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Where ageing goes nowadays: Mechanisms, pathways, biomarkers and anti-ageing strategies

Although ageing is (still) an inevitable biological process, humans currently are facing an unprecedented increase in their lifespan. However, healthy ageing has a primate above the simple increase in lifespan and thus the current anti-ageing strategies are switching the focus from suppressing ageing to promote successful ageing and healthspan. The main aim is not just to maximize the length of life, but instead to increase the period of life time spent free of detrimental conditions accompanying old age. Discovering fully the fundamental molecular mechanisms and factors underlying the process of ageing and longevity is a pre-requisite for developing appropriate strategies for increasing "healthy lifespan". In this respect ageing research nowadays goes to several directions: we still elucidate ageing mechanisms, we are seeking for the best model systems for ageing studies, we are trying to find reliable markers that should enable an early detection of an age-related diseases, and finally, we investigate potential anti-ageing strategies.

The recent IUBMB Focused Meeting on "Molecular aspects of ageing and longevity" (October 16th–19th 2017, Athens, Greece) focused exactly on these topics. Herein, we present a Special Issue based on this Meeting addressing some of the most critical aspects in the ageing field.

The answer to the question "why do we age" can only be given if we fully discover cellular mechanisms playing a fundamental role in the ageing process. There are several of them existing in a complex interplay and nematode *Caenorhabditis elegans* has proven extremely useful in identifying the main transcriptional regulators, longevity-regulating signals, cellular processes, epigenetic modifications and pharmacological agents that have been revealed to govern ageing (Denzel et al., 2018). In this manner several aspects of mitochondrial metabolism were identified as critical in lifespan regulation (Mammucari and Rizzuto, 2010). FAHD1, a member of the FAH superfamily of enzymes, has been suggested to play a pivotal role in the regulation of mitochondrial function. Pidder Jansen-Dürr and colleagues discuss the role of FAHD1 as a regulator of mitochondrial function in the context of a potentially reversible form of senescence named by the authors as senescence light (Etemad et al., 2018). On the other hand deregulated activity of SOX2 (Sex-determining region Y box 2), a transcription factor expressed in several fetal and adult tissues, has been linked to age-associated chronic diseases. The expression levels of SOX2 in various rodent and human tissues upon the progression of ageing have been revealed, as well as an inverse correlation of SOX2 expression with p16Ink4a levels. These findings indicated that the diminished SOX2 expression may serve as an ageing marker (Carrasco-Garcia et al., 2018).

Another key player with a critical function in cellular ageing is telomeres/telomerase system. Short telomeres trigger cellular senescence and genomic instability, leading to numerous degenerative and ageing-related diseases. The associations between oxidative stress and accelerated telomere shortening, and possible mechanisms and cellular pathways that protect telomeres from oxidative damage, have been reviewed by Barnes et al. (2018). The ubiquitin-proteasomal-system (UPS) and the autophagy-lysosomal-system (ALS) are also important regulatory mechanisms in cellular ageing. Disturbances in this system lead to the decline of protein degradation, accumulation of cellular damage and to the failure of cellular functionality. One of the examples is the involvement of UPS and ALS systems in the degradation of human amylin, a peptide prone to form aggregates and with role in Type 2 Diabetes (Press et al., 2018).

Epigenetic mechanisms are also involved in ageing, and by having a reversible nature represent promising targets for therapeutics against age-related decline and diseases. It has been reported that with age there is general loss of histones coupled with local and global chromatin remodeling and an imbalance of activating and repressive histone modifications (Sen et al., 2016). The correct interaction between the yeast linker histone and the actin-related protein 4 (Arp4) is necessary for genome stability maintenance and cellular resistance to various stresses. Upon loss of this interaction a premature ageing phenotype is established and the cells become more sensitive to stress, indicating the role of the linker histones and chromatin remodeling complexes in the regulation of ageing (Miloshev et al., 2018).

The extracellular matrix (ECM) is present within all tissues playing a role in cell morphology and tissue architecture and affecting several biological processes. De Luca discussed the literature on the role of the interactions between cells and ECM and the outcome in ageing and longevity. Furthermore, she focuses on the aged vasculature system and suggests a pivotal role of the interplay between cell-matrix interactions and the renin-angiotensin system on the age-dependent arterial stiffness (De Luca, 2018).

Dysregulation of nutrient sensing, altered intercellular communication, stem cell exhaustion, loss of proteostasis, and epigenetic alterations were detected as underlying cellular mechanisms for the hypothalamus-mediated ageing, with mTOR, NF-kB, autophagy, and SIRT1 as critical factors in these processes. Further dissection of these pathways or components that would expand the existing knowledge about the ageing process could pave the wave for developing novel therapeutic interventions for numerous age-related diseases (Kim and Choe, 2018).

A significant factor contributing to the ageing process could also be a dysregulation of adaptive homeostasis, especially in the final third of lifespan. Organisms/cells have to cope successfully with a range of intrinsic and extrinsic perturbations to adapt to the ever-changing environment. The term adaptive homeostasis refers to a plethora of transient changes that endows the organism to activate cellular defense pathways and be prepared for future insults. The role of dysregulated adaptive homeostasis in the ageing progression and the beneficial

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impact of its maintenance in lifespan extension has been summarized by Pomatto et al. (2018).

In addition, this special issue covers some new methodological approaches in the field of ageing research. Cellular senescence although represents an age-related process, also occurs during normal development and adult life. The short communication by Barbouti et al. (2018) represents the first *in situ* evidence linking cellular senescence with human thymic involution. The regulating mechanisms of this age related process are still not fully elucidated, thus the author, by using the novel chemical compound, a Sudan Black-B analogue- SenTraGorTM, demonstrates that cellular senescence occurs during human thymic involution, providing the further insights in thymus histophysiology (Barbouti et al., 2018). Schosserer et al., (2018) reviewed the current state of research in the field of modeling frailty and physical resilience in mice, and challenges in this process. As frailty and loss of resilience represent potential targets for geroprotectors, drugs that modulate mechanisms of ageing and are able to target multiple deficits, appropriate experimental models are extremely important. Modeling resilience in mice can be achieved by several methods. Herein authors review potential models of physical resilience, focusing on those that include sepsis, trauma, drug- and radiation exposure, kidney and brain ischemia, exposure to noise, heat and cold shock, and seeking for those where administration of acute stressors requires integrative responses and multiple tissues. On the other hand, the article by Viceconti and Dall'Ara expands the existing spectrum of the model systems, as in contrast with epidemiological and animal studies, the authors explore possibility how in silico medicine can help ageing research. They describe an initial exploration where a set of *in vivo* imaging based subject-specific technologies originally developed to predict the risk of femoral strength and hip fracture in osteoporotic patients, were adapted to assess the efficacy of bone drugs pre-clinically on mice (Viceconti and Dall'Ara, 2018).

A rapid model for ageing studies, by overexpression of the INhibitor of Growth 1 gene (ING1a) isoform has been suggested by the Bertschmann et al. (2018). This model rapidly induces a senescent phenotype in primary fibroblasts, epithelial and endothelial cells, resembles replicative senescence by most physical and biochemical measures and dissects the mechanisms that lead to RB activation and senescent state establishment.

Intervertebral discs (IVDs) and their degeneration (IDD) have been linked to low back pain, a major age-related disease. The characterization of the senescent IVD phenotype has never been performed in the harsh conditions that prevail in the disc (hyperosmolality, low oxygen and glucose concentration as well as in the absence of serum). The fate of IVD cells senescent phenotype under conditions simulating the in vivo IVD extracellular environment has been examined (Kouroumalis et al., 2018).

The establishment of markers of biological ageing is of high importance in the battle against age-related diseases as well as in the race for healthspan and lifespan extension. Moreno-Villanueva and Bürkle highlighted novel scientific insights with regard to epigenetic and redox biomarkers obtained during the implementation of MARK-AGE, a large-scale European study (Moreno-Villanueva and Bürkle, 2018). The same study (MARK-AGE) revealed that antioxidants and self-reported health are potential (bio)markers for detecting persons at risk of becoming frail (Rietman et al., 2018).

Skin can be considered both as an indicator of human health and as an organ where the first signs of ageing are mostly visible, thus possibilities for the establishment of clinical and laboratory skin biomarkers for systemic human ageing should be explored. Evaluation of skin morphology, advanced glycated end products (AGEs), dermal collagen content and changes of the expression of Wnt pathway proteins may predict – among others - the ageing magnitude and the course of several internal, organ-specific diseases. Those markers may serve as valuable laboratory biomarkers for arteriosclerosis and cardiovascular changes, bone density and neurodegenerative diseases, with special emphasis on the fact that gender-independent biomarkers of skin ageing have been documented (Zouboulis and Makrantonaki, 2018). On the other hand, normal visible signs of skin ageing, like sagging and wrinkles, influence psychological component of human ageing and the social and individual perception of people, imposing a strong need for a research in this area. Haydont et al. (2018a) provided a comprehensive overview of the current knowledge about the evolution of dermis characteristics at different life stages, from intra uterine to post-natal life. Haydont et al. (2018b) also revealed important ageing-associated signatures following genome-wide transcriptomic analysis of papillary (Fp) and reticular (Fr) fibroblasts extracted from young and old donors' skin biopsies They further show that the KN motif and ankyrin repeat-containing protein 4 (KANK4) is an original effector involved in the acquisition of aged properties in Fp, notably their increased contractility (Haydont et al., 2018b).

A potential biomarkers of "immunosenescence "associated with defined clinical outcomes were debated in a review by Pawelec (2018). The author discussed data originated from several different European countries and documented significant differences between presumably quite homogeneous populations. Although some simple immune characteristics correlate with frailty and mortality in the elderly, immune risk profiles were different in overtly similar European populations, indicating that immunological parameters are sensitive to context-dependent variation. These findings unfortunately impose difficulties into attempt to extrapolate biomarkers of longevity from one human population to another.

In parallel with expanding our knowledge about the ageing process itself, an exploration of potential therapeutics for ageing and age-related disease rapidly develops. Changes in a life style represents still one of the most promising approaches. Healthy nutrition, dietary restriction, intellectual activity and physical exercise, but also pharmacological interventions targeting common mechanisms of ageing, are still the most promising tactics in delaying ageing, diseases and disability (Figueira et al., 2016).

Nutrition is in the focus of the review by Green and Lamming (2018). By now it became evident that it is not only the quantity, but also the quality of nutritients that plays a role in metabolic health and disease. Authors discussed recent findings regarding the influence of dietary proteins, specific amino acids and reduction of their content on metabolic health, in a broad spectrum of model organisms, as well as potential molecular mechanisms underlying. It is confirmed that amino acid restriction may promote metabolic health *via* multiple molecular mechanisms, but with sexually dimorphic response present.

Ageing is a multifactorial process governed by both genetic factors and the exposome. It constitutes a main risk factor for age- and aggregation-related diseases. Its retardation is the holy grail of the field as this would also mean decrease and/or deceleration in the development and progression of age-associated degenerative diseases. With an ever-growing proportion of the elderly, there is an immense pressure to identify strategies to prevent or delay age-associated frailty and diseases. This is imperative for maintaining the health of the population, as well as global economy. However, in order to develop therapeutic strategies for delaying age-related pathology, a better understanding of the underlying causes of ageing and age-associated diseases is required. Therefore, elucidation of the regulatory pathways that are activated during normal ageing as well as during the onset of age-related diseases is of high importance. To fight ageing requires understanding of ageing, and in that battle scientific community should move forward by making many small steps.

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