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Editorial

Caloric Restriction Research: New Perspectives on the Biology of Aging

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The beneficial longevity effect of a simple reduction in calorie intake was first established in rodent studies more than 80 years ago (1). In the interim, the caloric restriction (CR) paradigm has gone from being a curious phenomenon of limited value to being recognized as a highly informative research tool with which we might enhance our understanding of the complex biology of aging (2). In the last few decades as genetic techniques have advanced we have seen considerable progress in identifying cellular and systemic processes that likely contribute to the increase in disease vulnerability that is associated with aging (3,4). Traditionally, these insights have come from studies of short-lived laboratory animals, but the recent confirmation of the relevance of the CR paradigm to primates has placed renewed emphasis on studies that delve into the mechanisms of delayed aging by CR (5). The principle of GeroScience is that aging itself is a worthy target for intervention: if aging can be offset then age-related vulnerability to diseases and disorders such as cancer, heart disease, frailty, and neurodegeneration, would be postponed and attenuated (6). If we could understand how CR exerts its effects to prolong health and delay mortality we will surely be able to identify key regulatory nodes involved in countering the causative factors in aging that lead to morbidity and mortality. In this special issue, we have collected a series of primary papers and reviews showcasing the breadth of CR research, including studies from the simple unicellular yeast to humans. Each model brings its own strengths and together CR studies continue to provide unique insights into aging biology.

The CALERIE study is the first human clinical trial of CR (7). Conducted across three sites in the United States, this pioneering work showed not only that CR could be tolerated in humans but it also produced beneficial effects on numerous clinical disease risk indices (8). In their primary research paper, Belsky et al. used published biomarker algorithms that inform of biological age to determine the impact of CR on human aging (9). Data from the CALERIE study were applied to both the Klemera-Doubal Method of Biological Age (10) and homeostatic dysregulation (11) approaches. These two distinct computational approaches were in agreement in identifying a slower pace of aging in the individuals in the CR group compared to the control subjects. This important discovery paves the way for high-resolution molecular studies of the response to CR in humans. These methods may provide a solution for much needed surrogate markers for healthy aging in future clinical trials to identify drugs and diets to enhance healthy aging.

Within the last 10 years, the long suspected but previously unconfirmed demonstration that primate aging is indeed malleable came from studies of CR in rhesus monkeys (12). Over the course of that ~30-year study longitudinal biometric, physical activity, and metabolic data, were captured and used by Yamada et al. to evaluate the monkey model as a means to investigate frailty (13). In their primary research paper, the authors present a multifactorial analysis that is a blend of two established methodologies for quantitation of frailty in humans, the Fried frailty phenotype (14) and the Rockwood-base frailty index (15). The group showed clear differences between control-fed and CR monkeys, expanding further the utility of this exceptionally translatable model to uncover the biology of aging including frailty.

The prevalence of locomotor impairment increases significantly with age and is a major factor in loss of independence and disability (16,17). In their primary research paper, Salvatore and colleagues use the rat model to dissect neurological mechanisms of age-related motor decline (18). They show that the Parkinsonism is linked to decreased dopamine receptor expression in the nigrostrial region of the brain, the area that has been linked to Parkinson's disease. By comparing aged rats with deficiencies in locomotor function to age-matched CR animals that were protected against age-related declines, the team was able to distinguish between coincident age

related changes in brain dopamine levels in the striatum and causal declines in substantial nigra that were specifically linked to compromised locomotor function. The study showcases the value of CR as a means to dissect causal from coincident events in disease progression, and provides further support for nutrition-based interventions as a means to delay brain aging and neurodegeneration (19).

The search for agents that can exert the beneficial effects of CR without the requirement for a reduction in calorie intake has undergone considerable expansion over the last decade (20). Among these aptly named "CR mimetics" are resveratrol, a plant derived polyphenol, and metformin, a widely prescribed antidiabetic drug, both of which have been shown to produce beneficial effects in rodents (21,22). In their primary research paper, Stockinger et al. compare the impact of resveratrol and metformin on skeletal muscle aging (23). Here, the authors show that both treatments and CR attenuate the hypertrophy and atrophy of muscle fibers as a function of age, and that CR and resveratrol also protect the neuromuscular junctions. This study points to potential new applications for these CR mimetics as a means to counter skeletal muscle aging. Furthermore, it demonstrates the power for mechanistic discovery in the application of CR mimetics to uncover the biology of discrete factors within tissues that contribute to the aging phenotype.

Rapamycin positively impacts lifespan in yeast, worm, and flies, and its target, the growth regulatory kinase mTOR, plays a prominent role in biology of aging research (24). Since the demonstration that rapamycin enhances longevity in rodents there has been considerable interest in understanding how this intervention differs mechanistically from CR (25,26). The two interventions are compared in side-by-side in a yeast model in the primary research paper from Choi et al. (27)Using complementary unbiased approaches of gene expression and metabolomic analysis, shared and exclusive features of rapamycin and CR are described. Critical differences lie in the metabolic response, leading the authors to conclude that the mechanisms by which longevity is conferred are distinct for the two interventions.

One of the earliest models to explain biology of aging, and the subject of Nobel prize-wining research, centers on telomeres (28). Telomeres are the protective ends on chromosomes that prevent loss of genetic information the might otherwise occur during DNA replication. The shortening of telomeres with repeated rounds of cell division has been linked to cellular senescence, another predominant model in biology of aging research (29). Telomere length shortening is a robust biomarker of aging with evidence from laboratory animal and human studies and is influenced by nutritional interventions (30). Skrobot Vidacek and colleagues explore the relationship between telomeres, genome integrity, and aging (31). The varied influences of oxidative species, nutrition, behavioral factors, and aging on telomere length maintenance are considered and the potential to harness this biomarker of human aging to inform about morbidity and mortality risk is discussed.

The final contribution to the special issue is a comprehensive perspective on the challenges of conducting CR research. Vaughan et al. take examples of rodent and nonhuman primate studies from the published literature to explore differences in study outcomes, and issues of terminology, methodology, and differences in diet implementation that can create conflicting interpretations (32). The importance of diet composition and macronutrient source, genetic background, and time of onset are also discussed. The authors conclude that differences in study design limit direct comparisons among studies, but that much of the conflict in the literature might be resolved by better recognition and qualification of those differences.

In summary, the contributions from authors to this special issue are terrific examples of the scope of CR research that touches on a range of aging-related biomarkers, processes, diseases, and disorders. Without doubt, these primary papers and reviews present compelling reasons to further pursue the mechanisms of CR and confirm the value of using CR as a means to understand the biology of aging.

Conflict of Interest

None reported.

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