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REVIEW

# A Narrative Review about Metabolic Pathways, Molecular Mechanisms and Clinical Implications of Intermittent Fasting as Autophagy Promotor

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## Abstract

**Purpose of Review** This research aims to elucidate the molecular mechanisms by which intermittent fasting (IF) induces autophagy and to evaluate its therapeutic potential across a range of pathologies. By synthesizing findings from preclinical and clinical studies, the review seeks to clarify the roles of key signaling pathways—such as the AMPK–mTOR axis, sirtuins, and β-hydroxybutyrate-mediated signaling—in orchestrating autophagic processes, thereby enhancing cellular resilience and metabolic homeostasis.

**Recent Findings** Recent evidence demonstrates that IF robustly activates autophagy in metabolically active tissues through conserved molecular pathways. Experimental studies reveal that fasting increases AMPK phosphorylation and inhibits mTOR activity, leading to enhanced expression of autophagy markers like LC3-II, Beclin-1, and ATG proteins. Additionally, IF has been shown to improve insulin sensitivity, reduce hepatic lipid accumulation, and mitigate neurodegenerative processes by promoting the clearance of toxic protein aggregates. Emerging clinical data further support these findings, indicating that tailored fasting protocols can modulate autophagy to yield benefits in metabolic, oncological, and neurodegenerative disorders.

**Summary** The scoped literature underscores IF as a promising non-pharmacological strategy to induce autophagy and improve overall health. While robust preclinical and clinical evidence supports its beneficial effects, challenges remain in standardizing fasting protocols and identifying optimal biomarkers for monitoring autophagic activity. Future research should focus on long-term, well-controlled trials and combined therapeutic approaches to refine IF strategies, ultimately translating these insights into personalized dietary interventions for disease prevention and health optimization.

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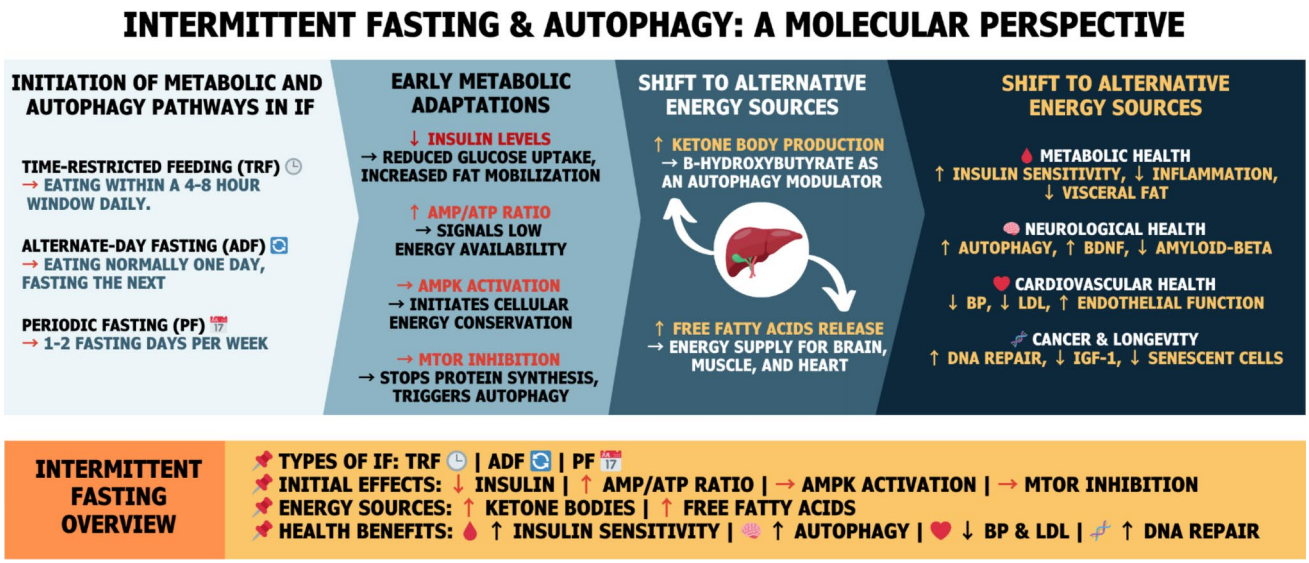
**Graphical Abstract**




**Keywords** Autophagy · Intermittent Fasting · Metabolism · AMPK · MTOR · Inflammation · Neurological · Cardiovascular

## Introduction

Intermittent fasting (IF) and autophagy have emerged as pivotal concepts in biomedical research due to their involvement in essential physiological processes such as energy metabolism and cellular homeostasis. Autophagy—often referred to as a cellular "self-digestion" mechanism—facilitates the degradation and recycling of cytoplasmic components, including damaged organelles and misfolded proteins, thereby maintaining cellular viability and homeostasis[1]. Of the three primary types of autophagy (macroautophagy, microautophagy, and chaperone-mediated autophagy), macroautophagy is the most extensively studied for its central role in cellular metabolism[2, 3].

IF, defined as a dietary pattern alternating feeding periods with calorie restriction, has been shown to trigger adaptive metabolic responses, notably the activation of autophagy[4, 5]. During fasting, intracellular energy levels drop, increasing the AMP/ATP ratio and activating AMPK while inhibiting mTOR—key regulators of autophagy[6]. This process supports cellular function under metabolic stress and is linked to beneficial effects in metabolic, inflammatory, and neurodegenerative conditions[2–5, 7]. Evidence further indicates that IF influences autophagy through highly conserved molecular pathways, such as the AMPK–mTOR–ULK1 axis, while also modulating mitochondrial remodeling and protein homeostasis[8]. Animal models suggest that IF positively regulates hepatic autophagy, reducing steatosis and improving overall metabolic function[2, 3]. These mechanisms also appear relevant to neuronal protection and muscle regeneration, two areas of growing research interest[4, 5, 7].

Given the therapeutic potential of IF-induced autophagy, recent work has focused on its tissue-specific effects in the liver, skeletal muscle, and brain, revealing benefits such as cellular regeneration, reduced oxidative damage, and improved insulin sensitivity[1, 7]. Moreover, modulating autophagy via IF has shown anti-aging properties and enhanced tolerance to chemotherapeutic treatments in both preclinical and clinical settings[2, 3, 7].

A key rationale for ongoing investigation is the identification of specific molecular pathways involved in IF-induced autophagy. Recent findings emphasize the roles of ATG5 and ATG7 in autophagic regulation and highlight their activation by IF-related signaling[4–6]. Expanding this research into various physiological and pathological contexts—including metabolic diseases, cancer, and neurodegenerative disorders—remains a critical objective[2, 3, 7, 9].

The main goal of this review is to elucidate how IF modulates autophagy, emphasizing the implicated molecular pathways and their clinical relevance. By synthesizing available evidence, it aims to reveal shared mechanisms across different tissues, potential therapeutic implications, and areas requiring further exploration. Additionally, this review delves into the underlying molecular mechanisms of IF-mediated autophagy and evaluates its potential applications in diseases such as type 2 diabetes, obesity[10], and cancer.

Further clarification on key concepts and their associated processes are presented now.

### Intermittent Fasting (IF)

IF alternates periods of normal food intake with caloric restriction or complete abstinence. Unlike continuous caloric restriction, IF induces distinct transient metabolic adaptations[11, 12]. Across the following regimens, IF promotes ketone body production during fasting periods and regulates the AMPK–mTOR pathways essential for autophagy and cell survival under energy stress[13, 14]. These processes help mitigate chronic inflammation and oxidative stress, reducing the risk of cardiovascular, neurodegenerative, and metabolic disorders[12, 15]. Although IF presents a promising therapeutic strategy for metabolic health, challenges remain regarding the standardization of protocols and the long-term evaluation of IF in diverse populations[16–18]. Some of the most common variants are described below.

- **Time-restricted feeding** (TRF) limits food consumption to a 4–8-h daily window, optimizing circadian rhythms, improving insulin sensitivity, and enhancing autophagy in organs such as the liver—thereby reducing inflammation and bolstering energy homeostasis[16, 18].
- **Alternate-day fasting** (ADF) involves normal eating on certain days and restricting caloric intake to about 25% on others. This pattern promotes the remodeling of adipose tissue toward a more metabolically active phenotype and lowers inflammatory markers and oxidative stress, both linked to aging and chronic diseases[13, 19].
- **Periodic fasting** (PF) —1–2 days of weekly caloric restriction— has been shown to slow the progression from nonalcoholic steatohepatitis (NASH) to hepatocellular carcinoma (HCC) by activating PPARα and PCK1, increasing fatty acid oxidation and reducing hepatic lipid accumulation[17, 18].
- **Ramadan Fasting** is another pretty popular fasting model coming from religious practices mostly extended in middle eastern and Muslim-predominant regions. A form of dawn-to-dusk IF, Ramadan fasting has been shown to effectively promote autophagy with results similar to other IF and caloric-restricted protocols[20, 21].
- **5:2 Fasting** is a popular form of IF involving two non-consecutive days of severe calorie restriction per week, has shown promising effects in clinical contexts, particularly in promoting autophagy and improving metabolic health. Clinically, the 5:2 diet has demonstrated superior outcomes compared to daily calorie restriction in reducing liver fibrosis and steatosis in patients with metabolic-associated fatty liver disease, even with similar weight loss, indicating a unique benefit potentially mediated by fasting-induced autophagy[22].

### Autophagy

Autophagy is an evolutionarily conserved biological process that preserves cellular homeostasis by degrading and recycling intracellular components. It safeguards the functionality of organelles and proteins, particularly under conditions of metabolic stress or nutrient deprivation. Beyond its role in cellular maintenance, autophagy governs critical physiological processes such as cell differentiation, tissue remodeling, and immune responses. Dysregulation of autophagy has been implicated in various human pathologies, including metabolic disorders, neurodegenerative diseases, and certain cancers[23, 24].

Under fasting conditions, autophagy serves as a key adaptive mechanism, mobilizing intracellular resources to generate energy and vital metabolic precursors. This strategy not only sustains the cell's energy balance but also removes damaged organelles and proteins, thereby protecting overall cellular function. Autophagy is especially relevant in preventing age-related diseases and mitigating oxidative stress and chronic inflammation[25, 26]. Recent findings further underscore its importance in metabolic stress responses, revealing how activation of molecular pathways such as AMPK–mTOR during fasting enhances autophagy and curbs the buildup of toxic intracellular components, thus delaying aging and warding off degenerative conditions (Table 1)[17].

## Metabolism, Molecular Processes and Key Genes

Being an extremely complex cellular process, autophagy is mediated by a plethora of molecular signals, which are also modulated by key genes and other complementary metabolic processes. These key insights are presented in this section. In Fig. 1 **a** summary of the most important molecular processes is depicted.

### Phagophore Formation and Lysosomal Degradation

Autophagy begins with the formation of the phagophore, a membrane structure that envelops intracellular components marked for degradation. This process is triggered by signals reflecting the cell's metabolic status—such as nutrient scarcity or intracellular damage—and depends on a coordinated network of autophagy-related proteins and genes (ATGs), which govern distinct stages of autophagy[4, 23]. Once the phagophore closes to form a double-membraned autophagosome, it fuses with lysosomes to create the autolysosome, where enzymatic

**Table 1** Summary of clinical evidence for medical conditions, reported IF strategies, and expected clinical outcomes

| Disease Category | Specific Disease/Condition | IF Protocol | Expected Clinical Outcome | Clinical Reference |
|---|---|---|---|---|
| **Metabolic** | Type 2 Diabetes Mellitus | 5:2 IF with meal replacements on 2 nonconsecutive days/week | ↓ HbA1c (–1.9% vs metformin – empagliflozin ~0.4%); improved glycemic control; weight loss | 56 |
| | | 10-h TRE (ad libitum eating, no calorie counting) | ↓ HbA1c; weight loss; improved glycemic control | 57 |
| | Overweight/Obesity | 16:8 TRE (eat 12 pm–8 pm; 16 h fast) | Weight loss; improved insulin sensitivity trends | 58 |
| | Metabolic Syndrome | 6-h early TRE (eat 7 am–3 pm) + energy restriction | Weight loss; ↓ diastolic BP; improved mood | 55 |
| **Cardiovascular** | Hypertension | 6-h early TRE (eat 7 am–3 pm) + energy restriction | ↓ Diastolic BP; weight loss; improved mood | 55 |
| **Liver** | NASH | 5:2 IF (two low-calorie days/week) | ↓ Fibrosis and steatosis; ↑ PPARα & PCK1; blunted progression to cancer | 17 |
| **Brain** | Insulin-resistant older adults (cognitive health) | 5:2 IF vs healthy-living diet (crossover, 8 weeks) | Improved functional brain connectivity; enhanced cognitive performance | 45 |
| | Alzheimer's Disease | 16:8 TRE | ↑ Plasma D-β-hydroxybutyrate; cognitive score improvements | 60 |
| **Cancer** | Hepatocellular Carcinoma (from NASH) | 5:2 IF | ↓ Progression to HCC from NASH; reduced fibrosis; improved liver histology | 17 |
| | Lung Cancer | 6-h TRE (fast 18 h/eat 6 h) | ↓ Tumor progression; reshaped circadian metabolism | 35 |

degradation occurs. Lysosomes supply the hydrolytic enzymes needed to break down proteins, lipids, and other macromolecules into basic units that can be recycled for cellular metabolism, highlighting their critical function in the autophagic pathway[27, 28].

## Ketogenesis and β-Hydroxybutyrate in Autophagy Regulation

During IF, ketogenesis yields ketone bodies—most notably β-hydroxybutyrate (βHB)—which play a pivotal role in autophagy regulation. βHB functions as a signaling molecule that directly promotes autophagy by inhibiting histone deacetylases (HDACs) and increasing the expression of autophagy-related genes such as LC3 and Beclin-1. Recent studies demonstrate that βHB enhances autophagic activity in neurons and hepatocytes, facilitating the clearance of toxic proteins and dysfunctional organelles[29]. In metabolic disease models, elevated βHB from IF boosts lipophagy in the liver and mitophagy in skeletal muscle, reducing inflammation and improving insulin sensitivity[30].

## LC3 as a Central Marker and Quality Control

LC3 (Microtubule-associated proteins 1 A/1B light chain 3) is a key and widely present autophagy marker. It plays a pivotal role in phagophore elongation and maturation. During autophagy, LC3-I undergoes a post-translational modification, a covalent conjugation to phosphatidylethanolamine, yielding LC3-II, which then interacts with specific autophagosome proteins, enabling both autophagosome maturation and selective substrate capture. Recent studies also underscore LC3's role in the targeted removal of dysfunctional organelles, such as damaged mitochondria, via mitophagy[4, 24, 31].

## Beclin-1 as Essential Initiator of Autophagy

Beclin-1 functions in the early stages of autophagy, forming complexes with proteins such as VPS34 and ATG14 that are critical for phagophore nucleation. These complexes regulate the production of phosphatidylinositol 3-phosphate (PI3P), a lipid essential for phagophore formation and for recruiting effector proteins involved in membrane elongation. Beclin-1 also participates in selective autophagy, enabling the

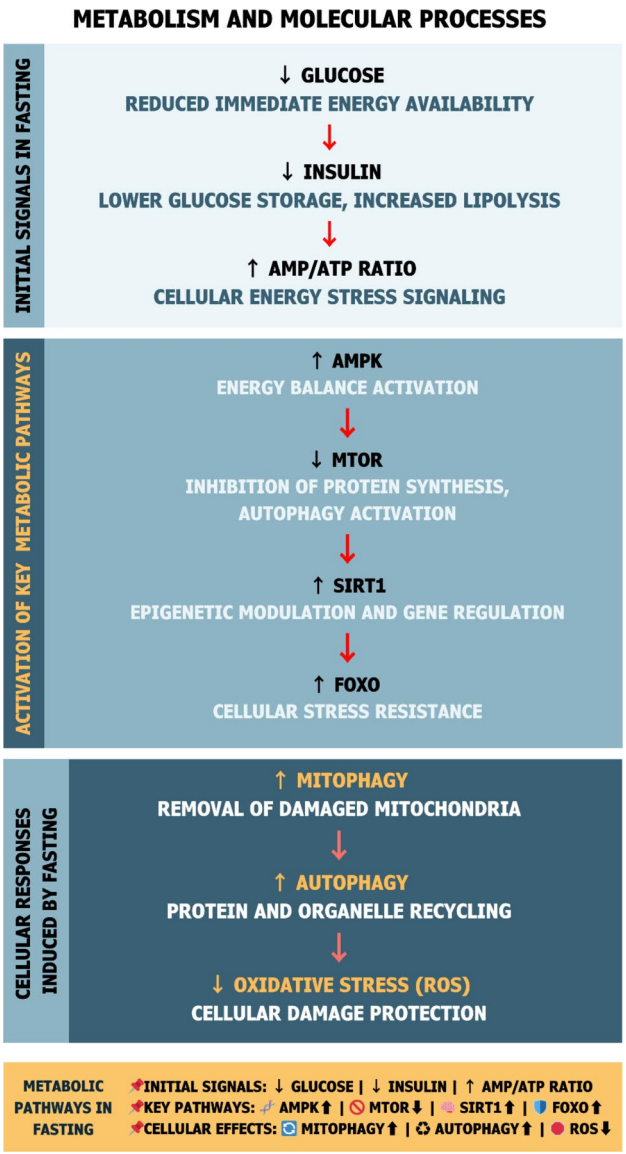



**Fig. 1** Summary of metabolic pathways and molecular processes associated with IF that are attributed to encompassing the majority of the health benefits for such protocols

targeted removal of protein aggregates and other damaged cellular components[4, 23].

## AMPK and mTOR in Autophagy

Intermittent fasting promotes autophagy largely by activating AMPK—an energy sensor upregulated under nutrient scarcity—and inhibiting mTOR, a central regulator of cell growth and energy metabolism. When AMPK is phosphorylated during fasting, it suppresses mTOR and initiates the ULK1 complex, triggering phagophore assembly. Experimental models demonstrate that IF raises AMPK phosphorylation and diminishes mTOR activity, thereby enhancing autophagy in metabolically active tissues like liver and skeletal muscle[25, 32]. Moreover, IF increases Beclin-1 and ATG5 expression—key proteins for autophagosome elongation and maturation—protecting hepatic cells from triglyceride overload and preventing steatosis[33]. This mTOR inhibition also improves insulin sensitivity, underscoring IF's therapeutic potential for metabolic diseases. The mammalian Target of Rapamycin (mTOR) complex acts as a key negative regulator of autophagy. Under nutrient-rich conditions, mTOR inhibits ULK1 activation and thus prevents autophagy initiation. In addition, pharmacological inhibition of mTOR with compounds such as rapamycin can enhance autophagic activity and confer benefits in disease models characterized by intracellular waste accumulation[17, 34].

## SIRT1 and SIRT3 as Epigenetic Regulators

SIRT1 (Sirtuin 1) plays a pivotal role in autophagy through its epigenetic and post-translational regulatory functions. By deacetylating critical factors such as p53 and metabolic regulators like PGC-1α, SIRT1 promotes autophagy in response to energy stress signals. This mechanism is especially relevant during fasting, when SIRT1 helps mobilize cellular resources, maintain energy homeostasis, and protect against oxidative damage[27, 28, 35]. SIRT3 is pivotal for regulating mitochondrial energy metabolism. A recent study found that IF upregulates SIRT3, thereby enhancing mitochondrial efficiency and lowering the production of reactive oxygen species (ROS)—factors closely linked to cellular aging and neurodegenerative disorders[25].

## Lysosomes as Central Workers in Autophagy and Metabolic Adaptations

Lysosomes are specialized organelles crucial for autophagy, serving as "recycling centers" that degrade proteins, lipids, and dysfunctional organelles into basic building blocks such as amino acids, fatty acids, and simple sugars. These metabolites are then reused by the cell for essential metabolic processes. Under fasting conditions, lysosomal activity rises significantly to accommodate the increased autophagic flux, facilitating cellular adaptation to metabolic stress and nutrient scarcity[28, 31]. During autophagy, double-membraned autophagosomes—formed to encapsulate damaged intracellular components—fuse with lysosomes to create autolysosomes. This fusion is regulated by proteins such as SNAREs and Rab7, while hydrolytic enzymes (proteases, lipases, and nucleases) perform substrate breakdown[23, 24, 36]. Prolonged fasting induces lysosomal biogenesis via Transcription Factor EB (TFEB), a master regulator of lysosomal function. When energy stress signals inactivate mTORC1, TFEB translocates to the nucleus and drives the expression of genes needed for lysosome formation and

vesicular trafficking[28, 37]. Consequently, lysosome number and size often increase, with fine-tuning of intralysosomal pH to optimize enzymatic efficiency[27, 31, 34]. A central benefit of elevated lysosomal function during fasting is the generation of essential metabolites. Intracellular protein breakdown supplies amino acids for hepatic gluconeogenesis, while the degradation of lipids (lipophagy) releases fatty acids that support ketogenesis in the liver. These ketone bodies serve as an alternative energy source for peripheral tissues, including the brain[17, 37]. Removal of defective organelles, such as damaged mitochondria via mitophagy, further prevents reactive oxygen species (ROS) buildup and oxidative damage[24]. Autophagy and lysosomal function are governed by a complex signaling network involving mTORC1, AMPK, and SIRT1. In nutrient-rich conditions, mTORC1 activity restricts TFEB's nuclear translocation and inhibits autophagy. During fasting, mTORC1 inactivation permits TFEB to enter the nucleus, upregulating lysosome- and autophagy-related genes[28, 31]. AMPK, an energy sensor, supports autophagy by directly activating ULK1 and suppressing mTORC1, whereas the $NAD^+$-dependent deacetylase SIRT1 positively regulates TFEB and additional factors linked to autophagy and lysosomal function[34]. Lysosomal dysfunction is implicated in a range of diseases, including neurodegenerative disorders (Alzheimer's and Parkinson's) and metabolic conditions such as nonalcoholic steatohepatitis (NASH), where insufficient or inefficient autophagy contributes to intracellular waste accumulation and disease progression. In contrast, pharmacological strategies that induce autophagy and enhance lysosomal activity have shown promise in preclinical models for treating these disorders[17, 27, 35].

### Ribosomes, the Ideal Sidekicks for Autophagy

Ribosomes play a critical role in cellular homeostasis by participating in autophagy, particularly through a specialized form known as ribophagy, which selectively degrades ribosomes under nutrient-starved conditions. This process ensures cellular adaptation and survival by recycling ribosomal RNA (rRNA) and proteins to meet metabolic demands[38]. The ubiquitin–proteasome system (UPS) and autophagic pathways regulate this turnover, with the Ubp3p/Bre5p ubiquitin protease playing a pivotal role in recognizing ribosomal subunits for degradation. Ribosome degradation is mediated through Atg8-interacting proteins and vacuolar trafficking, linking autophagy with protein translation control[39]. IF modulates ribosomal activity by affecting the mammalian target of rapamycin (mTOR) pathway, a master regulator of protein synthesis and autophagy. During fasting, the inhibition of mTOR leads to a reduction in ribosome biogenesis and an increase in autophagy, promoting the clearance of excess or damaged ribosomes[2]. Additionally, fasting induces the activation of AMP-activated protein kinase (AMPK), which further suppresses mTOR activity, shifting cellular metabolism towards catabolism and enhancing lysosomal degradation of ribosomes[40]. This regulatory interplay ensures metabolic balance by adjusting protein synthesis rates, conserving energy, and optimizing cellular function. By modulating ribosome activity and turnover, IF enhances proteostasis, reduces oxidative stress, and promotes longevity, making it a potential therapeutic strategy for age-related diseases and metabolic disorders[41].

As obese populations and their genomic expressions are particularly well suited targets for IF and autophagy oriented protocols, the authors would suggest taking a deep dive into available specialized literature[42].

As exposed, there are a few crucial genes that are critical to IF protocols' effectivity, they are summarized in Fig. 2.

## Health Relevance of IF and Autophagy

Autophagy is critical for preserving cellular homeostasis, and its dysfunction has been linked to a wide spectrum of pathologies, including metabolic and neurodegenerative disorders as well as various cancers. This evolutionarily conserved mechanism governs the clearance of damaged

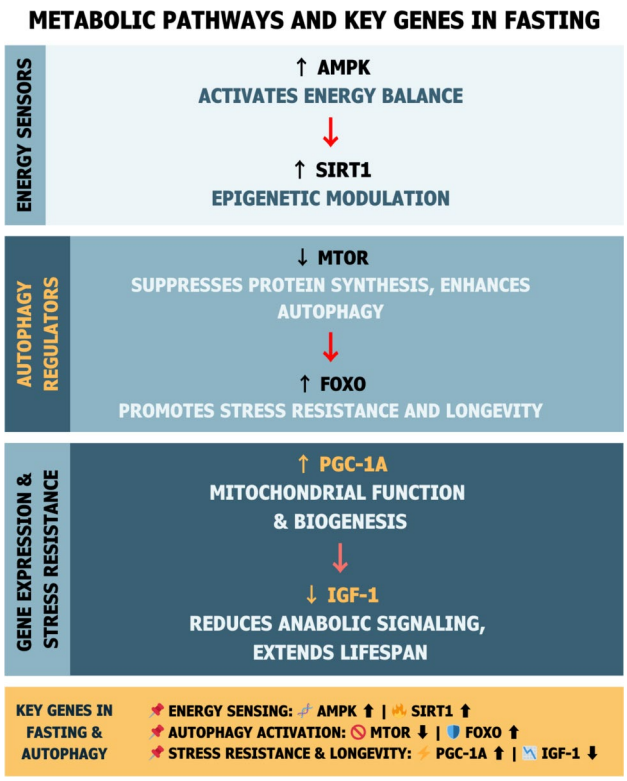



**Fig. 2** Summary of genetic factors and metabolic interactions crucial for IF and the associated health benefits

or dysfunctional intracellular components, enabling adaptation to metabolic stress and preventing diseases tied to cellular waste accumulation and oxidative damage. This section deals with specific conditions highlighting the evidence associated with IF, autophagy and treatment of those conditions. Afterwards, a deeper dive into preclinical and clinical evidence follows.

A recollection and summary of clinically relevant health effects for metabolic, cardiovascular, and neurological health, as well as for cancer and longevity is presented in Fig. 3.

## Metabolic Diseases

In metabolic disorders, autophagy is critical for maintaining energy balance and regulating lipid and carbohydrate metabolism. In the liver, autophagy prevents excessive intracellular lipid accumulation through lipophagy, breaking down lipid droplets to release fatty acids for oxidation or gluconeogenesis. Impairment of this process can contribute to nonalcoholic fatty liver disease (NAFLD) and its progression to nonalcoholic steatohepatitis (NASH), a precursor to hepatocellular carcinoma[43, 44]. Recent findings indicate that enhancing hepatic autophagy significantly lowers hepatic triglyceride levels and oxidative stress, thus helping curb disease progression[2]. In adipose tissue, autophagy governs the balance between energy storage and mobilization, an essential factor in preventing obesity and its associated metabolic complications. Autophagy dysfunction in adipocytes has been linked to insulin resistance, chronic inflammation, and type 2 diabetes, partly through the regulation of pro-inflammatory cytokines such as IL-6 and TNF-α in experimental models of metabolic syndrome[36, 45]. Furthermore, activating autophagy in skeletal muscle enhances insulin sensitivity and reduces reactive oxygen species, thereby offering protection against insulin resistance and other complications linked to metabolic syndrome[12].

## Neurodegenerative Diseases

In the nervous system, autophagy is indispensable for removing misfolded and toxic protein aggregates that underlie neurodegenerative conditions such as Alzheimer's, Parkinson's, and Huntington's diseases. The buildup of proteins like beta-amyloid (in Alzheimer's) or alpha-synuclein (in Parkinson's) disrupts neuronal function and triggers oxidative stress, mitochondrial dysfunction, and neuroinflammation[46]. Activating autophagy through interventions such as IF or caloric restriction mimetics has shown neuroprotective effects in preclinical models by facilitating the clearance of these aggregates and improving synaptic function[12, 47, 48]. Autophagy also supports mitochondrial health via mitophagy, which eliminates damaged mitochondria to prevent excessive reactive oxygen species (ROS) production. In experimental models, enhancing autophagy has slowed disease progression and improved neuronal survival, underscoring its promise as a therapeutic target[36, 49].

## Cancer

Autophagy in cancer is multifaceted and depends on both tumor type and stage. Early in tumorigenesis, it acts as a

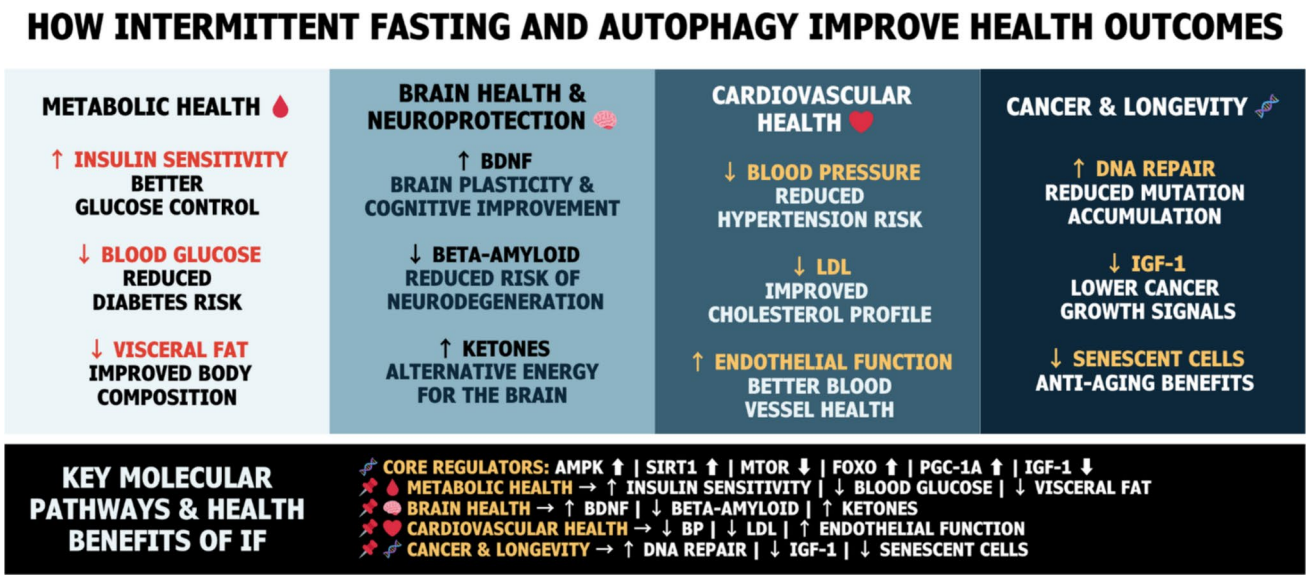



**Fig. 3** Summary of most important health benefits associated with IF, focusing on metabolic, cardiovascular and neurological health, while also covering cancer and longevity

suppressor by eliminating damaged cells and curbing pro-tumor inflammation. Yet in advanced tumors, cancer cells may exploit autophagy for survival under hypoxic and nutrient-deprived conditions[50, 51]. Key regulators such as mTORC1, Beclin-1, and p62 can either promote or inhibit tumor progression, depending on the cellular context[52]. Current research explores combining autophagy inhibitors with chemotherapy or radiotherapy to overcome treatment resistance. In parallel, IF paired with chemotherapy has shown promise in enhancing tumor sensitivity by increasing cellular stress and triggering apoptosis[2, 50, 53].

### Clinical Relevance of IF and Autophagy

The weight and connection of the latest preclinical and clinical evidence, as well as linkage between the two, are presented now. Collectively, both animal and human studies support IF as an effective strategy to induce autophagy and improve metabolic and health parameters. Nevertheless, challenges remain. Protocols vary widely—fast duration, feeding windows, and target populations—necessitating standardized approaches. Long-term studies are also required to assess potential risks and verify sustained benefits. Despite these gaps, the growing body of evidence strongly supports IF's capacity to modulate autophagy, paving the way for refined clinical protocols and improved therapeutic outcomes.

- **Preclinical Evidence:**Preclinical studies, primarily in animal models, have been instrumental in clarifying the molecular mechanisms through which intermittent fasting induces autophagy. Notably, IF activates AMPK, an energy sensor triggered under energetic stress (e.g., fasting). AMPK in turn inhibits mTOR, thereby promoting the formation of the ULK1 complex, a critical step in autophagy initiation. In murine models, IF has been shown to increase levels of key autophagy proteins such as LC3-II and Beclin-1, thereby enhancing the clearance of damaged organelles and misfolded proteins[2, 54]. One study demonstrated that IF-induced AMPK activation in hepatocytes stimulated lipophagy, significantly reducing hepatic triglycerides and preventing nonalcoholic fatty liver disease (NAFLD)[43]. In neurodegenerative models, IF improved the removal of alpha-synuclein and beta-amyloid aggregates, mitigating oxidative stress and supporting neuronal function[47, 48]. Research on time-restricted feeding (TRF) also revealed enhanced circadian autophagy in the liver and brain, correlating with increased longevity in flies and mice[27, 55].
- **Clinical Evidence:**Human trials corroborate most preclinical findings. In one study, participants following a 16-h daily fast (and eating within an 8-h window) showed elevated Beclin-1 and LC3-II expression in peripheral cells, coupled with improved insulin sensitivity and reduced inflammatory markers—demonstrating IF's therapeutic potential against metabolic disorders[44, 56–59].. Another prospective trial of overweight and obese adults reported a heightened expression of autophagy-related genes (ATG5, ATG7, and ULK1) at the end of fasting periods, accompanied by better insulin sensitivity and body composition[60]. In neurodegenerative contexts, a clinical study in patients with mild to moderate Alzheimer's disease revealed that IF protocols increased plasma levels of autophagy-associated markers, such as D-beta-hydroxybutyrate (D-BHB), and also produced cognitive improvements[61]. Similarly, in Huntington's disease, IF promoted mitophagy, enhanced mitochondrial health, and alleviated motor symptoms[47]. In oncology settings, combining IF with chemotherapy in lung cancer patients elevated LC3-II levels in tumor cells, suggesting autophagy-mediated enhancements in treatment sensitivity[36].

## Discussion

This section includes a discussion of the presented information, and a quick analysis of the literature gaps found during this narrative review.

### Therapeutic Potential of IF as Autophagy Promotor

Evidence supports IF's therapeutic promise in conditions linked to impaired autophagy. In metabolic diseases, IF has demonstrated efficacy in improving insulin sensitivity, reducing hepatic lipid accumulation, and preventing the progression to nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC)[18, 62]. Its ability to align circadian rhythms makes it appealing for addressing sleep disorders and enhancing energy metabolism[63, 64]. However, IF protocols must be tailored to individual factors such as age, sex, metabolic status, and comorbidities to maximize benefits and mitigate risks[11, 65]. In neurodegenerative contexts, preliminary data indicate that IF may foster neuronal protection by boosting autophagic clearance of amyloid proteins, although larger, long-term studies are needed[61, 66].

### Intermittent Fasting vs Continuous Caloric Restriction

IF (IF) has emerged as an effective strategy for inducing autophagy and enhancing metabolic health. While it shares common pathways with continuous caloric restriction (CR)—notably the activation of AMPK and inhibition of mTOR—IF also confers additional benefits, such as

synchronizing circadian rhythms and promoting ketogenesis. In experimental models, IF significantly elevates autophagy in metabolically active tissues, aiding the clearance of damaged organelles and reinforcing antioxidant defenses[11, 67]. Recent comparative studies suggest that IF may match or even surpass CR in improving metabolic and molecular parameters. For instance, a clinical trial in patients with type 2 diabetes found that 5:2 IF and time-restricted feeding (TRF) led to greater weight loss, decreased inflammatory markers, and higher LC3-II levels—indicating robust autophagic activity—compared to CR[18]. Nonetheless, direct head-to-head trials remain limited and some systematic reviews have found no noticeable difference between the outcomes of traditional caloric restriction protocols to those of IF protocols[68]. The authors would therefore suggest that, at the end of the day, the protocol that better suits the particularities of each patient should be the main working protocol; as some people may consider either one of them to be easier to stick to, which in the end is the main predictor of success on such protocols. Consistency and protocol adherence remain key in both cases.

### The Biggest Shadow in IF and Autophagy Literature is Methodological Heterogeneity

A notable challenge in IF research is the wide variability in fasting protocols—such as fasting duration, feeding windows, and the frequency of fasting days—making cross-study comparisons difficult. For example, shorter feeding windows (4–6 h) may yield stronger autophagic and metabolic benefits than longer ones (8–10 h). Additionally, study cohorts often focus on individuals with obesity or metabolic conditions, leaving gaps in knowledge about IF's impact on healthy adults, older populations, and those with neurodegenerative diseases or cancer[61, 66]. Having harder set standard for types of IF and associated measurements is key for further optimization of the promising health benefits of IF.

### Future Directions

Considering both the promising potential of IF as a non-pharmacological tool for inducing autophagy, as well as the deep gaps in literature pinpointed in this narrative review, the authors would like to present these final thoughts as potential future improvements for upcoming research, specially clinical trials. To advance IF research, well-controlled and longitudinal clinical trials are required. Such studies should therefore: (1) Standardize Protocols: Harmonize fasting windows and durations for consistent comparisons; (2) Standardized Correlated Biomarkers and Outcomes: Protocols for measurement of autophagy markers (e.g., LC3-II, Beclin-1) alongside clinical endpoints to clarify mechanisms and therapeutic impacts[61]; (3) Explore Combined Approaches: The potential for synergistic effects on autophagy and the associated improvements of metabolic markers when combined with precise exercise protocols or particular drugs, is intuitively clear for most researchers versed in the area. Nevertheless, lots of investigation is still lacking on this front, investigating IF in tandem with exercise or pharmacological therapies for improved benefits; (4) Utilization of Advanced Technologies: Incorporate omics analyses and functional imaging to deepen mechanistic insights[69]; (5) Inclusion of Diverse Populations: IF's role in regulating autophagy and improving clinical outcomes could be more accurately defined if there was a more diverse body of clinical literature supporting the tailoring of specifically targeted protocols for both genders, ethnic groups and age, among others (e.g.: the caloric needs as well as lifestyle of a kid, a teenager, and older adults vary widely).

## Conclusion

Intermittent fasting has gained considerable attention as a robust trigger of autophagy, with promising implications for metabolic syndromes, neurodegeneration, and many other conditions, including cancer therapeutics. At the molecular level, IF activates energy-sensing and stress-response pathways, most notably the AMPK–mTOR axis, sirtuin deacetylases, and β-hydroxybutyrate–mediated signaling, to facilitate the clearance of damaged organelles and protein aggregates, attenuate oxidative stress, and enhance metabolic flexibility. By synchronizing feeding–fasting cycles with circadian biology and promoting transient ketosis, IF may rival or even exceed the autophagy-inducing and metabolic benefits of continuous caloric restriction, though systematic reviews report mixed findings and underscore the need for head-to-head comparisons.

Clinically, IF regimens have been associated with improvements in insulin sensitivity, reductions in hepatic steatosis, and preliminary evidence of slowed neurodegenerative progression, likely via upregulated mitophagy and neuronal maintenance. However, the field is impeded by heterogeneous fasting protocols, small and demographically narrow cohorts, and inconsistent reporting of autophagic biomarkers (e.g., LC3-II, Beclin-1, ATG5). This variability hampers our ability to define dose–response relationships and translate molecular insights into standardized dietary guidelines.

To advance toward evidence-based application, future research should prioritize:

- **Rigorous, longitudinal randomized trials** comparing IF modalities (e.g., time-restricted feeding vs. alternate-day

fasting) and directly measuring both autophagy flux and clinical endpoints.
- **Biomarker harmonization** by establishing consensus on validated, minimally invasive assays for LC3 processing, p62 turnover, and related autophagy and/or metabolic markers.
- **Combination strategies** that investigate how exercise, pharmacological autophagy modulators, and precision-tailored nutrition interact with IF to potentiate cellular renewal.
- **Systems-level profiling** using multi-omics (transcriptomics, metabolomics, epigenomics) and functional imaging (PET/MRI) to map tissue-specific autophagic responses.
- **Population diversity and stratification**, ensuring inclusion of varied ages, sexes, ethnicities, and comorbidities to identify responders and mitigate potential risks such as lean-mass loss or nutrient deficiencies.

By addressing these gaps, the field can refine IF protocols for maximal therapeutic impact while safeguarding long-term safety. Ultimately, integrating mechanistic rigor with personalized nutrition frameworks will pave the way for autophagy-centered dietary interventions that prevent disease and optimize health across diverse populations.

## Key References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    - This reference is critical for understanding the molecular processes key for metabolic regulation that take place during IF protocols. It is part of one of the biggest collaborations in the field on this specific topic and provides strong mechanistic foundation for the discussions provided in this narrative review.
- **Of outstanding importance:** Stouth, D. W.; van-Lieshout, T. L.; Mikhail, A. I.; Ng, S. Y.; Raziee, R.; Edgett, B. A.; Vasam, G.; Webb, E. K.; Gilotra, K. S.; Markou, M.; Pineda, H. C.; Bettencourt-Mora, B. G.; Noor, H.; Moll, Z.; Bittner, M. E.; Gurd, B. J.; Menzies, K. J.; Ljubicic, V. CARM1 Drives Mitophagy and Autophagy Flux during Fasting-Induced Skeletal Muscle Atrophy. *Autophagy* **2024**, *20* (6), 1247–1269. https://doi.org/10.1080/15548627.2023.2288528.
    - This reference is extremely helpful for understanding the wide covet of molecular interactions associated with IF from a pre-clinical perspective (study in mice). It cover a wide range of metabolic signaling paths, including AMPK, ULK1, mTOR, FOXOs and others. It provides a good foundation for further developments in the area.
- **Of importance:** Shabkhizan, R.; Haiaty, S.; Moslehian, M. S.; Bazmani, A.; Sadeghsoltani, F.; Saghaei Bagheri, H.; Rahbarghazi, R.; Sakhinia, E. The Beneficial and Adverse Effects of Autophagic Response to Caloric Restriction and Fasting. *Adv. Nutr.* **2023**, *14* (5), 1211–1225. https://doi.org/10.1016/j.advnut.2023.07.006.
    - This review is of key importance for the area of IF research, as it lays out foundational cellular mechanisms that could invoke both positive and negative health outcomes, highlighting the molecular interactions responsible for such outcomes.


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## Declarations

**Competing interest** The authors declare no competing interests.

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