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EDITORIAL

Special issue on "Molecular genetics of aging and longevity": a critical time in the field of geroscience

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Although aging was long considered as a simple and unavoidable decay, accumulating work over the last three decades have revealed that the process is not only highly regulated, but also dependent on external environmental inputs (Kennedy et al. 2014; Lopez-Otin et al. 2013). Indeed, the existence of a genetic basis underlying aging became evident in the early 1990s with the discovery of specific genetic mutations that could double the lifespan of the nematode *C. elegans* (Kenyon et al. 1993). Since this seminal discovery, a number of core "hallmarks" of the aging process have been described, including genomic instability, inflammation, mitochondrial dysfunction, loss of protein homeostasis (i.e., "proteostasis") and (epi-)genomic alterations (Kennedy et al. 2014; Lopez-Otin et al. 2013). Aging is the single greatest risk factor for many chronic diseases (e.g., Alzheimer's, cancer, cardiovascular dysfunction, diabetes, etc.), which have a growing medical, financial, and societal burden due to the growing aging population. Not surprisingly, clinical frailty involves a cumulative decline in anatomical, physiological and molecular functions and is apparent at multiple levels of biological organization: genome, epigenome, tissues, organs, and the organism. Indeed, the "geroscience hypothesis" posits that aging is the underlying cause leading to the development of many chronic diseases (Kennedy et al. 2014), and thus requires an integrated research approach to human health. Detailed genome wide and populational investigations on the origins and effects of germline and somatic genetic and epigenetic alterations in interaction with the environment will open up the possibility to fully understand the process(es) of aging. From the perspective of precision medicine, it will be possible to identify individuals at higher risk of developing single or multiple morbidities for devising new preventive measures, such as specific senolytic treatments.

In this Special Issue, we assembled a collection of articles from expert in various aspects of aging biology, aimed to both lay out novel advances in the characterization of aging hallmarks (i.e., protein homeostasis, stem cell decline, genomic instability, and chromatin alterations), as well as highlight emerging topics of interest in the field of aging biology (i.e., importance of sex differences, novel aspects of genomic dysregulation such as miRNA or splicing, and mitochondrial genomics). The first conceptual set of articles spans topics that summarize and expand our knowledge of existing hallmarks of aging (Grassmann et al. 2019; Innan et al. 2019; McNeely et al. 2019; Wong et al. 2019; Yu et al. 2020). In the review by Wong and colleagues, the impact of autophagy on aging and longevity, a key mechanism in recycling cellular macromolecules which is key for proteostasis, is explored (Wong et al. 2019). The review by McNeely and colleagues explores the impact of lifelong DNA-damage accumulation of long-lived stem cells (McNeely et al. 2019), whereas the review by Yu et al. (2020) highlights loss of chromatin integrity as an important source of genotoxic stress with aging. The original study by Grassman and collaborators explores progressive Y-chromosome aneuploidy in patients with macular degeneration (Grassmann et al. 2019). Innan and colleagues propose a demographic model to explain age-related frailty and morbidity through mutation and epimutation accumulation (Innan et al. 2019).

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A second conceptual set of articles in this Issue cover emerging topics in aging research (Bhadra et al. 2019; Kinser and Pincus 2019; Reynolds et al. 2020; Sampathkumar et al. 2019). The review by Bhadra and colleagues highlights loss of precision in alternative splicing as emerging features of aging (Bhadra et al. 2019). In their review, Kinser and Pincus provide insights into the role of non-coding miRNA as master molecular regulators of the aging process, as well as biomarkers of aging (Kinser and Pincus 2019). Reynolds et al. discuss the intriguing impact of the breakdown of communication between the mitochondria and nuclear compartments during aging, and the importance of considering both of our genomes (i.e., nuclear and mitochondrial) in the study of aging genomics (Reynolds et al. 2020). Finally, Sampathkumar and colleagues summarize and discuss the overwhelming presence of sex-dimorphic phenotypes in aging, longevity, and age-related diseases and highlight the importance of considering sex as a point of interest in the study of aging rather than an incovenience to be taken into account (Sampathkumar et al. 2019).

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