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REVIEW ARTICLE

Role of Intermittent Fasting, Calorie Restriction and Autophagy in Healthy Aging: A Review of Literature

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Abstract:

Aging is a progressive process associated with decline in structure and function, hindered maintenance and repair systems, increased vulnerability to disease and death, and reduced reproductive capacity. Healthy aging can be prolonged by calorie limitation or by pharmacologic agents that mimic the effects of caloric restriction. Both fasting and the genetic inactivation of nutrient signaling converge on the induction of autophagy, a cytoplasmic recycling process that counteracts the age-associated accumulation of damaged organelles and proteins as it improves the metabolic fitness of cells. Holy Quran made it compulsory for all healthy adult Muslim to fast during Arabic month of Ramadan from early dawn to dusk. Believers of other religions also have the tradition of fasting as religious rituals in different way. The importance offasting and the autophagy process was highlighted very recently by Prof. Yoshinori Ohsumi, a Noble prize winner in medicine for his pioneering studies revealing the mechanisms of autophagy in baker's yeast 30 years ago. Here we made literature search to review experimental findings on intermittent fasting (IF) and autophagy that influences the major nutrient and growth-related signaling pathways as well as the up regulation of anti-aging pathways.

Keywords: *Aging, Fasting, Autophagy etc.*

Introduction:

Aging of population is a global public health challenge with significant implications on health care needs, as well as social burden especially to low resource countries. There is much flexibility in successful aging, but meeting the challenges will require advance planning and preparation. The extents to which research can find solutions that reduce physical and cognitive disability at older ages will determine how to cope with this fundamental transformation[1]. Successful treatment of non-communicable diseases have led to rapidly increasing number of older people, often encumbered with age-related disorders that are predicted to overwhelm health care systems[2]. Achieving healthy aging is a challenge and calorie restrictions are showing optimism in this aspect.

Autophagy and calorie restriction (CR)

Autophagy is a lysosomal degradation process or and protective housekeeping mechanism to eliminate damaged organelles, long-lived misfolded proteins and invading pathogens. Autophagy functions to recycle building blocks and energy for cellular renovation and homeostasis, allowing cells to adapt to stress. Modulation of autophagy is a potential therapeutic target for a diverse range of diseases, including metabolic conditions, neurodegenerative diseases, cancers and infectious diseases. Among inducers of autophagy, fasting and CR are the most potent non-genetic autophagy stimulators. The objective was to weigh the evidence relating the effect of CR or fasting on autophagy promotion. The evidence overwhelmingly suggests that autophagy is induced in a wide variety of tissues and organs in response to food deprivation[3].

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Autophagy is strongly activated by starvation conditions characterized by low levels of glucose or amino acids. When glucose levels are high, ATP is converted into cAMP and is itself further degraded into AMP. As such, a high AMP: ATP ratio reflect a high glucose level; while a reduced AMP:ATP ratio is typical of starvation conditions when glucose levels are low[4]. Autophagy functions essentially as an adaptive response to stress, particularly in the condition of nutrient deprivation, allowing for cell and organism survival. When nutrient resources are restricted, cells are able to break down and reprocess all sorts of macromolecules including proteins, lipids, and carbohydrates which can then be reused as essential building blocks for the synthesis of new macromolecules and the production of energy [5]. Autophagy facilitates the disposal of supernumerary or damaged proteins and organelles before they become toxic to the cell. A broad range of studies has revealed that basal autophagy decline is often associated with pathologies such as neurodegeneration, cancer and inflammation[6-9].

Transcriptomics

Malfunction of autophagy causes protein aggregation and neurodegeneration. Lipinski and colleagues investigated the transcriptional level alterations between healthy aging and Alzheimer disease (AD), and they found up-regulated autophagy in brain samples from AD patients compared to normal brain samples. Based on these observations, it was suggested that the up-regulated autophagy signatures in the AD patients could be a compensatory mechanism in order to remove the accumulated protein aggregates[10].

Besides its importance in neuronal functions, autophagy also influences the identity and function of myeloid cells as well. Huang et al. examined how the expression pattern of autophagy genes is changing when myeloid cells differentiate to monocytic and granulocytic cells. Based on the analysis of the temporal gene expression data using a standard clustering algorithm, 22 autophagy genes were found to be significantly altered during the monocytic and granulocytic differentiation process of myeloid progenitors into monocytes and granulocytes[11].

Metabolomics and lipidomics

Metabolomics is a recently emerging field aimed at the systemic profiling of the metabolites, which are the small molecule, intermediates and products of metabolism. Studies of the metabolome are based on two key techniques: nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry (MS)[12] . Because autophagy is tightly associated with the cell stress status, it is not surprising that autophagy-related metabolomes will be subject to changes depending on the nature of the stresses happening in the cells[4]. Lipidomics is a sub-category of metabolomics that focuses on the identification and quantification of cellular lipids. While it has been described that changes in the cellular level of ceramides, a family of lipids can affect autophagy, little is known about the regulation of these lipids by autophagy itself. A recently published study by Alexaki and colleagues sought to evaluate the implication of autophagy in the regulation of ceramides in the liver, as autophagy is essential in this organ to maintain homeostasis and prevent metabolic diseases[13].

Autophagy and cancer, regression of tumor: Cancer usually depends on high glucose level, Lashinger and colleagues have used a mouse model system to investigate the effect of caloric restriction and autophagy on the development of RAS (oncogene) driventumors. It has been shown that combining autophagy blockade and caloric restriction was sufficient to reduce the tumor volume significantly[14]. Observations made by Gaglio et al. found that blocking autophagy using the inhibitor chloroquine caused massive cell death of RAS cancer cells in vitro. However, using chloroquine in vivo did not produce any notable effect on highly aggressive RAS xenografts. Changes in the metabolome of the tumors were observed after treatment, suggesting that RAS-driven tumors have the ability to adapt to environmental modifications and metabolic stress using metabolic rewiring and alternative pathways[15]. The connections between cancer and autophagy is a growing research area. While on one hand autophagy suppresses tumorogenesis, cancer cells also activate the process to avoid the stress and up-regulate growth and tumor aggression [16].

Autophagy strongly influences cancer so that modulation of this process has been identified as a potential target for cancer therapy[17].Omics data integration is widely used to investigate the genomic events and their interactions, as well as the potential regulatory mechanisms affected in cancer[18]. To fill the gap in the number of autophagy inhibitors and potential therapeutic agents, Peppard and collaborators designed a phenotypic, cell image-based assay for small molecules that affects the accumulation of autophagosomes in starved cells expressing GFP-LC3 (green flurescent protein light chain 3)[19].

Calorie Restrictions and Intermittent fasting (IF)

Calorie restrictions mean reduced food intake and intermittent fasting means food intake at prong interval. This kind of food habit imparts many benefits in model organisms. CR also promotes stress resistance and metabolic fitness. Emerging data in experimental models and in humans indicate that these benefits occur rapidly upon initiation of CR, suggesting potential clinical relevance[20]. IF regimens that induce the metabolic switch have the potential to improve body composition in overweight individuals. Moreover, IF regimens also induce the coordinated activation of signaling pathways that optimize physiological function, enhance performance, and slow aging and disease processes. Future randomized controlled IF trials should use biomarkers of the metabolic switch as a measure of compliance and the magnitude of negative energy balance during the fasting period[21]. In recent studies conducted in overweight humans, caloric restriction has been shown to improve a number of health outcomes including reducing several cardiac risk factors[22, 23,24] improving insulin-sensitivity and enhancing mitochondrial function[25].

Several different biological mechanisms may account for the increase in health span and longevity observed in response to caloric restriction in preclinical models. For example, aging is characterized by an exponential increase of oxidatively damaged proteins, and caloric restriction has been found to down regulate the expression of genes involved in oxidative stress and ameliorate oxidative damage in several different tissues[26,27,28,29,30,31]. Additional biological changes associated with caloric restriction that may contribute to the observed increases in health span and longevity include enhanced cellular quality control through autophagy, improved function of the ubiquitin-proteosome system (UPS: removal damaged proteins), and the maintenance of a healthy population of mitochondria through biogenesis (generation of new mitochondria)[32, 33, 27, 28, 34, 35, 36]. One alternative dietary approach that may produce similar biological changes as caloric restriction that has received increasing interest from the scientific community is intermittent fasting. In contrast to traditional caloric restriction paradigms, food is not consumed during designated fasting time periods but is typically not restricted during designated feeding time periods. The length of the fasting time period can also vary but is frequently several continuous hours. Evidence that this approach may have beneficial effects on longevity first appeared several decade ago[37]. Since this time, a growing body of literature suggests that intermittent fasting regimens can trigger similar biological pathways as caloric restriction which can result in a host of beneficial biological effects including increased circulation and cardiovascular disease protection, and modulation of reactive oxygen species and inflammatory cytokines[38].

A growing body of evidence indicates that intermittent fasting regimens in particular can trigger similar biological pathways as caloric restriction. For this reason, there is increasing scientific interest in further exploring the biological and metabolic effects of intermittent fasting periods, as well as whether long-term compliance may be improved by this type of dietary approach[39]. During fasting, cells activate pathways that enhance intrinsic defenses against oxidative and metabolic stress and those that remove or repair damaged molecules. The extension of both median and maximum lifespan and the suppression of age-related diseases in laboratory animals by reduced food intake, i.e., calorie restriction (CR) are regarded as hallmarks of CR's anti-aging action. The diverse efficacy of CR to counteract aging

effects and its experimental reproducibility has made it the gold standard of many aging intervention studies of recent years. Advances in CR research on non-human primates and recent endeavors using human subjects offer a promising outlook for CR's beneficial effects in healthy human aging[40]. Restriction of the daily food intake results in weight loss, which is also, associated with better health outcomes including controlling lipid profiles, blood pressures, improving insulin sensitivity. Based on the qualitative analysis, intermittent fasting was found to be efficient in reducing weight, irrespective of the body mass index[41]. The peripheral nervous system (PNS) comprises of an extensive network of connections that convey information between the central nervous system (CNS) and peripheral organs. Long myelinated nerve fibers are particularly susceptible to age-related changes, as maintenance of the insulating glial membrane requires extensive synthesis and processing of many proteins. In rodent models, peripheral demyelination caused by genetic risk factors or by normal aging are attenuated by intermittent fasting (IF) or calorie restriction (CR)supporting a role for dietary intervention in preserving neural function[42].

Among the several approaches to interrupt aging processes, calorie restriction (CR) has been shown to recover and/or slow age-related functional declines in various organs, including the eye[43,44]. Exercise opposes deleterious effects of secondary aging by preventing the decline in mitochondrial respiration, mitigating aging-related loss of muscle mass and enhancing insulin sensitivity.[45]Preclinical studies and clinical trials have shown that intermittent fasting has broad-spectrum benefits for many health conditions, such as obesity, diabetes mellitus, cardiovascular disease, cancers, and neurologic disorders. After nearly a century of research on caloric restriction in animals, the overall conclusion was that reduced food intake robustly increases the life span. Studies of the mechanisms of caloric restriction and intermittent fasting in animal models have led to the development and testing of pharmacologic interventions that mimic the health and disease-modifying benefits of intermittent fasting. Available data from animal models suggests that the safety and efficacy of such pharmacological approaches are likely to be inferior to those of intermittent fasting[46].

Conclusions

An important objective for autophagy research in forthcoming years will be the identification of causal connections between autophagy and aging. We surmise that this goal will be facilitated by the identification of specific, highly potent pharmacologic activators or inhibitors of autophagy, as well as by the generation of sophisticated mouse models in which autophagy can be genetically switched on and off at will, in a spatially and temporarily controlled fashion. It will be necessary to assess which potential autophagy inducers are effective and applicable to humans. Recent research has indicated roles for autophagy in an increasing number of pathologies, from bacterial and viral infections to cancer, and more recently in neurodegenerative and other age-related diseases. Research also shows, caloric restriction is the most effective strategy to induce autophagy, as it activates multiple regulatory pathways. Despite the evidence for the health benefits of intermittent fasting and its applicability in many diseases, there are impediments to the widespread adoption of these eating patterns in the community and by patients. First, a diet of three meals with snacks every day is so ingrained in our culture that a change in this eating pattern will rarely be contemplated by patients or doctors.

The abundance of food and extensive marketing in developed nations are also major hurdles to be overcome. Second, on switching to an intermittent fasting regimen, many people will experience hunger, irritability, and a reduced ability to concentrate during periods of food restriction. If opulent understands the benefits of fasting they can donate their surplus food to the poverty perished people of low resource countries Muslims are habituated to fast as religious rituals and enjoying the benefits of healthy aging for thousands of years.

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