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Prospects and Perspectives in Primate Aging Research

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Abstract

As improvements in standard of living and advances in medicine have resulted in greater life expectancy, the relative proportion of elderly has continued to increase in human populations across the globe. The primary goal of aging research is to gain a better understanding of the series of events that lead to increased frailty and disease vulnerability with age. The direct study of human aging is an active area of research; however, the opportunity to conduct mechanistic studies and gain insights into the underlying biology is limited. In this special forum issue of *Antioxidant & Redox Signaling*, we present a selection of articles and reviews that illustrate some of the recent advances in primate aging research. The overarching goal of this work is to underscore the potential for mechanistic discovery that is presented by nonhuman primate models, and to promote studies that validate novel approaches and techniques in nonhuman primates before their adaptation for human health care. *Antioxid. Redox Signal.* 14, 203–205.

In many developed nations, the proportion of the population that may be considered aged has increased to unprecedented levels. A 2002 report by the Population Division at the United Nations World Assembly on Aging indicated that the global proportion of persons aged 60 years and over (19%) was slightly higher than the proportion of children below 15 years (18%). Projections based on the current demography suggest that by the year 2050 the number of older people will exceed the number of young people globally, representing 34% and 16% of the population, respectively (8). According to the U.S. Census Bureau (2), people 65 years or older represented 12.8% of the population in 2008; if this current trend continues, this number will rise to 21% of the total population by 2050. In addition, the older population itself is aging. The world's fastest growing age group is the oldest-old, those aged 80 years or older. These trends have major implications for social, economic, and political spheres, not least for the health-care sector. To absorb this population shift and improve the quality of life for elder individuals, it will be of utmost importance to discover and implement measures to preserve health in the elderly population.

The manifestations of aging are evident at the cellular, tissue, and systemic levels (Fig. 1). At the molecular and cellular level, aging impacts gene expression and the responsiveness of cell signaling pathways. Disruptions in cellular mechanisms for regulating gene expression, metabolism, cell division, and cell growth can lead to tumorigenesis and cancer. The impact of aging is highly tissue specific and largely distinct among tissues. Age-associated diseases that are associated with specific tissues may have a systemic impact. For example, sarcopenia is the age-associated loss of muscle mass that may influence energy utilization locally and metabolic homeostasis systemically. In addition to the age-associated decline in peripheral tissue function that can directly or indirectly impact systemic signaling, aging also impacts immune function and inflammation.

The primary goal of biology of aging research is to gain a better understanding of the series of events that lead to increased frailty and disease vulnerability that are associated with age. One of the greatest challenges lies in distinguishing elements that directly contribute to the aging process (causes) from elements that are induced or abrogated as part of an adaptation to the aging process (symptoms). In higher animals, including mammals, highly complex and interconnected regulatory systems allow communication between cells, within tissues, and among tissues. As a result, elucidation of the underlying mechanisms in the aging process in mammals has been challenging. It is useful to break down this formidable task by focusing on specific pathways, or tissue-specific processes and diseases, both of which can influence systemic signaling.

The direct study of human aging is an active area of research; however, there are several aspects that hinder mechanistic approaches in human studies, including the high

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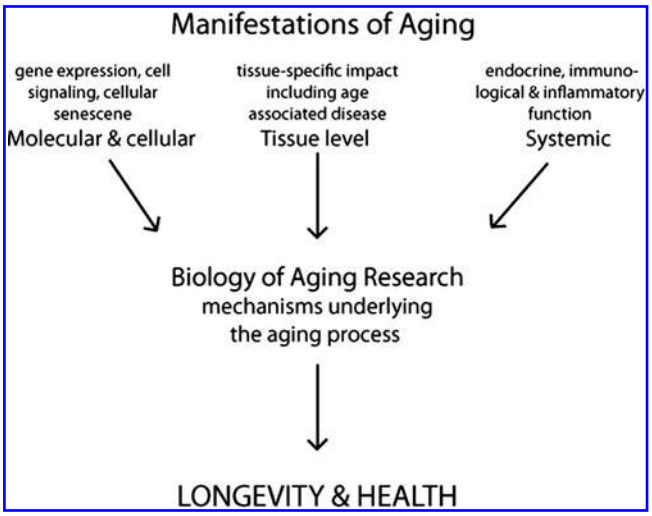

FIG. 1. A simplified schematic outlining an approach to mammalian aging studies. Due to the complexity of the aging process, biology of aging research is necessarily multifaceted. For simplicity, we assign the effects of aging to three fundamental hierarchical groups with the understanding that each of these is highly interdependent. Ultimately, increased understanding of the biology of aging will enable the identification of potential therapeutic and preventative targets for the improvement of human health and longevity.

degree of variability in genetic makeup within and across human populations, cultural and environmental influences, and the feasibility of conducting controlled long-term investigations. A preferable alternative is to study nonhuman primates. Advantages of using a nonhuman primate model include their close genetic relationship to humans and their shared biology and physiology. Although the genetic diversity in nonhuman primate populations closely mimics the human situation, extensive pedigree information and health records of related animals are often known. Unlike rodents, nonhuman primates share more similarities with humans in terms of behavior, disease vulnerability, and the dynamics of aging over decades of lifespan.

A number of significant technological advances have facilitated an accelerated pace of nonhuman primate aging research in recent years. In 2007 the rhesus macaque genome sequence was published by a highly collaborative team of investigators from 35 institutions, giving researchers access to unprecedented levels of sequence information that could be directly compared with human and chimp genomes. This knowledge can be used to explain similarities and differences in the biology of aging among these very closely related species. In the past decade, the increased commercial availability of nonhuman primate-compatible antibodies and immunodetection based kits has facilitated characterization of the impact of age on numerous biological parameters. Nonhuman primate studies are supported by the National Center for Research Resources in the form of eight National Primate Research Centers. Online resources include shared databases for imaging, gene expression microarray, and other biological measures. An emphasis on translational research at the National Institutes of Health has given investigators utilizing nonhuman primates access to funding through Clinical and Translational Research Centers, also funded by National Center for Research Resources. This combination of technological advance and infrastructural support is essential for the further development of nonhuman primates models, a critical bridge for basic and applied science and an invaluable resource for the investigation of complex processes such as aging.

This special issue of *Antioxidant & Redox Signaling* is devoted to primate aging. The contributions include reviews and original articles on a range of topics covering molecular, cellular, tissue-specific, and systemic aspects of aging. The dietary intervention calorie restriction delays the impact of aging in mammals, including primates, and has the potential to reveal key causative elements in the aging process. A review of calorie restriction studies in nonhuman species, including the mechanistic insights that they provide, leads the issue (1). It is followed by an original research article describing tissue specificity in the response of key cellular pathways to deregulated insulin signaling (5), a common feature of aging and of metabolic syndrome. Next, a review on the impact of age on immune cell repertoire (3) describes how changes in cellular populations impact systemic processes and highlights the utility of nonhuman primate research in this important aspect of disease control and vulnerability. An original research article on spontaneous neoplasias in rhesus monkeys follows, describing the incidence and categories of tumors for which there is an increased risk associated with age (7). This is followed by a review describing epigenetic gene regulation studies and how epigenetics may play a role in aging and age-associated disease (4). Finally, a review on calorie restriction studies in humans highlights physiological, psychological, and behavioral considerations and outcomes (6).

A wealth of information may be gained from the study of nonhuman primates, and the potential for mechanistic discovery and therapeutic validation is relatively untapped. It is our goal to convey through this special issue the exceptional utility of the nonhuman primate model for the study of the complex process of aging. Insights gleaned from studies to date attest to the translatability of the model, where data from nonhuman primate studies mirror those from studies in humans. Compared to human studies, nonhuman primate studies have the added advantage of increased capacity for in-depth mechanistic explorations to identify underlying contributing factors in the aging process. This research will be facilitated by continued development of quality reagents, increased availability and access to primate resources, and the expansion of collaborative efforts.

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