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Research Paper

Aging and Caloric Restriction Research: A Biological Perspective With Translational Potential

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ABSTRACT

Aging as a research pursuit is fairly new compared with traditional lines of medical research. A growing field of investigators is focused on understanding how changes in tissue biology, physiology, and systemic homeostasis, conspire to create increased vulnerability to disease as a function of age. Aging research as a discipline is necessarily broad; in part because aging itself is multi-faceted and in part because different model systems are employed to define the underlying biology. In this review we outline aspects of aging research that are likely to uncover the pivotal events leading to age-related disease vulnerability. We focus on studies of human aging and discuss the value of research on caloric restriction, an intervention with proven efficacy in delaying aging. We propose that studies such as these will deliver target factors and processes that create vulnerability in human aging, an advance that would potentially be transformative in clinical care.

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1. Introduction

The dramatic increase in average life expectancy has led to a rapid rise in the aging population across the globe (Christensen et al., 2009). Age is a robust and independent risk factor for a range of non-communicable diseases like cancer, diabetes, cardiovascular disease, and neurodegenerative disease, and so it follows that this newfound increase in longevity creates a substantial burden in disease incidence and health care costs (Bloom et al., 2015). Overwhelming evidence suggests that processes intrinsic to aging contribute to the pathogenesis of age-related diseases. Ongoing international efforts have made great strides in advancing our knowledge of the biology of aging and several "hallmarks" of aging have been identified that may play a causative role in the age-related increase in disease vulnerability (Kennedy et al., 2014; Lopez-Otin et al., 2013). These age-related changes include fundamental aspects of biology such as metabolic dysfunction, genomic instability, failure of quality control mechanisms, disruption in cellular pathways controlling growth and recycling, failure in integrity of cell-cell communication, and loss of regenerative capacity. Consequent changes in metabolic homeostasis and inflammatory tone are thought to further compound these primary defects of age (Finkel, 2015; Franceschi and Campisi, 2014), negatively influencing the tissue microenvironment to create a permissive state for disease incidence and progression.

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These last few years have seen a shift in emphasis from the investigation of individual age-related diseases in isolation toward a broader context to define the basic biology of aging. The concept behind the recently coined pursuit of GeroScience (Burch et al., 2014) is that a strategy to delay the aging process itself would decrease vulnerability across the age-related disease spectrum leading to lower morbidity and comorbidity. Indeed the concept that aging might be a suitable drug target in a clinical context is gaining traction and there is considerable effort being applied to bring this idea to fruition (Longo et al., 2015). One of the most valuable tools in aging research is caloric restriction (CR), a proven intervention to delay aging and age-related disease (Fig. 1). If we could understand what mechanisms are employed by CR to impinge on the aging process we could potentially identify causal networks that contribute to the increase in disease vulnerability as a function of normative aging.

2. Human Aging Studies

Several large-scale longitudinal aging studies have contributed enormously to our current understanding of the physiological changes during aging and their impact on health in old age. The Baltimore Longitudinal Study of Aging started in 1958, even before the foundation of the National Institute on Aging NIA in 1974. The study set out to determine the trajectory of change as a function of normal aging. Over the years 1300 participants have been monitored longitudinally, with health, cognitive and functional assessments conducted periodically. More recently, auxiliary studies have been conducted to identify the molecular signature of age related functional declines, including the investigation of the ability of biological markers such as serum metabolites to index physical function (Moaddel et al., 2016). Studies such as these will contribute new biomarkers with utility for diagnosis and treatment efficacy monitoring but also have potential to reveal the underlying biology of the age-related disorders. The Health Aging and Body Composition (Health ABC) is a longitudinal study of over 3000 subjects in the 70–79 year old age range that were recruited in 1997 and followed for a decade and a half. Data from this study have featured in hundreds of publications since 1999. Early reports focused on functional decline with age (Simonsick et al., 2001) but as the study progressed reports of interactions among measured parameters and their association with disease have emerged (Beavers et al., 2013). The survey of Midlife Development in the US (MIDUS) was launched in 1995 with the overarching goal to discover the contributions of behavioral, psychological, and social factors to variation in health and well-being as a function of age (Radler, 2014). A repository of data and specimens collected from subjects in the study has enabled the investigation of biological factors to determine how these impact aging and health, such as interactions among biological indices as predictors of health and the role of inflammatory tone (Elliot and Chapman, 2016).

The Wisconsin Longitudinal Study is a long-term study of a random sample of 10,317 men and women who graduated from Wisconsin high schools in 1957 (Herd et al., 2014). Survey data were collected from the original respondents and a selected sibling and from their spouses. Health, social, and economic data have been collected, with more recent initiatives including genetic studies of a sub-group of the cohort. The Health and Retirement Study based at the University of Michigan was initiated in 1992 and focused on the 51–61 year age group. Subjects, now in their 70s and 80s, were interviewed every two years. Additional groups were added later including a cohort older than 70, a cohort of subjects who had birth dates in the years of the depression who were in their 60s at the time of recruitment, and the "war babies" cohort who were in their early 50s. Currently the study has captured data from ~20,000 persons. Over the years the investigation has expanded to include on site physical assessments, biomarkers and genetics, allowing the biological underpinnings of age-related disease and disorders to be uncovered (Duchowny et al., 2017; Mezuk et al., 2016). Frameworks such as the studies described above have great potential to uncover factors contributing to multi-morbidity, a key aspect in geriatric care and a major factor in loss of independence (Fabbri et al., 2015). As more molecular level data emerge from analysis of collected biospecimens from each of these and other longitudinal aging studies we can anticipate the emergence of a whole new perspective on aging biology in humans at unprecedented resolution.

The Lothian Birth cohorts of 1921 and 1936 are studies that were initiated in 1999 and 2004 respectively, originally aimed at uncovering the genetic determinants of cognitive aging. These are follow up studies to the Scottish mental survey that tested the intelligence of almost all children aged 11 that attended Scottish school in 1932 and 1947 and were later recruited for the longitudinal study at the mean age of 79 and 70. In addition to genetic determinants, several other factors like physical fitness, inflammatory profile, renal function, VitB12 and folate, psycho-social and economic status were found to be associated with lifetime cognitive aging (Deary et al., 2012). The Leiden 85+ longitudinal study began in 1997 with 599 individuals aged 85 and older inhabiting the city of Leiden in Netherlands. They were followed up for the next five years with particular focus on inflammation and vascular factors linked with aging. These studies uncovered an association between atherosclerosis and dementia in old age (Vinkers et al., 2005). Extending the Leiden 85+ study, the Newcastle 85+ study comprises over 1000

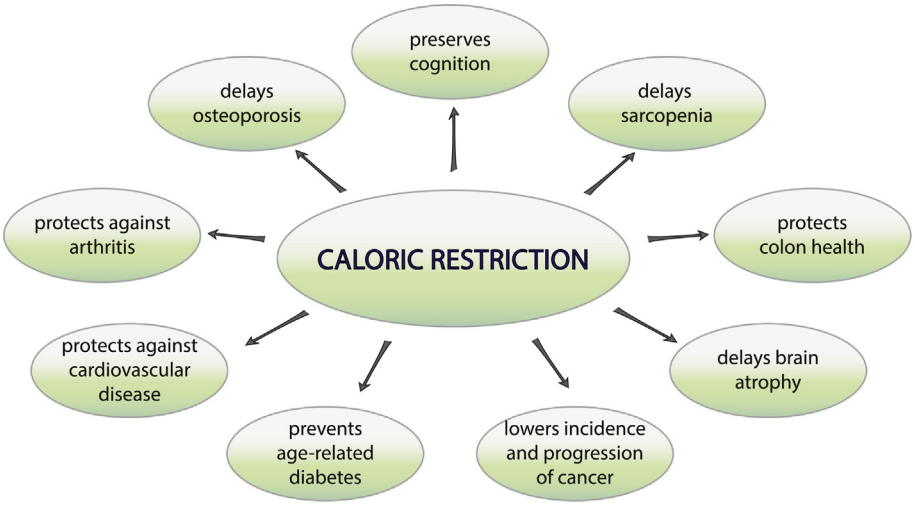

Fig. 1. Caloric Restriction (CR) delays the onset of age-related diseases. Studies in rodents and nonhuman primates have revealed a beneficial effect of CR on a diverse set of conditions related to human aging.

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