration [116]. Ageing-related phenotypes can emerge, progress or regress, solely at the level of protein damage (without the necessity for DNA alterations) although this may occur as a consequence of oxidative damage to proteins committed to maintaining DNA integrity [117]. It has been proposed that the principal determinant of protein damage is intrinsic protein resistance to oxidative damage, more so than the perturbations in ROS. The proteomes of aerobic organisms have evolved a remarkable resistance to oxidation, yet can be fragile and eroded by random errors in biosynthesis and inaccurate folding, as well as by silent missense mutations (polymorphisms). Accurate protein biosynthesis and chaperone-assisted folding are the cell's major energy (adenosine triphosphate, ATP) consumers; 25–30% in mammals [118] and 22–74% among larval families [119]. However, there is a trade-off between efficacy and perfection. While activated, the mechanistic target of rapamycin (mTOR) pathway accelerates translation to invest sufficient ATP production, it undesirably decreases the fidelity and increases misfolding that leads to reduced protein stability with augmented sensitivity to oxidation [120] (Figure 3A). Thus, all universal underlying molecular and cellular changes involved in ageing can be interpreted as a consequence of accumulated dysfunction of cells overwhelmed with oxidative protein damage [117]. A delayed ageing could thus be achieved via deactivation of mTOR pathway to reduces the susceptibility of proteins to oxidation (via reducing translational errors) or/and activation of FOXO (forkhead box) pathway to reduces the levels of ROS (via NRF2-dependent ROS detoxification). How this fits within the constraints of antagonistic pleiotropy remains to be determined. Furthermore, it does not address the impact of non-somatic mutations on the hallmarks of ageing [59].

The remarkable diversity among animals is reflected by a lifespan that differ more than 100-fold among different species. A metabolomic study in tissues from 26 mammalian species revealed distinctive signatures in lipid and amino acid levels in long-lived mammals [121]. Animals that exhibit superior resistance to age-related disease, seem to display negligible senescence and maintain protein homoeostasis in combination with robust mitochondrial function [122]. As an example, the protein oxidation resistance system in NMRs (e.g. low metabolic rates and fructose-driven

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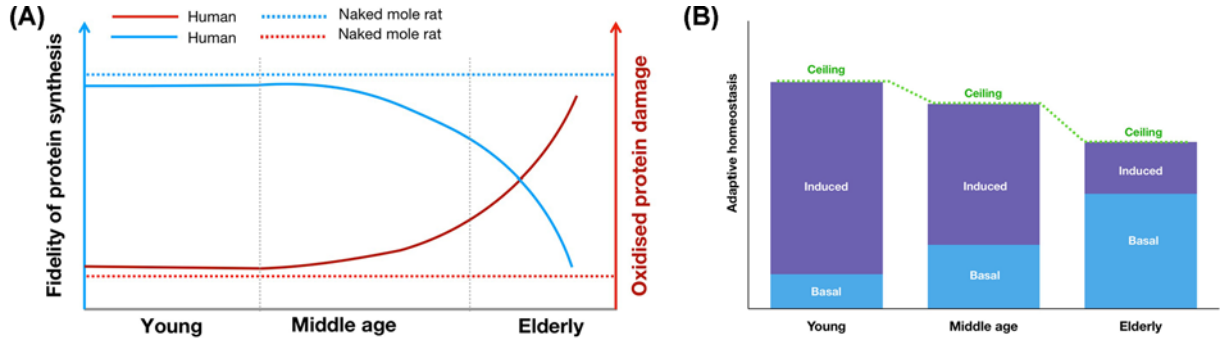

Figure 3. Protein damage and adaptive homoeostasis across lifespan

(**A**) **Fidelity of protein synthesis and oxidative protein damage across lifespan**. Fidelity and accuracy in protein biosynthesis with chaperone-assisted folding are the cell's major energy consumers. Although there is a trade-off between efficacy and quality, the essentials of natural selection through reproductive success must be taken into account. While activated mTOR pathway accelerates translation to invest sufficient ATP production, it undesirably decreases the fidelity and increases misfolding that results in reduced protein stability with augmented sensitivity to oxidation. Generally, nature selective process maximises the investment of energy production for parental proteome quality and sexual maturation to ensure the perpetuation of species, whereas the balance between energy supply and fidelity of protein translation, would diminish once reproduction is assured. As such, the fidelity of protein synthesis remains highly preserved at earlier stage of the human lifespan, but starts to decline after the reproductive period around middle adulthood followed with a dramatic decline in late final third of lifespan. In parallel with the decline of fidelity, the increased misfolding of proteins lose resilience to oxidative stress and succumb to oxidised protein damage accumulating with age. In the case of NMRs, the lifelong intrinsic reproductive capacity in these rodents ensures a parental proteome quality throughout the lifespan, where a high fidelity of protein synthesis and low protein damage is consistently maintained during the whole-life trajectories. (**B**) **Loss of stress-induced adaptive homoeostasis with age**. In early life, the human system maintains a low baseline activities of stress responsive network (e.g. NRF2/KEAP1 signalling and transcription of its downstream stress-protective genes). Exposure to stressors, such as oxidative stress initiates rapid activation and up-regulation of transcription and translation of cytoprotective and proteasome enzymes to counteract the oxidative stress and protein damage (induced adaptive homoeostasis). The big range between low baseline homoeostasis and high physiological ceiling ensures a large capacity of adaptive homoeostasis to cope with stress variance and maintain health in early life. In middle age, baseline levels of repair activities increase but the physiological ceiling of homoeostasis declines as the 'wear and tear' dysfunction across cell, tissue and organ levels (e.g. accumulative protein damage). As a result, stress-induced response is compressed with reduced capacity to maintain adaptive homoeostasis. This range of adaptive homoeostasis between basal and physiological ceiling is further compressed in the later life where a high baseline adaptive homoeostasis is exploited to cope with day-to-day stress perturbations with extremely restricted physiological ceiling. As a result, the organism system eventually loses the capacity of adaptive homoeostasis to counteract any extra stressors and are imposed to increased risk of burden of lifestyle diseases. Abbreviation: KEAP1, Kelch-like ECH-associated protein 1.

glycolysis) can be exemplified as a key strategy to maintain health span with decreased translational errors and reduced ROS production. Indeed, NMRs display low protein carbonylation, with approximately ten-fold reduction in translational error rate [103] and an increased structure-based protein stability [123] when compared with mouse proteins. This can be further exploited to explain the paradox observed in the subterranean NMRs – the phenomenon between an exposome with persistent oxidative stress, an insufficient DNA repair system and undiminished health. We surmise that the 'elixir' that has evolved in NMRs to counteract ROS and ageing is not established by DNA repair capacity but instead dominated by its resilience to oxidative protein damage. Furthermore, the unique defensive system for resisting protein damage explains the parallel of lifelong reproductive activities and health span observed in NMRs. Generally, natural selection would maximise the investment of energy production for parental proteome quality and sexual maturation to ensure the perpetuation of species [124]. Hence, the balance between energy supply and fidelity of protein translation, should diminish once reproduction is assured. Contradicting the 'disposable *soma theory of ageing*' where a dilemma arises between reproduction and survival needs, the NMR possesses lifelong reproductive activities. As the balance of energy supply and proteasome quality is generally and fairly guaranteed before organisms complete their reproductive mission, the lifelong intrinsic reproductive capacity in NMRs ensures that such equilibrium is maintained during the entire life course (Figure 3A). As such, largely due to this reproductive dividend, a bonus of perpetual health is also achieved via a sustainable high quality protein production and resistance to protein damage. Taken together, the well-preserved resilience of protein oxidation/damage in the longevity and

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health span of NMRs may provide a novel paradigm in ageing research, demonstrating that ageing-related disorders are the consequence of molecular and cellular dysfunction caused by augmented protein damage, albeit within the constraints detailed above.

Bats constitute another example of organisms that rarely show overt signs of ageing and cancer. They live four-times longer than similar sized animals [125]. Bats have also developed ingenious augmented immune response mechanisms enabling them to host viruses, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Ebolavirus, without presenting signs of clinical disease [126]. Their protection against ageing and immune-mediated tissue damage may depend on robust anti-inflammatory defence mechanisms due to an up-regulation of the cyto-protective transcription factor NRF2 [127] reduction in inflammasome pathways via regulation of caspases [128] and DNA hypermethylation of age- and longevity-associated sites [129].

Other hallmarks of ageing, such as telomere attrition and genome instability, can also be interpreted as downstream consequences of proteome damage. Critical telomere shortening with consequent onset of telomere DNA damage and cellular senescence determine the lifespan of different species [130]. In fact, telomerase is among the least abundant cellular proteins with high sensitivity to carbonylation [131]. In addition, the protein oxidation/damage can serve as the link between oxidative stress and the activated TOR signalling. The biological effects of rapamycin, metformin and antioxidants upon ageing, can also be better understood at the base of mitigating protein damage. The theory of protein damage in ageing may also provide ground for alternative therapies for ageing and age-related disease (i.e. protein therapy). Heterochronic parabiosis experiments in mice have shown ageing phenotypes such as cardiac, bone and cognitive functions are reversible [132–134], suggesting the potential to compensate ageing by reducing protein damage and/or stimulating protein turnover. Meanwhile, effective anti-ageing antioxidants, neutralisers and ROS detoxifiers need further exploration with regard to the dosage and their long-term effect on health and longevity.

Diving into the oceans to discover secrets of ageing

There is a growing interest in bivalve models of successful ageing, as this invertebrate group includes species with the longest metazoan lifespans, with many species surviving >100 years. Among these is the ocean quahog (*Arctica islandica)*, the longest lived non-colonial metazoan known on earth, with a recorded lifespan of >500 years [134]. Evolution has created a myriad of adaptive strategies in organisms living in extreme habits, among which the preservation of stable proteolytic activity seems pivotal in maintaining lifespan. This is well-illustrated in the ocean quahog, where proteasome activity shows no age-dependent changes [134]. It has been suggested that the ocean quahog has preserved a proteasome system where it maintains a relatively low baseline proteasome activity for a considerable amount of lifespan, and thus delays the entry of its final life zone. This may indicate that a low baseline proteolysis in organisms which has evolved as an effective strategy to preserve the potential of adaptive homoeostasis in response to acute or chronic stress during their life course [135].

Similar findings have also been reported in sea urchin species – a novel model of ageing research to study longevity and negligible senescence. Despite the differences of life expectancies across different species (from 4 to >200 years), these marine invertebrates maintain huge regenerative and reproductive capacity throughout their lifespan. This contradicts the theory that short-lived species would invest more in reproduction and less in maintenance and repair. In fact, sea urchins with different lifespans were found to maintain similar proteasome activities across all ages, without big differences in protein carbonylation. This supports the theory of protein damage resistance as previously discussed. Interestingly, in a comparative study, long-lived urchins exhibited lower proteasome activity in contrast with the higher proteasome activity in short-lived urchins [136]. It can thus be speculated that the longer lived urchins preserve a similar level of damaged proteins while using less of their proteolytic capacity, coinciding with the lower baseline proteasome activities observed in the long-lived ocean quahog.

Other inspiration for longevity in an aquatic environment can be acquired from studies on fish. These present a range of distinct ageing trajectories: rapid (killifish), gradual (platyfish) and negligible (sturgeons and rockfish) ageing. Among the long-lived fish with negligible senescence, the Greenland shark (*Somniosus microcephalus*) has been documented as the longest lived vertebrate on record, with a lifespan of >400 years [137]. Unusually short lifespan fish can also be of great interest, given their particular advantage of being easy to study. For example, the naturally short-lived (maximal lifespan of 13 weeks) African turquoise killifish (*Nothobranchius furzeri*), is an emerging model for ageing research as it provides a unique resource to explore the genomic factors that shape lifespans. Comparative genomics and linkage analysis have identified key ageing genes associated with lifespan differences between various turquoise killifish strains [138]. Intriguingly, these genes are linked to sex, suggesting the role of sex determination in the course of lifespan. Baumgart et al. [139] identified mitochondrial complex I as a central hub for genes whose expression negatively correlates with lifespan in killifish. Moreover, inhibition of complex I reactivated the

transcriptome and extended lifespan, indicating that the maintenance of mitochondrial function is a key target for treating ageing and age-related physiological degeneration.

Long-lived marine mammals have also brought insights for ageing. Investigations of Bowhead whales (*Balaena mysticetus*, maximum lifespan >200 years) have a higher expression of proteasome-associated genes and duplication of 26S proteasome genes [140–142]. Given that gene signatures can be regarded as a driver of evolutionary phenotypic remodelling and gene duplications can increase expression diversity to facilitate an organism's response to new exposome conditions, the alteration of proteasome genes in Bowhead whales could be a key factor for adaptive longevity. The modifications of these proteasome genes may thus allow these whales to maintain protein homoeostasis, beyond the limits of the defensive ceiling contained in other mammals, and eventually, to achieve greater longevity and health span.

Adaptive homoeostasis across the tree of life

Adaptive homoeostasis arising in marine creatures living in extreme environments, as a means of dealing with exposome stressors, such as cold stress, hypoxia and osmotic pressure, may have enabled improved health span and lifespan. Adaptive homoeostasis is defined as '*the transient expansion or contraction of the homeostatic range in response to exposure to subtoxic, non-damaging, signalling molecules or events, or the removal or cessation of such molecules or events*' [135]. In fact, adaptive homoeostasis is a ubiquitous defensive system that has been observed across different taxa, including bacteria [142], yeast [143], nematodes [144], fruit flies [144], mice [145] and man [146]. Adaptive homoeostasis enables biological systems to initiate rapid and transient adjustments for optimal functioning in response to internal and external perturbations, including oxidative stress, inflammation, hypoxia, heat/cold shock, osmotic stress, caloric restriction, mechanical stress and physiological stress [135]. Although various stressors may induce different responsive signalling pathways, accumulating evidence suggest the loss of adaptive homoeostasis is the common pathway manifest in ageing and age-related disorders, particularly in the last third of the lifespan [147] (Figure 3B). Studies show that insufficient adaptive homoeostasis contributes to age-dependent physiological senescence [148], as well as the onset and progression of chronic burden of lifestyle diseases [149–151]. Hence, the decline in adaptive homoeostasis can be seen as a hallmark of ageing process. The essential modulator in maintaining the capacity of adaptive homoeostasis is the NRF2/Kelch-like ECH-associated protein 1 (KEAP1) signalling pathway, that targets hundreds of stress responsive genes, including subunits of the 20S proteasome, genes related to glutathione metabolism, and synthesis of nicotinamide adenine dinucleotide phosphate (NADPH) quinone oxidoreductase 1 (NQO1), by binding to antioxidant response elements (AREs). Thus, activation of the cytoprotector NRF2 could lead to the up-regulation of these stress-protective enzymes to exert a globally cytotoxic protection and stress resistance [152,153].

One of the most evident features of biological ageing (i.e. miles on the clock' as opposed to years since birth) lies in the impaired adaptive homoeostasis response to oxidative stress. *In vitro*, a senescence-dependent decline in activating stress-responsive enzyme (e.g. the mitochondrial Lon protease) has been observed in human lung fibroblasts [154], where young mice adapted well to low levels of oxidants and old mice failed to adapt so [145]. However, it is worth noting that despite the central role of antioxidants and other stress-responsive enzymes in resisting these insults, a chronic or redundant expression of defensive enzymes is not ultimately redemptive at restoring adaptation and may actually exacerbate the situation. By way of example, with respect to NRF2, *in vivo* studies have shown that KEAP1 knockout in mice was embryonically lethal [155] while NRF2 activation aggravated podocyte injury and exacerbated proteinuria in CKD [156]. Although another study has shown that Bardoxolone – an NRF2 agonist – reduced proteinuria by modulating mitochondrial function in mice [157] elucidation of the subtleties of NRF2 activation within the adaptive response is still required. In addition, ageing *per se* is characterised by an elevated baseline adaptive homoeostasis [145]. Compared with short-lived organisms, long-lived organisms have lower baseline stress-responsive enzymes and protein repair activities [137,158–160]. Such preservation of lower baseline adaptive homoeostasis creates a greater distance between the baseline and the physiological ceiling, therefore enhancing their capacity to combat acute and chronic oxidative stress through life. In this regard, one promising strategy to harness the endogenous defence system in combating ageing is to decrease the accumulation of ROS, rather than to overexpress the stress responsive repair system. This accords with Benjamin Franklin's quote "*An ounce of prevention is worth a pound of cure*".

Another feature of adaptive homoeostasis in ageing can be explained by maintenance of proteostasis. In long-lived marine organisms (*vide supra*) proteolytic activity is maintained, either by a low basal proteolytic activity or enhanced proteostasis capacity with intrinsic gene coding. Two major enzymes in intracellular proteostasis are the ubiquitous proteasome and the mitochondrial Lon protease (comprising LonP1 and LonP2). Pomatto et al. [160] have reported

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that the suppression of the subunits of the 20S proteasome (either β1 or β2) shortens the lifespan of fruit flies, signifying the critical role of 20S proteasome in survival. In fact, the decline of the 20S proteasome and consequent protein aggregation are features typically extensively manifested in ARE-related neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases [161]. Another mode for degradation of protein aggregates is through the Lon protease in the mitochondria, which is also diminished in activity in ageing and disease [162,163]. As NRF2/KEAP1 plays a key role in the synthesis of proteasome enzymes, a rapid and transient activation of NRF2, or suppression of inhibitors, such as Bach1 and c-Myc, could ideally minimise and remove the protein aggregates and therefore prevent cytotoxic effects. However, a degree of caution is still needed before the results from several clinical trials on the safety NRF2 activation in the context of burden of lifestyle diseases, are fully understood [152].

Lessons from hibernating species to target the diseasome of ageing

Aside from those with extreme longevity or short lifespan, animals equipped with unique physiology to survive extreme habits could also be used as models to understand the pathophysiology of human diseases. Ground squirrels is an example of small mammal that have been successfully used to prove cardioprotective mechanisms, such as myocardial resistance to ischaemia and suppression of coagulation, during hibernation and phases of torpor [164]. It is also truly remarkable that hibernators endure repetitive cycles of low temperature and reduced cerebral blood flow without disturbances in synaptic activity and neuronal histopathology [165].

For studies of hibernation, bears are of particular interest since they have adapted to a lifestyle of fasting and immobilisation for up to 6 months of hibernation in winter with only mild reduction in body temperature. Bears are spared from complications related to a '*diseasome of ageing*' including CKD, diabetes, CVD, osteoporosis, muscle wasting arteriosclerosis and organ dysfunction [97,166]. It is likely that bears hold key insights for decoding lifestyle-related diseases in humans. In late summer and fall, brown bears develop hyperphagia and gain up to 30% in body mass compared with spring and dramatically switch to starvation during hibernation, while presenting with unchanged insulin sensitivity. Seasonal lipogenesis- and lipolysis-related gene expression changes in white adipose tissue and skeletal muscle are likely to be responsible for this metabolic shift in black bears [167,168]. It has also been suggested that diversity in the gut microbiota during hibernation is involved in these metabolic changes [169]. Indeed, transplantation of bear microbiota collected in summer and winter to germ-free mice, resulted in the mice developing adiposity with normal glucose tolerance [169]. The fact that the bears develop no clinical signs of uraemia and azotaemia is intriguing, given that they have anuria with 90% reduction in kidney blood flow and 50–70% decline in GFR during hibernation [170,171]. The protective metabolic physiology behind this may give insights into how to avoid ischaemia–reperfusion injury during kidney transplantation. Sarcopenia is another typical phenotype in burden of lifestyle diseases associated with ageing. Despite a long period of immobilisation, muscle mass and strength are well maintained in bears during hibernation. Studies have revealed a shift in metabolic profile with a slow-oxidative fibre and mitochondrial biogenesis involved during hibernation [172,173]. Recently, Vella et al. [174] reported that high cortisol levels and AMP-activated protein kinase/peroxisome proliferator-activated receptor γ-co-activator 1α (AMPK/PGC-1α) signalling were key players in regulating the metabolic profile in skeletal muscle and adipose tissue. By acting as an adaptive response to reduced metabolism, mRNA expression of PGC-1α was down-regulated and conserved in hibernating bears [174]. Additionally, in contrast with humans, bears do not suffer osteoporosis and bone loss by being physically inactive during long periods. It has been reported that a hormone known to down-regulate bone resorption, i.e. cocaine and amphetamine regulated transcript (CART), was 15-fold higher in the circulation during hibernation [175]. Moreover, adipose tissue-derived stem cells from brown bears can undergo osteogenic and chondrogenic differentiations and take part in bone regeneration [176]. Albeit not fully deciphered, a mapping of proteome and the dynamics in protein expression can hopefully provide a wholesome picture of pathways involved in the metabolic adaptions in hibernating bears. This can eventually be decoded as novel strategies to combat burden of lifestyle diseases-related ageing [166].

In contrast with the capacity to maintain physical integrity through seasonal metabolic changes, as observed in hibernating bears, Landes et al. [177] used captive grey mouse lemurs (*microcebus murinus*) to show that seasonally related metabolic state transitions may have a fundamental impact on biological age and mortality. Manipulation and increasing the frequency of seasonal cycles caused accelerated ageing phenotypes and increased mortality in these small jungle primates [177]. The authors emphasised that the increased frequency of physiological and metabolic transitions incited by the intensified seasonal fluctuations were the cost of such adaption. Hence, it can be speculated that temporal physiological transitions induced by the external environment are pivotal mediators between the biological and chronological ages of an organism. As such, individuals at the same chronological age that undergo

big metabolic fluctuations are biologically older than those with stable, regular metabolic output. In support, a recent study showed that NRF2-deficient mice showed an increase in ageing-associated metabolites when sent to space [178].

In the Anthropocene, climate change induced seasonal shift, as well as other post-industrial sequelae, such as air pollution, water shortage, deforestation and loss of biodiversity could inevitably have a global impact on human health. Indeed, it is staggering that declines in number of animal pollinators may promote global health burdens from both non-communicable diseases and micronutrient deficiencies [179]. To achieve the United Nations Sustainable Development Goals, a 'planetary health' approach is urgently needed [180], with a focus on human health in relation to the wellbeing of the whole planet and Earth's natural systems. The current pandemic and the cross-species transmission of SARS-CoV-2 is the ultimate call for sustainable human and ecosystem health [126].

Other lessons from the animal kingdom to target the diseasome of ageing

Elephants, like NMRs and bats, are naturally resistant to cancer. Their genome analysis indicates that the elephant has increased cellular apoptotic responses to DNA damage, potentially explained by the multiple copies of the *p53* gene [181]. Lessons can also be learned from animals with an exceptional high risk of cancer, such as the Tasmanian devil (*Sarcophilus harrisii*), which has become endangered due to the spread of a transmissible facial cancer [182]. Elucidating the underlying mechanism of this dreadful cancer can not only give insights for humans, but also it can provide strategies to tackle the lethal threat in this species and therefore help to preserve planetary biodiversity. Another inspiring disease-resistant animal mode is the giraffe (*Giraffa*) that have adapted to a high arterial blood pressure with huge hydrostatic pressure as to supply oxygen to the brain 2.5–3.0 m above the heart. Despite signs of arterial smooth muscle hypertrophy, cardiac, brain and renal damage is fully spared in giraffes [183]. A recent study identified the giraffe *FGFRL1* gene as an outlier compared with other ruminants and when this mutation was inserted into the *FGFRL1* gene in mice significantly less fibrosis in heart and kidneys were observed during hypertension [184]. Thus, an understanding of the protective physiology behind this may yield valuable preventive and therapeutic opportunities for treating complications related to hypertension. Another extreme metabolic profile has been acquired by hummingbirds, a species that possesses the highest mass-specific metabolic rates known among vertebrates [185]. They consume a high-sugar diet to meet the high metabolic fuel requirements, which consequently leads to extreme high blood glucose levels. Also, these birds increase >40% body fat before migration [186]. Despite hyperglycaemia and a seasonally obese status, they do not seem to develop complications of diabetes. Untangling their protective mechanisms could offer solutions for better treatment and prevention of metabolic syndrome. The effects of a glucagon-like receptor agonist from the Gila Monster's saliva should also be mentioned as a possibility to handle obesity and dyslipidaemia [187].

Conclusions

During the last decade, enormous human and financial resources, have been exploited for biomedical research in ageing, ranging from mechanisms to interventions. Though our understanding of the molecular basis of ageing and age-associated diseases is improving, many challenges in the ageing research exist, both in the sense of science and society. To this end it is important to realise: (1) the translational value of identified ageing mechanisms-interventions from standard mice and rat models to humans; (2) the identification of reliable biomarkers for diagnostic and therapeutic purpose; (3) the orientation of drug innovation or repurposing in the treatment of age-related diseases. It is also worth mentioning that while the complex process of ageing does not preclude a plausible simple upstream cause (i.e. a 'silver bullet'), studies of traditional animal models are unlikely to help us fully understand the ageing processes. Hence, it is questionable that the mainstream standardised biomedical approach will help us decode ageing and age-related diseases. We believe that a 'biomimetic' strategy to understand ageing mechanisms will be more insightful as nature has already successfully used evolution by natural selection to achieve many of our desired research goals. In this regard, we should apply a comparative approach integrating knowledge from species living in extreme environments that have developed successful adaptive systems. It should be emphasised that most of the biomimetic examples provided in this review are correlative, which leave causation to be determined. To determine causation and ensure development of safe treatment strategies the utility of molecular genetics, as illustrated by a recent study of giraffes [184], should be part of biomimetic research. As discussed above, it will be resourceful to study the particularities and comparative patterns among organisms featured with longevity, short lifespans and unique metabolic profiles. Based upon what nature can teach, we have highlighted several common causes of ageing that are worth renewed focus in the study of physiology of ageing and age-related disease, such as the diet-microbiome-health axis,

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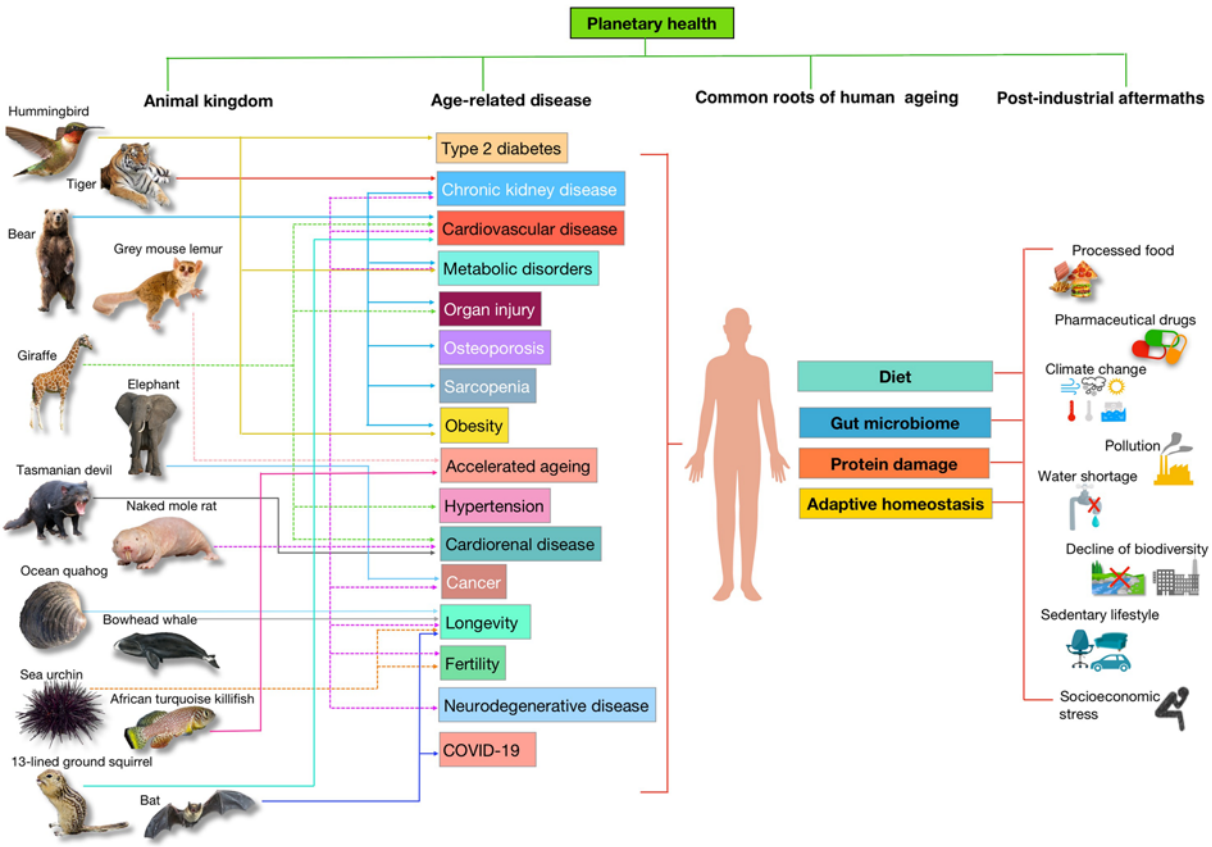

Figure 4. Biomimetic lessons, human ageing and planetary health

We propose a biomimetic and natural sciences approach to better understand processes of ageing in burden of lifestyle diseases. This requires a comparative and evolutionary strategy to integrate knowledge from species living in extreme environments that have developed successful adaptive systems. Biomimetics can provide lessons' examples from the differences and commonalities between organisms in the natural world, endowed with exceptional longevity, or short lifespan, as well as unique metabolic profiles that have been evolved over the course of natural selection. Based upon lessons from nature, we have highlighted several common causes of ageing that are worth renewed focus in the understanding of ageing and age-related disease, including the diet-microbiome-health axis, oxidative protein damage and adaptive homoeostasis. Humans are exposed to a spectrum of post-industrial aftermath including global climate change, industrially processed food, pharmaceutical drugs consumption, water shortage, pollution, loss of biodiversity, sedentary lifestyle and socio-economic stress. To survive in a rapidly changing environment, humans rely upon evolutionarily physiological adjustments to adapt these challenges. However, the evolution of adaptive systems to cope with a rapidly changing anthropogenic environment are too slow to cope. As a result, humans are imposed to all these post-industrial factors that may directly or indirectly stimulate '*diseasome of ageing*' through diet, microbiome, protein damage and adaptive homoeostasis. A '*planetary health*' approach is urgently needed, with a focus on human health in relation to the wellbeing of the whole planet, including animals, and Earth's natural systems.

oxidative protein damage, adaptive homoeostasis and planetary health (Figure 4). A '*biomimetic alliance for better health*' with collaborative research among natural scientists and including different disciplines, from zoology, ecology, biology and anthropology coupled with such disciplines as medicine and sociology, could contribute to not only better understanding of diseases but also a better sustainable environment with long-term utility (Box 1).

Box 1 Glossary

Antagonistic pleiotropy: At least one of the traits controlled by a gene is beneficial to the organism's fitness early on in life and at least one is detrimental to the organism's fitness later on due to a decline in the force of natural selection.

Anthropocene: Proposed geological epoch dating from the beginning of significant human impact on our planet's ecosystems.
Biomimetics: Emulation of the models, systems and elements of nature for the purpose of solving complex human problems.
Diseasome: An approach to conzeptualise gene–disease relationships.
Disposable soma theory: A theory stating that organisms age due to an evolutionary trade-off among reproduction, growth and DNA repair maintenance.
Exposome: The measure of all the exposures of an individual during the lifetime and how such exposures relate to health.
Inflammageing: A new concept that refers to the role of inflammation in ageing processes.
Metagenomics: The study of genetic material from environmental samples.
Methylome: Nucleic acid methylation modifications in a particular cell or in an organism's genome.
Proteostasis: A dynamic regulation of a functional and balanced proteome.

Competing Interests

P.S. is on scientific advisory boards of REATA, Baxter, Vifor and AstraZeneca. L.S. receives grants from Nattopharma ASA and is consultant for IDS. P.G.S. is funded by awards from 4D Pharma, Constant Pharma and acts as a consultant for Mars UK.

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Abbreviations

ARE, antioxidant response element; ATP, adenosine triphosphate; CKD, chronic kidney disease; CVD, cardiovascular disease; FGF23, fibroblast growth factor 23; FMO3, flavin-containing monooxygenase 3; KEAP1, Kelch-like ECH-associated protein 1; mTOR, mechanistic target of rapamycin; NMR, naked mole-rat; NRF2, nuclear factor erythroid 2-related factor 2; PAG, phenylacetylglutamine; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCFA, short-chain fatty acid; TMA, trimethylamine; TMAO, trimethylamine N-oxide.

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