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Circulating markers of ageing and allostatic load: A slow train coming ☆

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ABSTRACT

Dealing with the growing burden of age-related morbidities is one of the greatest challenges facing modern society. How we age across the lifecourse and how psychosocial and lifestyle factors interplay with the biology of ageing remains to be fully elucidated. Sensitive and specific biomarkers with which to interrogate the biology of the ageing process are sparse. Recent evidence suggests that non-coding RNAs are key determinants of such processes and that these can be used as potential circulatory bio-markers of ageing. They may also provide a mechanism which mediates the spread of allostatic load across the body over time, ultimately reflecting the immunological health and physiological status of tissues and organs. The interplay between exosomal microRNAs and ageing processes is still relatively unexplored, although circulating microRNAs have been linked to the regulation of a range of physiological and pathological processes and offer insight into mechanistic determinants of healthspan.

Contents

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1. Introduction

Physiological, cellular and psychological changes over the life course inevitably lead to the impaired function of an organism [1]. These changes are currently considered to be leading risk factors for the development of a range of morbidities. As the global population distribution shows a growing preponderance of elderly individuals, by 2050 those aged over 65 years are expected to outnumber children below 15 years of age (http://www.who.int/world-health-day/2012/toolkit/background/en/). This shift will bring with it an elevated burden of age-related disease and will represent a major drain on health care resources worldwide.

Conceptualization of the underlying mechanisms of ageing has identified nine hallmarks [1] comprising: genomic instability, telomere shortening, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, senescence, stem cell exhaustion and alterations in intercellular communication. However, not all of these hallmarks have been validated in clinical studies. Although research into the mechanisms of ageing processes is very dynamic there is still a pressing need for better understanding of ageing throughout the lifecourse. This is pertinent in the context of age-related morbidities and their relationship with psychosocial, nutritional and lifestyle factors, as well as with genetic and epigenetic determinants of ageing [2,3]. It still remains to be determined whether such factors act cumulatively, interactively or individually, in predisposition and progression of age related disease. We will now discuss how these factors might interplay and how they might regulate ageing processes across organ systems through the life course.

Many age-related morbidities share an underlying pathophysiological mechanism linked to ageing processes and thus present with a premature ageing phenotype [4,5]. Such phenotypes can be a direct result of disruption of cellular homeostasis, which can be further accelerated by both environmental factors and intrinsic metabolic activity leading to the generation of oxidative stress/damage, endoplasmic reticulum stress and mitochondrial dysfunction [3,6]. The cumulative result of this burden of stress and the consequent adaptation to maintain and restore physiological homeostasis through physiological or behavioural changes has been termed allostasis [7]. Constant activation, or overload of allostatic mechanisms, results in systemic problems. Allostasis adaptation in chronic age-associated diseases, for example, may result in an increase in oxidative stress, an increase in the activity of innate immunity and constant low-grade inflammation [2]. This is in keeping with the hypothesis that cellular dysregulation is a catalyst for accelerated ageing and can be considered a disease-causing agent [8].

A direct link between increasing allostatic load and all-cause mortality has been established in longitudinal studies [9]. Links between allostatic load and specific health outcomes or disease (cardiovascular disease, diabetes, osteoporosis, chronic kidney disease and chronic obstructive pulmonary disease), as well as a general decline in physical and cognitive function, have also been established [4, 10–13]. Furthermore, the occurrence of age-related disorders has also been linked with the dysregulation of normal immune responses involved in the clearance of resident senescent cells within tissues. These cells are characterised by loss of proliferative function, resistance to death signals and promiscuous gene expression profiles [14], allowing their accumulation in aged organs/organisms. This situation has been observed across a broad range of degenerative disorders, including progeroid mice and also in cancer cells, suggesting that the selective removal of senescent cells *via* immune surveillance might be associated with delayed age-related deterioration [14–16].

2. Biomarkers of ageing

The ageing process is characterised by the presence of high inter-individual variation between individuals of the same chronological age; therefore there is an urgent need to identify informative biomarkers of ageing (BoA) to monitor the underlying molecular changes associated with ageing. The American Federation for Aging Research (AFAR) have proposed criteria for BoAs for ageing research; these state that a BoA must: (i) predict the rate of ageing and be a better predictor of lifespan than chronological age; (ii) monitor a basic process that underlies the ageing process, not the effects of disease; (iii) be able to be tested repeatedly without harming the individual; and (iv) be measurable in humans and in laboratory animals [17].

A sequitur for any valid BoA, under these criteria, would be that it shows a statistically significant association with a measure of health or organ functional capacity and chronological age. Furthermore, such a relationship must be statistically significant for all three pairwise associations. This is critical when applying BoA in the context of morbidities; features related to a specific morbidity must be delineated from those of the ageing process *per se*. Consequently, there is a paucity of biomarkers fulfilling these criteria in any robust fashion.

Recent approaches to identify more robust biomarkers have focussed on using renal allografts as a source of healthy tissue whose function can be followed longitudinally and in which context BoA can be compared 'head to head'. This approach initially identified CDKN2A expression as a robust biomarker, outperforming telomere length (a more traditional biomarker of ageing) in explaining inter-individual variation in renal function with age. Notably, many putative BoA identified in studies in model organisms failed to meet the AFAR criteria in the human specific renal system, indicating that they were more intimately linked to disease processes rather than ageing [18–21].

More recently, epigenetic analyses of the ageing process has led to the identification of a small number of micro RNAs (miRNAs), regulating the CDKN2 locus and associated with biochemical pathways implicated in regulating organismal longevity [22]. Critically, these miRNAs regulate common cellular metabolic pathways linked to nutritional stress, DNA

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repair processes, autophagy and protein synthesis. Moreover, these biochemical functions are common across taxa, indicating the substantive biological commonality in fundamental ageing processes. These observations are in keeping with the original mitochondrion/telomere nucleoprotein complex/ribosome (MTR) postulate of Shiels and Davies [24], whereby cellular ageing processes are linked tightly to macromolecular damage responses, energy availability and utilization [23,24]. The question remains, however, as to how one can extrapolate markers of cellular ageing to the ageing of the whole organism and whether these markers remain reflective of allostatic load, or reflect ongoing aspects of more local disease processes? This is particularly pertinent in the context of segmental ageing, where individual genes, such as those that give rise to unimodal progerias (*e.g.* WRN, Lamin A, BLM [25,26]) or genetic pathways that extend lifespan (*e.g.* mechanistic target of rapamycin [mTOR]) are likely to have non-uniform and non-cell-autonomous effects on the decline in tissue and organ function with increasing age. By extension, this implies that there is a direct interconnection between separate systems for tissue/organ and organismal ageing. In this context, regulation of circadian rhythms at a cellular, tissue and organismal level may provide an appropriate paradigm [2,3]. Of note, under the aegis of such a hypothesis, interventions to combat age-related decline in organ and tissue function might have unintended adverse consequences. By way of illustration, the use of caloric restriction to improve healthspan, for example, has resulted in a reduction in bone mineral density [27].

3. Exosomes, ageing and allostatic load

How ageing in one organ spreads its effects across the whole body and contributes to organismal allostatic load is an area of intense investigation. The BoA signature of age-related healthy renal function points towards epigenetic regulation as being a key feature of such a process. This is pertinent to the capacity of extracellular secretory vesicles (ESVs) to impact on non-cell autonomous ageing processes, which may be coupled with autophagy. A key class of such ESVs subject to much investigation are exosomes.

Exosomes are small, extracellular secretory vesicles (30–100 nm) containing a membranous lipid bilayer and originating from intercellular endosomal compartments, the contents of which vary significantly between cell types [28–30]. These have been demonstrated to facilitate intercellular communication, including stimulation of immune responses to promote wound healing [31] and may have a role in maintaining tissue homeostasis. Exosomes have also been postulated as a therapeutic vehicle to treat diseases of ageing, such as diabetes [32,33], cardiovascular disease [34], Alzheimer's disease [35] and chronic kidney disease [36–38].

Interestingly, altered miRNA profiles and lysosomal profiles have also been found in exosomes collected from subjects diagnosed with diseases of ageing, such as Parkinson's and Alzheimer's diseases [39,40]. The presence of misfolded proteins in exosomes, particularly prion-like proteins, has also been demonstrated in other neurodegenerative diseases including Creutzfeldt-Jakob disease [41].

There is a growing body of evidence demonstrating modulation of exosomal, contents by stress induction [42], which may impact the lifecourse, and therefore will be associated with allostatic load and driven by ageing. These modulators include both biophysical and metabolic stressors, such as nutrient deprivation [43], heat [44], hypoxia, or irradiation [45]. Critically, following on from a thesis that stress accelerates ageing and that early onset of diseases of ageing result from this, exosomal contents are modified by several of the “stress” hormones. For example, corticosteroid can induce myocilin (MYOC), which is linked to glaucoma [46]. Glucocorticoid stimulation can also increase the levels of specific miRNAs namely miR-23a [47] and miR-182 [48] within exosomes without influencing the secretion levels of exosomes overall. These miRNAs have also been linked to regulation of FOXP3 and calcineurin signalling in muscle atrophy and muscle wasting.

These observations are pertinent to psychosocial and lifestyle factors, which are both associated with the accrual of allostatic load and the acceleration of ageing [4,49–51] and may link accelerated ageing with poor nutrition and inflammation, both at a cellular level and at a general population level.

This association with inflammation and nutrition has been further strengthened by the observations that hyperphosphataemia, a proven cause of accelerated ageing in mammals [52–55], is nutritionally driven. Furthermore, it is linked to accelerated ageing and early onset disease in man and associated with the frequency of red meat consumption in a setting of social deprivation [56]. The importance of phosphate in the accelerated ageing phenotype can be linked to vascular calcification and formation of cytotoxic calciprotein particles (CPPs), a common feature of many metabolic and accelerated ageing syndromes. Since phosphate activates the ACT/mTORC1 blockade of mTORC1 may have therapeutic potential for premature aging-like symptoms [57]. Vascular calcification, a common feature in the ageing process, can be counteracted by Fetuin A, a putative marker of ageing, characterised by reduced concentration in a number of pathologies associated with accelerated ageing including chronic kidney disease and cancer [58–60]. Recent *in vivo* and *in vitro* results also suggest that lamin A plays an important role in the process of premature vascular ageing [61]. Recent studies investigating the role of senescent associated phenotype (SASP) in smooth vascular cell ageing has revealed that changes in expression and contents of exosomes are associated with vascular calcification [62]. Exosomes generated from senescent vascular smooth muscle cells are altered in terms of the proteins, miRNAs and minerals they contain [62]. These exosomes directly drive the disease pathology, demonstrated by blocking of exosome secretion and subsequent amelioration of pathology [63].

The link between ageing, inflammation and nutrition is also pertinent to non-coding RNA regulation of healthy ageing processes [64]. Recently, changes in both circulating and membrane marker levels, used to classify a broad range of

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extracellular vesicles (EVs) including exosomes, have been observed in association with age-related structural and functional changes in solid organs, [65]. In this context, the exosomal secretome from senescent cells has been hypothesized as a potential contributor to age-associated inflammation and decline in immune function [66–72]. This, when coupled with DNA damage response (DDR) signaling, has been implicated in the generation of pro-inflammatory senescence-associated secretory phenotype (SASP). The relative contribution of the SASP to age-related inflammatory status, while intuitive, has proved to be modest in general population cohort studies, where BoAs, such as telomere length in circulating leukocytes, have explained less than 10% of inter-individual variation in inflammatory status [51,73–75].

The contribution of exosomal non-coding RNAs in this context remains to be proven, but might well help to explain a greater proportion of this inter-individual variation in the inflammatory status or a correlative predisposition to age-related diseases [72]. Additionally, it may help to explain how exosomes are able to generate a pro-tumor environment that is essential for carcinogenesis through maintenance of an oncogenic niche and modulation of immune function [76].

4. Conclusions

Modulation of the ageing process over the lifecourse is complex, comprising advertent regulation of a range of biochemical processes *via* psychosocial, lifestyle and nutritional factors in association with genetic and epigenetic determinants of ageing. The cumulative result of their actions is morbidity and eventual mortality. A range of biomarker studies, as we have described, indicates that the accumulation of senescent cells results in decreased tissue and organ function, increased allostatic load and accompanying inflammatory burden. The epigenetic component, which has the capacity to transmit both intergenerationally and transgenerationally, is particularly intriguing, as it may act as the body's hamartia in facilitating the spread of allostatic load across the whole organism. Consequently, this process may, through the transmission of exosome non-coding RNAs, help regulate niches for the progression and spread of disease as well as providing system-wide cues for allostatic responses. The expression, composition and function of exosomes are modulated by a range of stress hormones enabling a dynamic response to environmental triggers at a cellular level. As such, their modulation may serve as an excellent target for future therapeutic interventions in reducing age-related morbidities and improving health span. It is also likely that better understanding of the biology of exceptionally long-lived animals, such as naked mole rats, which possess a 30 year lifespan, will contribute to better understanding of ageing processes [5].

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