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Allostatic load and ageing; linking the microbiome and nutrition with age related health.

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Abstract

Ageing is a process of decline in physiological function and capability over time. It is an anticipated major burden on societal health-care costs due to an increasingly aged global population. Accelerated biological ageing is a feature of age-related morbidities, which also appear to share common underpinning features, including low-grade persistent inflammation, phosphate toxicity, diminished Nrf2 activity, a depleted metabolic capability, depressed mitochondrial biogenesis and a low diversity gut microbiome.

Social, psychological, life-style and nutritional risk factors can all influence the trajectory of age-related health, as part of an individual's exposome, which reflects the interplay between the genome and the environment. This is manifest as allostatic (over)load reflecting burden of lifestyle/disease at both a physiological and molecular level. In particular, age-related genomic methylation levels and inflammatory status reflect exposome differences. These features may be mediated by changes in microbial diversity. This can drive the generation of proinflammatory factors, such as TMAO, implicated in the 'diseasome' of ageing. Additionally, it can be influenced by the 'foodome', via nutritional differences affecting the availability of methyl donors required for maintenance of the epigenome and by provision of nutritionally derived Nrf2 agonists. Both these factors influence age related physiological resilience and health. This offers novel insights into possible interventions to improve health span, including a rage of emerging senotherapies and simple modifications of the nutritional and environmental exposome. In essence, the emerging strategy is to treat ageing processes common to the diseasome of ageing itself and thus preempt the development or progression of a range of age related morbidities.

Perspective

- Age related health is a growing global concern and an emerging view in the field is to treat ageing like a disease.
- We have proposed that a 'diseasome of ageing' reflects allostatic (over)load as a burden of life style and that age related diseases share common underpinning features. This suggests that treating ageing via senotherapies, rather than an individual disease, may be of real benefit.
- Nutritional and microbiome differences are emerging as key determinants of age related health and resilience. Novel senotherapies designed to modulate a 'Foodome' and thus the microbiome, hold great promise for improving health span

Introduction

What is ageing?

Ageing is a process, not simply a collection of morbidities during the final decades of our life. It has been described as an accumulation of deficits taking place in each individual in different ways with specific organ systems varying in the rate at which these deficits accumulate[1]. In essence, ageing leads to a segmental and progressive loss of physiological function and physical capability over time, resulting in relative physiological frailty and loss of resilience[2 3 4 5 6]. It is actively modulated by distinct biochemical pathways and has been characterised by a series of molecular and cellular hallmarks, which are common across taxa[7]. These hallmarks comprise genomic instability, telomere attrition, epigenetic dysregulation, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication.

Human ageing is gradual, complex and highly heterogeneous. It starts at birth, with differing trajectories in relation to health across the life course for different individuals. As such, there is no 'gold standard' for determining what constitutes normative ageing. In its latter stages in man, it is often characterized by a cluster of burden of life style diseases typified by low-grade persistent inflammation[8]. By 2020 people aged 60 years and older will outnumber children younger than 5 years, and by 2050, the over 60s are anticipated to outnumber those younger than 14 years and constitute 2 billion people worldwide (United Nations, Department of Economic and Social Affairs, Population Division (2015). *World Population Ageing 2015* (ST/ESA/SER.A/390)). As such, this changing demographic profile is an anticipated to generate a major global health problem, bringing with it significant associated societal health-care costs. The associated cost in non communicable diseases (NCDs) is expected to total $47 trillion in the decades spanning 2010-2030.[9] Significantly, as human lifespans have been extended over the preceding centuries, extension in health span (years of healthy living) has not kept pace with this. An ability to understand and separate natural

ageing processes from the processes specific to individual diseases and to morbidities, is therefore required to understand the heterogeneity observed in the processes of age-related physiological dysfunction in individuals of the same chronological age. This also is apparent in the predisposition to and progression of, age-related morbidities.

Accelerated biological ageing (i.e. ‘miles on the clock’), is also a feature of age-related morbidities, where disease-specific processes are layered upon dysregulated ageing processes. This thesis has been extensively exemplified for the renal system, where chronic kidney disease (CKD), has been classified as a clinical model of accelerated ageing[10]. Typically, it manifests with an increased frequency of associated age-related complications, such as vascular stiffening, osteoporosis, muscle wasting, depression, cognitive dysfunction and frailty [10,11].

A growing body of evidence has revealed that social, psychological life-style and nutritional risk factors can all influence the trajectory of age-related health and age-related morbidities, such as CKD, by acting either independently, cumulatively, or synergistically with an individual’s genetics, and in particular epigenetics, thus determining health span[12,13]. Recently, evidence has emerged indicating that epigenetic regulation of nutrient sensing pathways and nutritional differences tied to socioeconomic position (SEP), can differentially affect the ageing process; in particular age-related genomic hypomethylation and inflammatory status [12,12].

Ageing in humans is associated with chronic inflammation (also known as ‘inflammageing’), which is itself a proven risk factor for morbidity and mortality in the aged, along with phosphate toxicity, depressed Nrf2 activity[14,37], and acquisition of a low diversity gut microbiome with depleted metabolic capability and depressed mitochondrial biogenesis. A study in 9 different diseases, isolated from 11 rodent disease model tissues, not only suggests that inflammation is a key driver in a cluster of different diseases, but also pinpoints potential targets for intervention in various common diseases[15] .

The aetiology of inflammageing remains undetermined. However, the loss of anti-inflammatory taxa within the gut microbiome has also been associated with inflammageing[15]. Intuitively, the burden of aged (senescent cells) contributes to a pro-inflammatory environment via a senescence associated secretory phenotype (SASP). However, when assessed in epidemiological cohorts, less than 15% of the level of inflammation in the circulation can be explained on the basis of cellular ageing[16,13]. As the gut microbiome changes with both chronological and biological age [17], one novel hypothesis that has gained much traction is that the microbial metabolite trimethylamine N-oxide (TMAO) is central to the inter-relationship between inflammageing, health span and the age-related epigenome. This pro-atherogenic and pro-inflammatory compound is derived from microbial metabolism of phosphatidylcholine, L-carnitine and lecithin, which are found in red meat, fish and eggs, so providing a mechanistic link between nutrition and ageing and the epigenome[2]. Production of TMA (the precursor to TMAO) has been reported as greater in frail older people that consumed a restricted diet than healthy older people, in a manner that could be linked to differences in their microbiome coding capacity[18]. It has recently been demonstrated that the gut microbiome serves as an important mediator of arterial dysfunction related to ageing and oxidative stress[18]. TMAO has also been linked to endothelial cell senescence, vascular and brain ageing and cognitive impairment. There is also a further emerging role for the microbiome in epigenetics through production of butyrate, a short chain fatty acid produced in the intestinal lumen by bacterial fermentation, which inhibits histone deacetylases[19] and so influences chromatin regulation. Intuitively, this will impact on physiological frailty as a direct consequence. Such a hypothesis is supported by the observations in murine models that indicate some benefits of caloric restriction are mediated by the gut microbiome, including mitigation of muscle atrophy [20,21].

Measuring wear and tear and the burden of lifestyle.

Allostatic load was a term first coined by McEwen and Stellar to describe the ‘wear and tear’ on the body as a result of exposure to chronic stress. In its original formulation, this was ascribed to activation of the Hypothalmic

Pituitary Adrenal (HPA) axis via increased levels of Corticotropin-Releasing Factor (CRH) and altered cortisol production, leading to impaired immune cell activity, elevated inflammatory responses, activation of the sympathetic nervous system and increased blood sugar levels [22].

In more recent times, this concept has been extended to implicate allostatic (over)load as a contributory factor in diseases associated with ageing and, or lifestyle factors [3,8,24], such as cardiovascular disease, diabetes, cancer and CKD [6,8,9,25]. These can be regarded as constituting a 'diseaseome' of ageing, underpinned by a range of common features, typified by dampened Nuclear factor erythroid 2-related factor 2 (Nrf2) expression [6,26,37].

Nrf2 regulates a battery of over 350 cellular stress defence genes and has a role in stress resistance which may be directly linked to species longevity and health span. Indeed, rodents typically show decreasing Nrf 2 activity with increasing age.[23] Furthermore, differences in rodent longevity correlate with higher levels of Nrf 2 activity, linked directly to species differences in Kelch-like ECH-Associated Protein 1 (Keap1) and β-transducin repeat-containing protein (βTrCP) regulation of Nrf2 activity, which are lower in long lived species.[24]

However, Nrf2 has been regarded as a double-edged sword [25]and elevated Nrf2 expression have been detected in cancer tumours [26] and over-activation has been reported to promote oncogenesis [27]. Consequently, a "sweet-spot" for Nrf2 activation currently needs identification.

Inherent in the concept of allostasis, is the interplay between the genome and the environment. The latter constitutes an 'exposome' (Figure 1) for the individual, comprising psychosocial factors, nutrition, lifestyle and physical environment[28-29]. How such interactions lead to DNA damage or physiological dysfunction is not well understood. The epigenome, however, may provide a means for dynamic response to environmental changes. Recent research on

a number of different fronts has provided insight into how this may be achieved.

A slew of evidence has indicated that SEP is one such factor that can influence ageing trajectories within humans[16,28,30,31,32]. Those at lower SEP exhibit features of accelerated ageing, including shorter mean telomere length, genomic hypomethylation and elevated levels of circulating pro-inflammatory cytokines. While the latter is in keeping with the presence of more senescent cells and an associated SASP, inter-individual variation in biological age explains less than 15% of this inflammatory burden[16]. Epigenetic differences, namely differences in genomic DNA methylation content explain only 11% of this inflammatory burden[13] . Consistent with this scenario, longitudinal analyses have indicated that inflammation and not biological age determined by measurement of telomere length, explains successful ageing in supercentinarians[33].

Recent observations have indicated that a transcriptomic signature for age-related allostatic load may also be an informative approach to assess health span. This also can provide a means of measuring physiological resilience [38,] based around IFN gamma signaling networks and the repression of dsRNA viruses (e,g. LINEs) [34]. Use of renal allografts to provide a source of healthy tissue whose function can be tracked longitudinally has proven to be a rich source of information on the molecular and cellular requisites of healthy age-related physiological function. Ostensibly healthy organs, which fail to work immediately following transplant (described as exhibiting Delayed Graft Function (DGF), as opposed to immediate graft function (IGF) appear to exhibit molecular features consistent with allostatic overload. Significantly, organs exhibiting poorer function display elevated levels of CDKN2A/p16ink4a and elevated expression of LINE related transcripts, consistent with accelerated biological age[35,36]. As such, they show a change in transcriptional amplitude in response to stress for genes involved in IFN gamma signaling networks an order of magnitude greater than organs

exhibiting IGF. Additionally, these genes are hypomethylated in comparison to their state in organs that work immediately. Notably, the signature gene set involved shows similar properties in a range of other renal pathologies, consistent with allostatic load also being an underpinning feature in these dysfunctions.

The response of these organs to their exposome is complex to analyse. Both IGF and DGF organs exhibit a similar transcriptional response to transplantation stresses, yet respond differently to the stress of encountering a new immune system within the recipient. Organs with high biological age show both decreased physiological function and less resilience in this context. As the latter appears to be mediated by IFN gamma signaling, it indicates how both immune related stress and age related biological resilience are interlinked. Notably, restoration of physiological and transcriptional homeostasis takes longer in organs exhibiting DGF and may thus constitute a direct indication of a pre-existing lack of resilience. Understanding resilience and how this interplays with inflammatory processes and ageing is not straightforward and requires a deeper understanding of how our exposomes interplay with the epigenome of ageing.

Food and ageing

All disease begins in the gut — **Hippocrates**.

One key feature of our exposome that has shown consistent prevalence is nutrition. A link between nutrition (i.e. the “foodome” including the individual diet, its ingredients and their chemical structure), particularly dietary restriction, and both age-related health and longevity has been consistently described across taxa,[37], since the early 1900s, although its mechanistic basis is still not fully understood. What is also becoming more apparent is that genetic heterogeneity appears to play a major role in the responsiveness of individuals to a particular dietary intervention. That is, a specific dietary intervention that may improve health outcomes for one individual (or genetic

background) may not generate the same magnitude of effect in another individual (or genetic background)[38].

While dysregulated nutrient sensing is postulated as a key component of the hallmarks of ageing, in mammals there may be additional, related features, such as hyperphosphataemic generation of calciprotein particles, (CPPs) and changes in microbiota[6,10]. Hyperphosphataemia appears to be a fundamental component of age-related health in mammals. The negative correlation between nutritionally derived serum phosphate levels and mammalian lifespan is exceptionally strong[6]. Indeed, diseases of accelerated ageing, such as CKD and progeroid syndromes, like Hutchinson's Guilford's, are characterised by elevated levels of serum phosphate[2,6]. The mechanistic basis of this correlation derives from the generation of CPPs. These nanocrystaline particles are the product of Fetuin A, a circulating inhibitor of vascular calcification and calcium phosphate. CPPs enable phosphate homeostasis in the circulation however in excess they are endocytosed and the calcium released intracellularly, causing cytotoxic effects and mitochondrial dysfunction. In population studies, nutritionally derived phosphate correlates with accelerated ageing, lower SEP and an imbalanced diet, namely over frequent consumption of red meat. Significantly, red meat consumption provides a mechanistic basis for affecting the microbiota and their contribution to age related health. Red meat is not only a source of phosphate, but contains carnitine, which acts as a substrate for TMA production by gut microbes[6]. TMA is a precursor for TMAO production by the liver, which is a potent inflammatory agent. TMAO has been implicated in the diseasome of ageing and mortality [6,10], including CVD, CKD and neurological disorders[39],[39]. How TMAO levels changes with normative ageing and differing exposome features, such as SEP remains to be determined.

Those at low SEP typically have imbalanced diets and low intake of fruit and vegetables. This is pertinent to recent observations indicating that diets lacking sufficient fruit and vegetable intake lack sufficient phenolic acids that can be converted by key gut microbes to alkyl catechols [8,40,40] . The latter are potent Nrf2 agonists and thus are important mediators of cellular stress

defenses, in particular against oxidative damage[8]. Significantly, alkyl catechols, such as fisetin and quercetin, have been identified as potent senolytic agents, able to induce apoptosis in senescent cells[41]. Elimination of senescent cells by a range of senolytic agents has already been demonstrated to increase lifespan and health span in mice [42].

Considerations for Interventions

"If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health." — **Hippocrates**.

Interventional strategies designed to improve health span are extremely exciting and hold great promise for alleviating the effects of the diseasome of ageing (Figure 2). As allostatic load is cumulative and systemic, focal interventions, such as the use of senolytics, may not always be appropriate. Non-senolytic or combinatorial senotherapies may thus be merited, especially outwith the setting of a tightly controlled clinical environment and in the complexity of a human exposome. Senolytic agents appear exceptionally effective in pre-clinical models of ageing[42]. A number of immediate questions remain be considered, though their address, it must be stated, would not preclude the clinical translation of these agents. How for example, will senolytics combat the effects of hyperphosphataemic toxicity? How will they address the effects or allostatic overload? How, will they affect the microbiome? How will they function in a multimorbid milieu? Will they function equivalently across the life course? Should they be given alone or in combinations?

Human cells have finite replicative lifespans. Indeed, even stem cells can be exhausted both in terms of replicative potential and number over the life course. Will senolytics accelerate this process and leave older organs with tissue or cellular insufficiency, despite removing senescent cells? If so, will this exacerbate physiological decline? [43]. Murine studies argue against this, but life course treatment with a drug in mice is not wholly equivalent to

intervention in an aged human displaying multi-morbidity, where repair potential may be limited. Thus, when and where in the life-course to administer any intervention will be a critical factor. The same considerations are likely to apply to the composition of any nutritional interventions over the life span. Low protein intake during middle age, followed by moderate to high protein consumption in old adults may be optimal for health span and longevity. It has already been demonstrated that low protein intake during middle age followed by moderate to high protein consumption in old adults may optimize longevity[44]. It is notable that recent comparisons of senescent cell accumulation in the skin and immune system of aged individuals did not show a strong correlation, indicating that there limited evidence for a link between skin- and immune-senescence within individuals[45].

Other interventions to address lack of physiological resilience, in addition to removal of senescent cells by senolytics, fall under the aegis of senotherapies. These include modification of elements of the exposome, such as enhancement/maintenance of the epigenome via nutrition[44], or via live therapeutics to restore optimal diversity to the microbiome[17], and more intuitive salutorial interventions (i.e interventions designed to improve health through manipulation of physical environments) to enable a lifespan in a more benign environment[27,30], as well as more traditional enhancement of stress defenses, such as via Nrf 2 agonists[37] .

Development and implementation of any such strategies is not as straightforward as it seems. Typically, translation outside a specific clinical context is not easily achievable by a single discipline and may require multiple cross-disciplinary interactions to develop, administer and track effects. Critically, it will require compliance from any patient or public groups. However, given the major problems ageing brings to society and the exciting developments in Geroscience, a more holistic approach to tackle age-related health looks to promising.

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Figure 1: The Exposome

Legend: interactions between an individual's exposome and their genome/epigenome results in differential accumulation of allostatic load and thus healthspan. Factors key to this include socioeconomic position (SEP), lifestyle and behaviour, psychosocial and physical environments and nutrition,

Figure 2: How the Foodome impacts age related health

Legend: An imbalanced or suboptimal Foodome results in loss of microbial diversity, phosphate toxicity and facilitates development of the diseasome of ageing. An optimal foodome is a key component in developing and enhancing senotherapeutic efficacy,