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Fasting-Driven Autophagy and Mitochondrial Reprogramming

Shakthi CM[1], Swapna S[2], Prajna P Shetty[3]

[1]Intern, Sharada Yoga and Naturopathy Medical College
[2]Professor, Department of Research Methodology, Sharada Yoga and Naturopathy Medical College
[3]CMO, Department of Clinical Naturopathy, Sharada Yoga and Naturopathy Medical College

Abstract
Cellular health relies on the capacity to detect metabolic stress, eliminate damaged parts, and regenerate vital organelles. Fasting serves as a biological cue that prompts cells to transition from growth to repair by triggering conserved stress-response mechanisms. At the heart of this process are autophagy and mitophagy, which selectively break down faulty proteins and mitochondria, maintaining cellular integrity. Mitochondria are crucial for energy production, redox regulation, and survival signaling, making their renewal vital for continuous cell function. When autophagy and mitochondrial quality control are compromised, oxidative stress, inflammation, and disease can develop. Fasting-driven changes in nutrient-sensing pathways like mTOR, AMPK, and sirtuins help restore equilibrium, supporting mitochondrial renewal and cellular resilience.

Keyword: Fasting, Autophagy, Mitophagy, Oxidative stress, Mitochondria

Introduction

Fasting has a longstanding history, but only recently have studies uncovered its ability to trigger adaptive cellular mechanisms that reduce oxidative damage and inflammation, boost energy metabolism, and strengthen cellular defences[1]. Fasting involves voluntary avoidance of some or all food and drink for therapeutic, spiritual, or political reasons. Recent research in animals and humans demonstrates that fasting can promote beneficial physiological changes, such as increasing ketone production, altering hormone levels, lowering oxidative stress and inflammation, and improving stress resistance, fat metabolism, and autophagy[2]. Autophagy is a process where cells break down and recycle damaged or unneeded components via lysosomes. Once thought to be a simple housekeeping function, autophagy is now recognized as vital for various physiological and disease processes[3]. Of the organelles regulated by autophagy, mitochondria are especially important for energy balance and determining cell fate. The targeted removal of dysfunctional mitochondria, known as mitophagy, is critical for maintaining mitochondrial quality, cellular integrity, and overall health[4]. Mitochondrial dysfunction contributes to many age-related diseases, making mitochondrial population balance regulated by mitophagy essential for health. Caloric restriction (CR) is among the strongest non-genetic inducers of mitophagy[5]. Evidence suggests dietary restriction (DR), including lower calorie intake, changes in diet composition (like protein content), and meal timing adjustments (such as intermittent fasting [IF]), aids in preventing and managing chronic illnesses[6]. IF typically involves scheduled fasting days (one to three per week) alternated with unrestricted eating. One major mechanism behind fasting's metabolic benefits is autophagy activation[7].

Engaging adaptive cellular stress pathways through fasting enhances mitochondrial health, supports DNA repair, and increases autophagic activity considered core ways intermittent fasting (IF) provides health benefits and slows disease progression[8]. IF also affects several signaling pathways, including inhibition of mTOR, increased mitochondrial efficiency, stimulation of mitochondrial formation, and promotion of autophagy[9]. Both fasting and caloric restriction (CR) can activate autophagy, a crucial cellular process that preserves normal function and homeostasis. By removing damaged proteins and organelles and encouraging renewal, autophagy improves metabolism, supports stress adaptation, and ultimately bolsters cellular and overall physiological health[10].

Methodology

Body

FASTING

Fasting in humans refers to the complete or substantial restriction of food and calorie-containing beverages for a defined period, which may range from approximately 12 hours to several weeks. Apart from its physiological significance, fasting has long been incorporated into various religious and cultural practices. For instance, Muslims observe fasting from dawn until sunset during Ramadan, whereas Christians, Jews, Buddhists, and Hindus undertake fasting on designated days or during specific periods of the year [11]. Fasting should be distinguished from caloric restriction (CR), which involves a sustained reduction of daily energy intake by approximately 20–40% while maintaining a relatively consistent meal pattern. Starvation, in comparison, represents a more severe and prolonged state of nutritional deprivation that may result in tissue deterioration and, in extreme circumstances, death. Although fasting and starvation are occasionally used synonymously, particularly in studies involving lower eukaryotic organisms, they represent physiologically distinct conditions [12].

During fasting, the body undergoes a series of coordinated metabolic adaptations that conserve glucose and promote the utilization of fat as the primary energy source. These adaptations help preserve limited carbohydrate reserves, while gluconeogenesis contributes to maintaining glucose availability through the utilization of substrates such as amino acids and glycerol. Ketone bodies also become increasingly important as alternative energy substrates during prolonged fasting [13].

Fasting practices have evolved considerably from their traditional origins, with contemporary approaches increasingly shaped by advances in nutritional and metabolic research. Modern fasting protocols are generally classified according to their duration, eating patterns, physiological mechanisms, and potential health outcomes [14]. Time-restricted feeding (TRF) involves consuming all daily meals within a predetermined eating window. Intermittent fasting (IF) follows a cyclical pattern of eating and fasting, usually involving fasting periods of up to 24 hours, and includes approaches such as alternate-day fasting (ADF) and modified alternate-day fasting (MADF). Prolonged fasting (PF), in contrast, involves abstaining from food for periods extending beyond 48 hours [15].

Intermittent fasting has emerged as a dietary intervention involving repeated alternation between periods of food consumption and restricted or absent caloric intake. During fasting intervals, individuals refrain from consuming energy-containing foods and beverages. The approach encompasses several protocols, including alternate-day fasting, time-restricted feeding, whole-day fasting, and modified fasting regimens [16]. In alternate-day fasting, fasting and feeding days occur in succession. Depending on the protocol, fasting days may involve complete abstinence from caloric intake or a substantial reduction in energy

consumption to approximately 25% of usual daily requirements (around 2090 kJ), whereas food intake is generally unrestricted on feeding days [16].

Varady and Hellerstein (2007), in their review of alternate-day fasting research conducted in rodent models, demonstrated that this dietary intervention produced effects comparable to conventional caloric restriction in reducing body weight and improving obesity-associated metabolic parameters, particularly fasting glucose and insulin concentrations [17].

Currently, three prominent dietary approaches involving fasting are widely discussed: time-restricted feeding (TRF), intermittent fasting (IF), and the fasting-mimicking diet (FMD). TRF restricts daily food consumption to a specific period, commonly ranging from 4 to 12 hours, without necessarily reducing overall caloric intake. IF involves alternating periods of habitual eating with intervals of reduced or absent energy consumption. FMD, however, is a specifically formulated, low-calorie, predominantly plant-based dietary intervention intended to reproduce certain physiological responses associated with fasting while providing essential nutrients, including vitamins and minerals [18].

In recent years, intermittent fasting has attracted considerable scientific and public interest as a potential dietary strategy for improving health and metabolic function. It is characterized by recurring periods of minimal or zero energy intake, which may extend from approximately 24 hours to several consecutive days, depending on the protocol employed [19]. Emerging evidence also indicates that intermittent fasting may influence the composition and activity of the intestinal microbiota. Such alterations in the gut microbial environment may subsequently affect several aspects of host physiology, particularly immune responses and metabolic homeostasis. The gut microbiota itself is an essential component of human health, contributing to normal physiological functioning and influencing susceptibility to various diseases [20].

Furthermore, fasting has been associated with improvements in several circulating biomarkers related to metabolic health, enhanced cellular stress resistance, and the regulation of inflammatory processes. Its growing popularity is also linked to proposed benefits such as body-weight management, preservation of cognitive function, and the promotion of healthy ageing and longevity [21]. At the cellular and molecular levels, fasting stimulates ketone body production and induces substantial alterations in metabolic pathways and cellular activities, including lipolysis, autophagy, and stress-response mechanisms. These physiological adaptations have also generated interest in the therapeutic potential of fasting in certain medical conditions. Reported applications include the reduction of seizure activity and associated neuronal damage, as well as potential benefits in inflammatory disorders such as rheumatoid arthritis [22].

AUTOPHAGY

Autophagy is an essential intracellular catabolic mechanism through which cytoplasmic components are transported to lysosomes for degradation. Although the process may appear relatively straightforward, extensive research has revealed its involvement in numerous physiological and pathological processes, many of which are highly complex [23]. The term autophagy is derived from Greek roots meaning "self-eating." Macroautophagy, commonly referred to as autophagy, is a fundamental cellular mechanism responsible for preserving cellular and tissue homeostasis. Dysregulation of this process has been associated with several pathological conditions, including neurodegenerative disorders, cardiomyopathy, cancer, diabetes mellitus, fatty liver disease, and Crohn's disease [24].

The autophagic process begins with the formation of a double-membrane-bound structure called an autophagosome within the cytoplasm. This vesicle encloses portions of the cytoplasm or selectively identified cellular components targeted for degradation. Subsequently, the autophagosome fuses with a

lysosome, allowing its internal vesicle, known as the autophagic body, to enter the lysosomal compartment. The enclosed cellular materials are then broken down by lysosomal hydrolytic enzymes into simpler molecular constituents, which are recycled and reused by the cell to support essential metabolic and cellular functions [25].

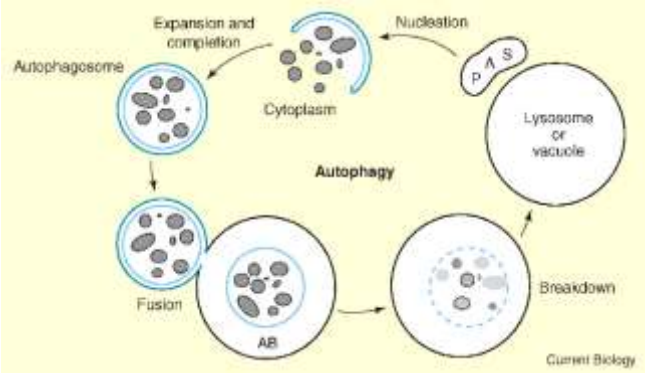


Figure.1:Autophagy

Autophagy occurs continuously at basal levels in most cell types, where it functions as a cellular maintenance mechanism by eliminating damaged proteins and dysfunctional organelles, thereby maintaining intracellular quality and homeostasis. Under conditions of nutrient deprivation, however, autophagic activity is substantially enhanced. This upregulation represents an important adaptive response that allows cells and organisms to withstand periods of limited nutrient availability by mobilizing intracellular resources and promoting survival until adequate nutrients become available again [26].

Autophagy is a tightly controlled intracellular degradation process involving a series of sequential and interconnected molecular events. The major stages include: (a) **Initiation**, during which the phagophore, or isolation membrane, begins to develop through the activation of the Beclin-1/VPS34 complex at the endoplasmic reticulum and other intracellular membrane sources in response to stress signals; (b) **Atg protein complex formation**, involving the conjugation of Atg12 with Atg5 and its subsequent association with Atg16L to form a complex that facilitates phagophore expansion; (c) **LC3 processing and lipidation**, through which LC3 is processed and incorporated into the developing phagophore membrane; (d) **Cargo sequestration and autophagosome maturation**, involving the enclosure of selected or non-selective cellular components within the expanding membrane, followed by autophagosome completion and LC3-II/ATG8 recycling mediated by ATG4; and (e) **Autophagosome–lysosome fusion**, wherein the mature autophagosome merges with the lysosome, allowing lysosomal proteases to degrade the enclosed cellular materials [27].

Mitophagy is a specialized form of selective autophagy responsible for the recognition and removal of damaged or dysfunctional mitochondria. This process plays a crucial role in maintaining mitochondrial quality and cellular homeostasis while preventing excessive accumulation of reactive oxygen species (ROS), which can otherwise contribute to oxidative stress and cellular damage [28].

MITOPHAGY

Mitochondria are essential cellular organelles that play a fundamental role in energy production, the regulation of cellular metabolism, and the control of programmed cell death. Maintaining mitochondrial quality is therefore crucial for normal cellular functioning. The selective removal of damaged or

dysfunctional mitochondria through autophagy, a process known as mitophagy, represents an important mechanism for preserving cellular homeostasis [29]. The term mitophagy was first introduced by Lemasters to describe the selective degradation of mitochondria through the autophagic pathway [30].

Mitophagy is a specialized type of macroautophagy in which mitochondria are selectively recognized, transported to lysosomes, and subsequently degraded. This process is activated when mitochondrial damage exceeds the capacity of existing mitochondrial quality-control mechanisms or when the removal of mitochondria becomes necessary to accommodate changing cellular metabolic requirements. In contrast to non-selective autophagy, mitophagy involves specific recognition mechanisms, including the recruitment of mitochondrial receptor proteins and the activation of distinct molecular signaling pathways that facilitate the selective elimination of mitochondria [31].

Early evidence supporting mitochondrial degradation through lysosomes was provided by Ashford and Porter, who observed mitochondrial structures within a large proportion of lysosomes, frequently accompanied by other cellular components. Based on these observations, they proposed that mitochondria undergo degradation within lysosomal compartments. However, the precise sequence of events remained unclear, particularly whether mitochondrial deterioration occurred before their incorporation into lysosomes or developed as a consequence of lysosomal engulfment [32].

Despite considerable advances in this field, the molecular mechanisms and signaling networks responsible for regulating mitophagy in mammalian cells are not yet completely elucidated. Current evidence indicates that mitochondrial homeostasis is maintained through the coordinated activity of several regulatory molecules and mechanisms, involving both autophagy-dependent and autophagy-independent pathways [33].

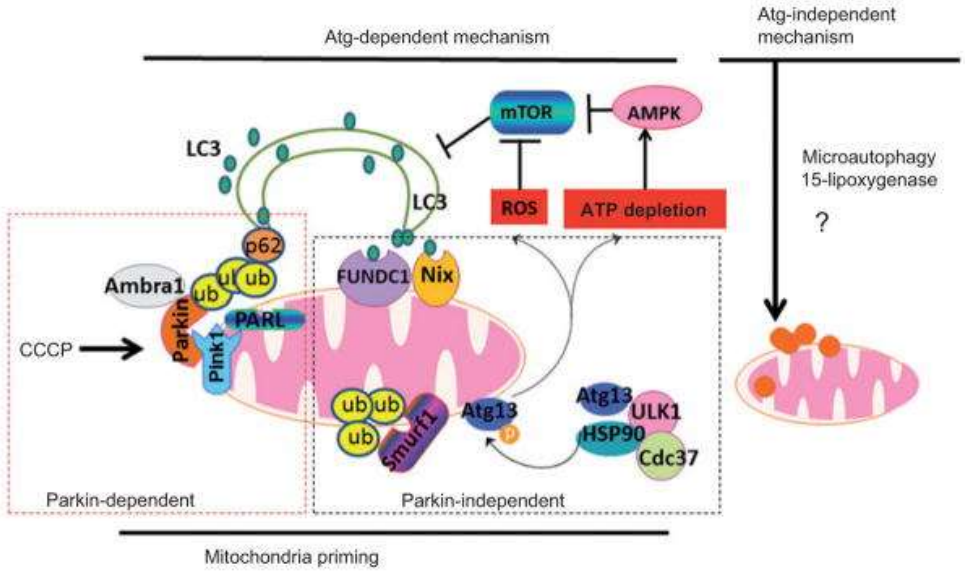


Figure.2 : Proposed models for mitophagy in mammalian cells[29]

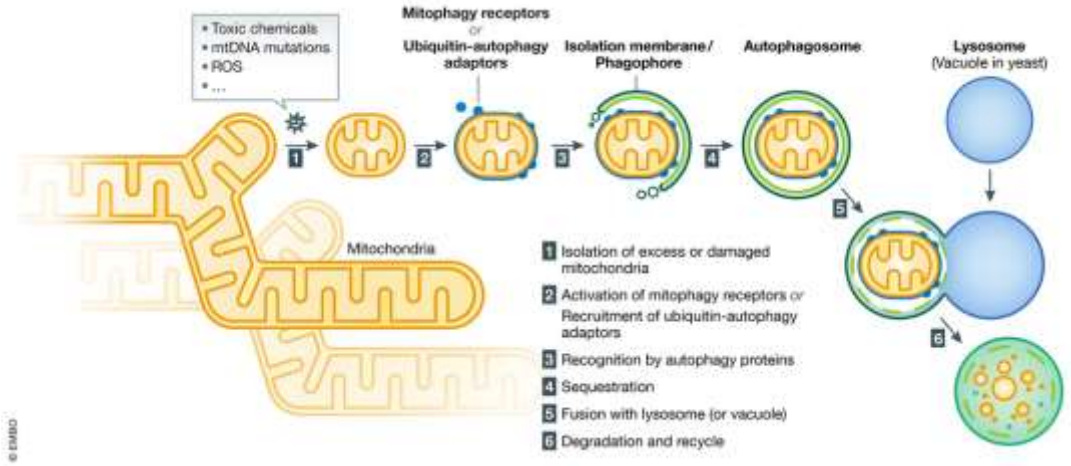


Figure.3 : Molecular mechanisms and physiological functions of mitophagy[34]

The process of mitophagy is initiated in response to various intracellular and extracellular signals that promote the fragmentation and segregation of damaged or surplus mitochondria. Following this, specific mitophagy receptors or ubiquitin-binding autophagy adaptor proteins are recruited to the mitochondrial membrane, facilitating the selective recognition of these organelles by the autophagic machinery. Subsequently, autophagy-related proteins coordinate the formation of a phagophore around the targeted mitochondria, resulting in the development of mitochondria-containing autophagosomes. These structures then fuse with lysosomes in mammalian cells or vacuoles in yeast, where lysosomal or vacuolar hydrolases break down the mitochondrial components. The degraded products are subsequently recycled and utilized by the cell [34].

In mammalian cells, mitophagy is broadly regulated through two major mechanisms: damage-induced mitophagy and developmentally controlled mitophagy. The damage-induced pathway is predominantly mediated by two important regulatory proteins: (i) PTEN-induced putative kinase 1 (PINK1), a serine/threonine protein kinase, and (ii) Parkin, an E3 ubiquitin ligase. Together, these proteins play a central role in identifying damaged mitochondria and promoting their selective removal through the autophagic machinery [35].

Accumulating experimental evidence suggests that caloric restriction (CR) and fasting can stimulate mitophagy and increase the expression of proteins associated with mitochondrial quality control and mitophagic activity [5]. Furthermore, dietary restriction (DR), achieved through modifications in total caloric consumption, nutritional composition, particularly protein intake, and meal timing, including intermittent fasting, has emerged as an important approach with potential benefits in the prevention and management of various chronic diseases [36].

Pathophysiology

A growing body of research suggests that dietary restriction (DR), achieved through modifications in energy intake, nutritional composition, particularly protein consumption, and eating patterns such as intermittent fasting (IF), may contribute significantly to the prevention and management of chronic diseases [37].

The beneficial effects of dietary restriction on longevity and health span are mediated by several interconnected molecular signaling pathways. Under conditions of nutrient abundance, nutrient-sensing

pathways become activated, stimulating cellular growth, proliferation, and metabolic activity [38]. Conversely, reduced nutrient availability or deprivation of specific macromolecules suppresses these signaling pathways and initiates adaptive cellular responses. These responses promote protective metabolic mechanisms, restrict excessive cellular proliferation, minimize the accumulation of cellular damage, and activate stress-responsive transcription factors that counteract molecular pathways associated with ageing [39].

Fasting and caloric restriction (CR) influence several intracellular signaling networks, thereby initiating systemic adaptations that contribute to improved health and metabolic regulation. At the molecular level, these interventions suppress insulin-like growth factor-1 (IGF-1) receptor signaling, target of rapamycin (TOR) activity, and nuclear factor-kappa B (NF-κB) signaling. Simultaneously, they stimulate pathways involving AMP-activated protein kinase (AMPK), sirtuins, Forkhead box O (FoxO) transcription factors, and nuclear factor erythroid 2-related factor 2 (Nrf2) [40].

Furthermore, fasting and caloric restriction promote the activity of cyclic AMP response element-binding protein (CREB) and enhance the expression of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 2 (FGF-2). Together, these molecular adaptations contribute to increased autophagic activity, attenuation of inflammatory responses and oxidative stress, regulation of cellular proliferation, and improvement in mitochondrial function. At the whole-body level, these changes have been associated with reductions in body temperature, circulating insulin and leptin concentrations, adiposity, and blood pressure, alongside potential improvements in longevity [41].

Collectively, these physiological and molecular adaptations suggest that fasting and caloric restriction may provide protective effects against several age-associated disorders. These include neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, as well as metabolic and systemic conditions including cardiovascular diseases, diabetes mellitus, and cancer [42].

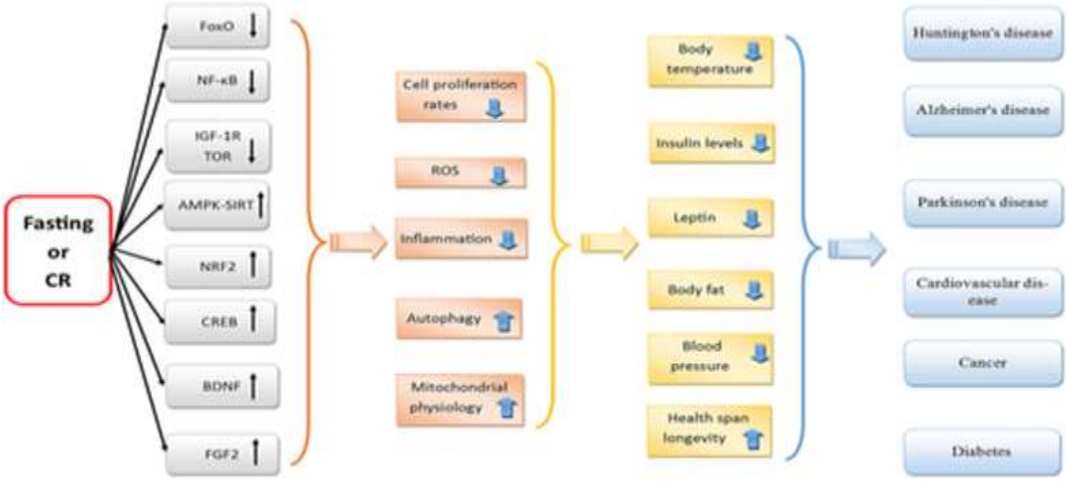


Figure.4 : Calorie restriction effect on cellular pathway [40]

Indication

The induction of autophagy and mitophagy through fasting and dietary restriction may offer potential preventive and supportive benefits in various pathological conditions associated with metabolic disturbances, mitochondrial dysfunction, and persistent inflammation. These conditions include obesity, insulin resistance, type 2 diabetes mellitus, cardiovascular disorders, and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. Furthermore, these interventions

may have relevance in mitigating age-related physiological deterioration and influencing cancer-related processes. Beyond their potential therapeutic applications, fasting-based dietary interventions may also serve as complementary lifestyle strategies in healthy individuals by enhancing cellular stress resistance, improving metabolic flexibility, maintaining mitochondrial function, and supporting healthy ageing.

Current evidence

Emerging scientific evidence suggests that fasting may promote cellular maintenance and renewal by influencing nutrient-sensing mechanisms involved in the regulation of autophagy and mitochondrial homeostasis. Bensalem et al. (2025) observed that intermittent time-restricted eating may affect autophagic flux in humans; however, these findings remain preliminary and exploratory in nature [43]. Similarly, Espinoza et al. provided preliminary evidence indicating alterations in autophagic flux and metabolic biomarkers following the implementation of a fasting-mimicking diet in healthy adults [44]. In addition, a controlled cohort study conducted in 2025 examining the effects of Ramadan fasting reported potential changes in autophagy-associated proteins and gene expression, suggesting that fasting may influence cellular recycling mechanisms [45].

Nevertheless, evidence regarding the effects of fasting on mitochondrial adaptations in humans remains inconclusive. A systematic review investigating fasting-induced AMPK–PGC-1α signaling reported that evidence supporting mitochondrial biogenesis in human skeletal muscle was less consistent than that observed in animal experimental models [46]. Furthermore, Liu et al. (2024) highlighted the essential contributions of mitochondrial biogenesis, mitochondrial dynamics, and mitophagy in maintaining cellular integrity and metabolic homeostasis [47].

Taken together, these findings provide a scientific basis for the potential role of fasting in regulating cellular maintenance, autophagy, and mitochondrial quality control. However, despite encouraging preliminary observations, further large-scale, well-controlled human studies are necessary to determine whether fasting consistently enhances autophagic flux, stimulates mitophagy, and improves mitochondrial function across different tissues and physiological conditions.

Future direction

Despite considerable experimental evidence demonstrating the potential of fasting and dietary restriction to stimulate autophagy and mitophagy, several aspects of these processes remain insufficiently understood. Future investigations should prioritize well-structured, long-term human clinical studies to determine the optimal duration, frequency, and pattern of fasting while accounting for individual physiological differences. Further research is also required to elucidate tissue-specific variations in mitophagic activity, sex-related differences in metabolic responses, and the influence of circadian rhythms and gut microbiota on fasting-induced cellular adaptations. Moreover, incorporating reliable molecular biomarkers associated with autophagy and mitophagy into clinical research would provide a better understanding of the underlying mechanisms and facilitate the translation of experimental findings into clinically relevant, individualized therapeutic approaches.

Conclusion

Fasting and dietary restriction are increasingly recognized as important non-pharmacological approaches capable of stimulating autophagy and mitophagy, thereby contributing to mitochondrial quality maintenance, improved metabolic regulation, and the preservation of cellular homeostasis. Through the

regulation of key nutrient-sensing and cellular stress-response signaling pathways, these interventions may help minimize oxidative damage, suppress inflammatory processes, and attenuate cellular alterations associated with ageing. Accumulating evidence suggests that the activation of autophagy and mitophagy represents an important underlying mechanism through which fasting may exert beneficial effects on metabolic health, promote healthy ageing, enhance health span, and potentially protect against various chronic and age-related disorders.

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