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Metabolic adventures in aging research

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Metabolism is broadly defined as the chemical processes that occur in a living organism in order to maintain homeostasis and life. As an organism ages, cellular demands change and metabolic changes take place that shift resource utilization including anabolic and catabolic activities and processes that recycle resources, repair and remove damaged cellular components, and dispose of metabolic waste. Thus, metabolic modifications may underlie much of what we believe constitutes aging in terms of physiological decline and vulnerability to age-related disease.

The regulation of metabolic health as a function of age is a rapidly emerging area of investigation with particular emphasis on the molecular mechanisms that are responsible for the effects of various nutritional interventions on health and longevity. We have assembled this Special Issue on the Metabolism of Aging to present current investigations and discussions at multiple levels from molecular to system-wide, aimed at providing a deeper understanding of this relationship. Reviews of specific topics and primary research papers cover a wide range of topics encompassing metabolism and aging that include emerging mechanisms of aging, senescence, nutritional interventions, epigenetics, and mitochondrial connections, amongst others. These contributions are interdisciplinary and multifaceted, and several present the potential for translational application in the near future. We hope to convey through this Special Issue the complex links between metabolism, aging, age-related disease, and longevity regulation, an area of investigation that is currently a major focus in Biology of Aging research.

The activity and coordination of immune responses are dependent on the metabolic state of the organism. A progressive decline in immune system function is associated with aging leading to increased susceptibility to infection, autoimmune disease, and chronic inflammation. Dysregulated T-cell homeostasis in particular is thought to underlie some autoimmune diseases. Choi, Lee, and Longo (2017) (pp. 4e12) describe the effects of calorie restriction (CR), intermittent fasting, and fasting mimicking diets on several autoimmune disorders. CR protects against age-related disease including autoimmunity but long-term

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compliance is a significant concern. Fortunately, periodic fasting and fasting mimicking diets are also very effective and exhibit fewer side effects and compliance issues. Thus, there appears to be great promise in using dietary interventions to enhance T cell diversity and function, suppressing autoimmune cells and inducing generation of cells to rejuvenate damaged tissues.

Cummings and Lamming (2017) (pp. 13e22) review the emerging evidence that suggests that dietary composition may be as important as the amount of calories consumed in terms of health span and lifespan. For decades, reports have shown that reducing caloric intake improves many metabolic indicators of health, delays or reduces age-related decline and disease, and extends life in many different organisms. More recent work has demonstrated that the macronutrient composition may also be playing a key role in health and aging. In particular, differences in dietary protein levels and composition impact growth signaling such as the mTOR pathway, are a widely acknowledged mediator of longevity and a key regulator of glycemic control and metabolic health. Exciting new findings on the specific role of Branched Chain Amino Acids in mTOR regulation and consequent metabolic homeostasis are also discussed.

Reduction of signaling through the somatotropic axis was one of the first genetic manipulations to exhibit enhanced longevity in rodent models. The connection between aging and growth signaling is explored in the progressive decline in primordial follicle reserve that is a significant aspect of female reproductive aging and the main determinant of menopause. Mechanisms underlying this age-related decline are relatively unknown. In their primary research paper Schneider et al. (2017) (pp. 23e32) explore the role of growth hormone (GH) in maintenance of primordial follicles using GH-deficient and GH-overexpressing mice and find that increased circulating GH is linked to reduced ovarian primordial follicle reserve and an increase in the inactive form of oocyte FOXO3a. FOXO3a is critical for ovarian maturation and reproductive fitness. This new study now links growth signaling to FOXO3a in loss of reproductive capacity with age.

Identifying the cellular processes at the heart of longevity regulation is a central question in aging research currently. Mobb’s review (2017) (pp. 33e40) describes potential epigenetic mechanisms that may be responsible for the protective effects of CR and fasting on insulin signaling, cognition, and inflammatory markers. A linking factor may be ketogenesis, a glucose sparing mechanism normally engaged during fasting. Restrictive diets as well as ketogenic diets (very high fat content) promote ketogenesis and this metabolic shift is associated with chromatin remodeling though modulation of histone modifications. In particular, inhibition of Class I histone deacetylases and activation of CREB-binding protein and sirtuins (Class III deacetylases) could serve as potential pharmacological analogs to target for drug development and mimic the effects of dietary interventions that are difficult to implement.

Modification of mitochondrial function is another prominent area of investigation in aging research and is thought to be a key element in the mechanisms of delayed aging by CR. In their primary research paper, Selman et al. (2017) (pp. 41e53) take advantage of genetic heterogeneity in the response to CR. Strains of mice that respond differently to CR in terms

of lifespan (extension, reduction, no effect) reveal key differences in metabolic preference and mitochondrial adaptation. They show that CR-induced longevity is associated with changes in mitochondrial function in the absence of mitochondrial biogenesis and that the mitochondrial response to CR is tissue-type specific. The authors point out that new insights into CR's potential mechanisms may be gleaned from comparative studies among genetically heterogeneous mouse strains that could not be revealed in studies involving only a single inbred genetic line of mice.

The idea mentioned above is further extended in the contribution from Dhillon and Denu (2017) (pp. 54e61). Their review describes energy metabolism in organisms with vastly different lifespans that they suggest may provide a greater understanding of the factors that lead to mitochondrial dysfunction. The influence of changes in energy requirement and energy expenditure on mitochondrial parameters is discussed. The authors propose that post translational modifications, specifically hyperacetylation, significantly impair mitochondrial function across diverse organisms and contribute to aging processes. Several examples of the deacetylase activities of NAD-dependent SIRT3 on mitochondrial function, energy metabolism and age-related disease are provided that implicate this modification in vulnerability to disease.

NAD (nicotinamide adenine dinucleotide) is a molecule that is tightly linked to mitochondrial metabolism serving as a cofactor as well as a substrate in numerous reactions. In this comprehensive review Chini et al. (2017) (pp. 62e74) discuss the intersection of NAD metabolism and aging. Several molecular mechanisms involved in aging, such as oxidative stress, DNA damage, senescence and inflammation are viewed in the context of the age-related decline in tissue NAD and the consequent loss of metabolic integrity. The authors discuss the factors involved in aging-related NAD decline including the balance of pathways synthesizing and consuming NAD, as well as the potential of NAD-replacement therapies as an anti-aging intervention.

The NAD-dependent protein deacetylase SIRT1 removes acetyl groups from histones and non-histone proteins. SIRT1 is implicated in longevity regulation and more recently has been shown to modulate the activities of genes that maintain stem cell function and delay cellular senescence. In this review, Yu and Dang (2017) (pp. 75e82) demonstrate that SIRT1 also functions as an anti-aging regulator for adult stem cells. There appears to be cross-talk between SIRT1 and mTOR as well as other metabolic regulators that together modulate different physiological conditions and contribute to stem cell aging. A better understanding of the mechanisms involved will serve in the development of stem cell management therapies to delay aging and prevent age-related pathological conditions.

Metabolism in cellular senescence can also be targeted for potential interventions to prevent or delay aging and disease susceptibility. Changes in metabolism, specifically in mitochondria and growth signaling pathways, occur as an organism ages. The connections between these aging related changes and factors regulating senescence are the focus of the review by Nacarelli and Sell (2017) (pp. 83e92). There is controversy in the literature as to the direct causal events leading to senescence and the SASP (Senescence associated secretory phenotype) that promotes local and systemic inflammation. Current evidence of

the metabolic contribution to cellular senescence and how that plays into aging and longevity regulation is described. The authors also discuss how life-extending treatments might prevent metabolic stress associated with the senescence program.

Schafer et al. (2017) (pp. 93e102) review the growing body of evidence implicating nutrient excess and systemic metabolic dysfunction in driving senescence in several cell types. Obesity and disruption of whole-body metabolism may prematurely activate cellular senescence leading to age-related disease. Biomarkers of senescent cells have been demonstrated in fat, liver, skeletal muscle, pancreas and other tissues, suggesting that many of these metabolically driven tissues could be subject to interventions that alter the abundance of these dysfunctional cells. Studies involving therapies that clear senescent cells (senolytics) or alter the behavior of these cells may lead to prevention or resolution of disease. The prospect for clinical application of this exciting and emerging approach for longevity regulation is also discussed.

Mitochondrial dysfunction has been shown to contribute to many physiological parameters that decline with age. Hill et al. (2017) (pp. 103e114) present their primary research paper focused on cytochrome c oxidase, Complex IV of the electron transport system (ETS). Mutations in this complex have been associated with fatal metabolic disorders such as Leigh syndrome, cardiomyopathy, and spinal muscular atrophy among others. The authors contrast the phenotypes of two mutant mouse strains with reduced COX IV activity that exhibit opposing effects on metabolism and health. The tissue specific impact of depletion of ETS assembly factor Sco2 is described in terms of mitochondrial parameters such as mitochondrial number, unfolded protein response, and respiration. The study demonstrates the crucial role of mitochondrial function in system level homeostasis and investigates parameters that differ significantly between the two lines of mice that might explain the striking and unexpected differences in body composition, glucoregulatory function, and longevity.

One of the key factors linked to mitochondrial function is the regulation of lipid flux, the balance of synthesis, storage, and utilization of cellular lipid species. Impaired fatty acid oxidation and increased de novo lipogenesis contribute to the age-associated increase in hepatic steatosis. Dysregulated hepatic lipid metabolism is linked to insulin resistance and age related increases in circulating free fatty acids. Individuals of advanced age with hepatic lipid dysfunction exhibit more severe histological changes and adverse clinical outcomes. In their review Gong et al. (2017) (pp. 115e130) discuss the roles of established and novel mediators in lipid metabolic regulation, their effects on aging and age-related disease, and their therapeutic potential to improve hepatic lipid metabolism and metabolic health.

One of the recently discovered mechanisms of homeostatic regulation involves gene regulation via microRNAs. It has become clear that aging impinges on miRNA processing but their role in metabolic regulation is only now emerging. In this review Victoria et al. (2017) (pp. 131e147) outline the potential roles of microRNAs in aging and metabolism. Specific microRNAs are important for maintenance of cellular homeostasis but can be protective or pro-aging. They also introduce a new designation of fecal microRNAs that are produced by intestinal epithelial cells and appear to enter gut bacteria and alter transcription.

Evidence is presented showing that this new family of small non-coding RNAs may be relevant to aging too.

The final paper in this Special Issue describes the impact of CR in humans. Sai Das et al. (2017) (pp. 148e157) provide an in-depth review of the clinical trial termed 'Comprehensive Assessment of the Long-Term Effects of Reducing Intake of Energy (CALERIE)' that has been completed recently. Questions addressed include the feasibility of CR in humans, comparisons between results in nonhuman primates versus humans, whether metabolic health improves to the level of disease risk-reduction, and whether there are potential long-term impacts of CR on human aging. Overall, translating reduced caloric intake protocols from animal systems to humans is feasible and effective in terms of beneficial metabolic parameters, and in depth studies of the CR response in human subjects may provide clues as to how long term well-being might otherwise be attained.

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