EDITORIAL ARTICLE

The current obsession of age-related diseases and the race in identifying effective treatments and preventive interventions

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Balistreri CR. The current obsession of age-related diseases and the race in identifying effective treatments and preventive interventions. J Pathobiol Physiol. December-2017;1(1):2.

Today, the phenomenon of ageing characterizes our populations, causing a large impact in our countries, principally for the growing increase of both incidence and prevalence of not evolutionarily programmed diseases, the age-related diseases (ARDs), including cardiovascular diseases (CVDs), neurodegenerative diseases, metabolic diseases (i.e. insulin resistance, diabetes and metabolic syndrome), and cancer [1]. By 2030, approximately 20% of the population will be aged 65 or older [2]. In this age group, ARDs, and particularly the CVDs, will result in 40% of all deaths and rank as the leading cause [3]. On the other hand, the most important determinant of cardiovascular health is person's age, and precisely the person biological age, as recently suggested in our studies [4,5]. Accordingly, biological age seems clearly to be a better predictor of vascular risk rather than chronological age [4,5]. This concept is supported by key assumptions that peripheral blood leukocyte telomere content accurately reflects that of the vascular wall and its decrease is associated with premature vascular disease [4,5]. In fact, telomere shortening is currently considered the best ageing biomarker, but is also a predictor for ARDs, including CVDs [4,5]. A progressive impairment of the cellular processes (i.e. mitochondrial dysfunction, telomere attrition, genomic instability and epigenetic alterations; see Fig.4 of review from Balistreri and co-workers [6]), regulating cardiac and vascular homeostasis, characterizes the vascular ageing, causing as long term effects, endothelium dysfunction, medial degeneration, vascular remodeling and dysfunction [7,8]. They represent pathological entities significantly associated with the onset of a large CVD panel, but also of other ARDs. Endothelium dysfunction is the first pathological condition associated not only with all CVDs, but also with other ARDs, being the endothelial cells (ECs) components of the stroma of all tissues, organs, and the niches of adult stem cells (ASCs) [9]. This last favors the ASC senescence and increases their susceptibility to neoplastic transformation and onset of cancer (i.e. myeloid leukemia), and it temporally reduces their ability to self-repair and regeneration of tissues and organs by facilitating the onset of degenerative diseases, such as CVDs and neurodegenerative diseases [6,9,10].

This current reality of our countries, it is becoming an obsession for both scientific community and institutions/organizations. The first has focused its goal in understanding the biology of ageing and ARDs, and to translate the potential scientific insights obtained into effective interventions, in order to improve the health in old ages and to retard and/or to delay the onset of ARDs. The second are promoting health promotion's programs. In particular, among the researchers is strong opinion that the solution, to counteract the ARD onset has the roots in the cellular mechanisms and evolutionarily conserved signaling pathways of the cells, as the stem and progenitor cells (i.e. hematopoietic and no-hematopoietic stem cells and their progenitors), involved in the genesis of all tissues, organs and

systems [11]. This is in accordance to the innovative concepts of fetal programming-imprinting based on theory popularized, for the first time in 1989, by Dr David Barker, and defined as "the fetal origin of adult disease (FOAD)", as stressed and emphasized in our recent papers, and the emerging concept of maternal imprinting and its influence in fetal developing, programming and fate in adult age [amply quoted in 11 reference]. Based on these observations, the field of stem cell biology and evolutionarily conserved signaling pathways (i.e. Notch, TLR-4 and others) is becoming the gold object of research of a large number of studies [6,11]. Conserved signaling pathways seem to mediate a double role in adult tissues, organs and systems, contributing of their homeostasis, but also the onset of their diseases, such as ARDs. A model has been proposed of our group in recent papers [6,11].

Temporally, this growing research in effective therapies and interventions is becoming a very business for several biotechnological companies, which are promoting a growing number of therapeutic approaches as anti-ageing and anti-ARD treatments, ranging from oxidant drugs, hormones, vitamins and diet supplements to various aesthetic drugs and techniques. In fact, these approaches are particularly costly for gullible patients in searching of well-being and abused by a carefully organized marketing involving tacit complicity of doctors, laboratories and companies [12]. However, the major number of these treatments until now constitute more a palliative care than a very "long-life elixir", which has long represented for humans a dream, a vanity's sin for remaining young and to long survive [12]. This leads to the extemporaneous consideration that the way for developing effective anti-ageing and anti-inflamm-ageing treatments in humans is distant. Despite this, there is among the ageing's researchers the optimistic hope in identifying successful treatments and approaches for humans too. It derives from the increase of lifespan observed in short-lived model organisms (i.e. yeast, worm, fillies, mice and rats) undergone to various genetic, dietary, and pharmacological interventions [12]. In addition, some of these treatments have also demonstrated to retard the onset of ARDs and consequently to extend the health-span (i.e. the length of time one lives in good health), as evidenced in 2014 by Kennedy and co-workers [13]. Thus, it is possible to affirm that this evidence in animal models leads to the promise to develop effective life-extending interventions in humans too. Recently, different approaches are emerging ranging from pharmacological targeting of ageing, basic biological assays, big data analysis to the recent use of young blood, metformin and melatonin treatments, nutritional approaches, stem cells, cellular, genetic and epigenetic reprogramming or other techniques of regenerative medicine. Thus, a large number of potential anti-ageing interventions currently exist, but only a little fraction has the features for its testing in clinical applications [14].

In addition, it is emerging the necessity to developing different treatments or interventions for male and female individuals in old age, and particularly for female subjects. For example, accruing evidence indicates that women and men experience the diabetes and CVDs differently and it

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has been also observed that the relative risk for fatal ischemic heart disease associated with diabetes is 50% higher in women than in men [15]. Thus, sex dimorphism determines a complex pathological picture in onset of these ARDs, and in women it is exacerbated by the complex interaction among genetic, hormonal and environmental factors, as described in 2005 by Mendelsohn and Karas in Science journal [16] and stressed in our paper [15]. Regarding the role of genetic factors, studies on sex chromosomes, their gene content and the related disease risk are emerging. Wiham and co-workers are recently summarized some new literature data and stressed that CVDs, as well as diabetes, represent complex genetic traits with phenotypes influenced by genetic, hormonal, environmental, and cultural variables [17]. Thus sex differences must be considered in the future investigations and the development of effective therapies and preventive approaches.

We recently suggested that each individual is the result of the sophisticated interplay between environmental factors and its genome, trascriptome, proteome, metabolome, microbiome, epigenome, exposome [6,18]. Thus, it is necessary to perform a more complex combination of investigations based on genetic, transcriptomic, proteomic, metabolomic, microbiomic and epigenetic evaluations, for obtaining interesting data in the study of these diseases. In addition, computational investigations are also recommended, as well as collecting environmental and biometric data, medical/scientific/health care records [6,18]. Thus, we have proposed that the integration of all data, obtained in this large panel of investigations, and their elaboration might lead to the development of appropriate agonists, antagonists, inhibitors of specific signaling disease pathways, which might be used in a near future as personalized treatments for these diseases, facilitating their management and outcome [6,18]. Thus, the solution might be in looking with new eyes the goal of ageing and ARD research in order to make new discoveries, although, the ways to execute still are long and difficult [18].

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