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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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