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Autophagy and Metabolism

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Abstract

Autophagy is a process of self-cannibalization. Cells capture their own cytoplasm and organelles and consume them in lysosomes. The resulting breakdown products are inputs to cellular metabolism, through which they are used to generate energy and to build new proteins and membranes. Autophagy preserves the health of cells and tissues by replacing outdated and damaged cellular components with fresh ones. In starvation, it provides an internal source of nutrients for energy generation and, thus, survival. A powerful promoter of metabolic homeostasis at both the cellular and whole-animal level, autophagy prevents degenerative diseases. It does have a downside, however—cancer cells exploit it to survive in nutrient-poor tumors.

Living organisms from yeast to humans are capable of eating parts of themselves in order to survive. This involves the degradation of cellular components, either because they are deleterious (e.g., damaged organelles and microbial invaders) or because the resulting breakdown products are needed to support metabolism. This process was aptly termed autophagy from the Greek “auto” or oneself and “phagy” or to eat. It has gained attention recently as an essential contributor to human health and disease.

There are several forms of autophagy, each of which involves delivering intracellular cargo to lysosomes for degradation. The predominant form, macroautophagy (autophagy hereafter), produces vesicles called autophagosomes that capture and deliver cytoplasmic material to lysosomes (1). The autophagy-related genes (the *atg* genes) are conserved from yeast to mammals and regulate the cannibalism of intracellular cytoplasm, proteins, and organelles.

Autophagy is the only mechanism to degrade large structures such as organelles and protein aggregates. In the absence of stress, basal autophagy serves a housekeeping function. It provides a routine “garbage disposal” service to cells, eliminating damaged components that could otherwise become toxic. Such cellular refreshing is particularly important in quiescent and terminally differentiated cells, where damaged components are not diluted by cell replication. In starvation, autophagy provides a nutrient source, promoting survival. Autophagy is induced by a broad range of other stressors and can degrade protein aggregates, oxidized lipids, damaged organelles, and even intracellular pathogens. Although it is not always possible to resolve the metabolic and garbage disposal roles for autophagy, it is clear that autophagy prevents disease. Defects in autophagy are linked to liver disease, neurodegeneration, Crohn’s disease, aging, cancer, and metabolic syndrome.

Process of Autophagy

A series of protein complexes composed of *atg* gene products coordinate the formation of autophagosomes. The Atg1/ULK1 complex (Atg1 in yeast and ULK1 in mammals) is an essential positive regulator of autophagosome formation (1). When nutrients are abundant, binding of the ULK1 complex by the mammalian target of rapamycin (mTOR) complex 1 (mTORC1) inhibits autophagy. mTORC1 is an important regulator of cell growth and metabolism. It is composed of five subunits that include Raptor, which binds ULK1, and mTOR, a serine-threonine kinase. By phosphorylating ULK1 and another complex member (the mammalian homolog of yeast Atg13), mTOR inhibits autophagy initiation. In starvation, mTORC1 dissociates from the ULK1 complex, freeing it to trigger autophagosome nucleation and elongation.

Autophagosome nucleation requires a complex containing Atg6 or its mammalian homolog, Beclin 1, that recruits the class III phosphatidylinositol 3-kinase VPS34 to generate phosphatidylinositol 3-phosphate (2). Expansion of autophagosome membranes involves two ubiquitin-like molecules, Atg12 and Atg8 (called LC3 in mammals), and two associated conjugation systems. The E1-like Atg7 and E2-like Atg10 covalently link Atg12 with Atg5, which together bind Atg16L1 to form pre-autophagosomal structures. In the second ubiquitin-like reaction, LC3 is cleaved by the protease Atg4. Phosphatidylethanolamine is conjugated to cleaved LC3 by Atg7 and a second E2-like enzyme, Atg3, and this lipidated LC3-II associates with newly forming autophagosome membranes. LC3-II remains on mature autophagosomes until after fusion with lysosomes and is commonly used to monitor autophagy.

The process beginning with the Beclin 1 complex gives rise to nascent autophagosome membranes. These membranes assemble around cargo, encapsulating the cargo in a vesicle that subsequently fuses with a lysosome, generating an auto-lysosome. The contents are then degraded by proteases, lipases, nucleases, and glycosidases. Lysosomal permeases release the breakdown products—amino acids, lipids, nucleosides, and carbohydrates—into the cytosol, where they are available for synthetic and metabolic pathways (Fig. 1).

Substrates of Autophagy

Autophagy can be nonselective or selective. Non-selective, bulk degradation of cytoplasm and organelles by autophagy provides material to support metabolism during starvation. It also contributes to extensive tissue remodeling, as in *Drosophila* morphogenesis (3). Whether mechanisms exist to prevent bulk autophagy from consuming essential components, such as a cell's final mitochondrion, remains unclear, and in some cases such consumption may lead to cell death.

Selective autophagy of proteins and of organelles such as mitochondria (mitophagy), ribosomes (ribophagy), endoplasmic reticulum (reticulophagy), peroxisomes (pexophagy), and lipids (lipophagy) occurs in specific situations. In mammals, the signal for targeting proteins for degradation by either the autophagy or proteasome pathways is ubiquitination. Many proteins accumulate in autophagy-defective mammalian cells, indicating that autophagy has a major role in controlling the cellular proteome and that proteasome-mediated degradation cannot compensate for defective autophagy (4). To target proteins for autophagic degradation, ubiquitin on modified proteins is recognized and bound by autophagy receptors, such as p62 or Nbr1, which interact with LC3 to deliver cargo to autophagosomes (1).

Mechanisms regulating selective autophagy of organelles are more elaborate. In yeast, Atg32 localized in mitochondria is a receptor that interacts with Atg8 and Atg11 to produce

selective mitochondrial autophagy (5,6). In mammals, autophagy of depolarized mitochondria, which protects cells from toxic reactive oxygen species, is initiated by Pink1-dependent mitochondrial translocation of Parkin. This is followed by ubiquitination of mitochondrial proteins and recruitment of p62 to direct mitochondria to autophagosomes (7,8). The pruning of damaged mitochondria by autophagy has two homeostatic functions. The first is limiting oxidative damage. The second is in maintaining a functional mitochondrial pool.

Regulation of Autophagy

Cells integrate information regarding nutrient availability, growth factor and hormonal receptor activation, stress, and internal energy through an elaborate array of signaling pathways (Fig. 2). In mammals, insulin—the master hormone of the fed state—blocks autophagy.

A major intracellular hub for integrating autophagy-related signals is mTORC1 (9). In the presence of abundant nutrients and growth factors including insulin, mTORC1 promotes cell growth and metabolic activity while suppressing the ULK1 complex and autophagy. In deprivation or stress, numerous signaling pathways inactivate mTORC1 kinase activity. This both suppresses cell growth to reduce energy demand and induces autophagy to enable stress adaptation and survival. A second mTOR complex, mTORC2, positively regulates mTORC1. Upstream of mTORC1 is the cellular energy-sensing pathway controlled by adenosine monophosphate-activated protein kinase (AMPK) (10). High concentrations of AMP signal energy depletion, activate AMPK, and inhibit mTORC1, thus promoting autophagy (Fig. 2).

Regulation of autophagy also occurs through the forkhead box or FOXO transcription factors, whose activation leads to transcription of *atg* genes (11). Similarly, hypoxia and activation of hypoxia-inducible factors, or HIFs, induces the transcription of mitophagy-specific genes and mitophagy (Fig. 2) (12). Less well-characterized mTOR-independent regulators of autophagy also exist. One is ammonia, a by-product of amino acid catabolism, which stimulates autophagy, likely in poorly perfused tissues and tumors (13). Glucagon, a predominant hormone of the fasted state, also triggers autophagy in the liver. Adrenergic receptor activation, which like glucagon activates adenylate cyclase and cyclic adenosine monophosphate (cAMP) production, also stimulates liver autophagy.

Autophagy and Starvation

All cells have internal nutrient stores for use during starvation. Glycogen and lipid droplets are overtly designed for this purpose. Their contents are accessed primarily through the actions of dedicated enzymes, such as glycogen phosphorylase and hormone-sensitive lipase. Many other cellular components have a dual function as nutrient stores. For example, ribosomes occupy ~50% of the dry weight of rapidly growing microbes. In addition to enabling rapid protein synthesis when nutrient conditions are favorable, this provides a store of amino acids for proteome remodeling when conditions turn for the worse. Autophagy has a key role in providing access to such undedicated nutrient stores.

Limitation for any of the major elemental nutrients triggers autophagy in yeast, with nitrogen limitation the strongest stimulus (14). When nitrogen is removed, yeast defective in autophagy become severely depleted of internal amino acids. This precludes the synthesis of proteins important for surviving nitrogen starvation and accelerates cell death (15). Thus, autophagy provides the primary route to nitrogen during starvation.

Unlike microbes, mammalian cells benefit from a relatively constant nutrient environment. Nevertheless, autophagy can support mammalian cells through nutrient deprivation. For example, in lymphocytes, the ability to consume environmental nutrients is growth factor-dependent. In the absence of growth factor stimulation, energy charge is maintained through autophagy, with cells shrinking ~50% in size over 3 months of self-cannibalization (16).

At the organismal level, autophagy is required at multiple stages of mammalian development. The first directly follows oocyte fertilization, with autophagy essential to feed the developing embryo before it gains access to the maternal blood supply. Autophagy-defective embryos fail to reach the blastocyst stage (17). Maternally supplied autophagy proteins enable autophagy-deficient offspring to complete embryogenesis, revealing a second requirement for autophagy: when access to the maternal blood supply is suddenly lost due to birth. Autophagy-defective pups die within 24 hours of delivery. Both circulating and tissue amino acid levels are reduced, and AMPK is activated in the heart, which shows electrocardiographic changes analogous to those observed with severe myocardial infarction (18).

In adult starvation, autophagy also has a central role, increasing within 24 hours in liver, pancreas, kidney, skeletal muscle, and heart; the brain is spared (19). Pharmacological blockade of autophagy results in cardiac dysfunction early in starvation (20). Although autophagy levels return to normal in liver 2 days into starvation, it remains increased in both cardiac and skeletal muscle. Liver mass, however, persistently falls faster than muscle or total body mass. This decline is consistent with a failure of biosynthesis to balance basal consumption of liver by autophagy (21). As liver mass falls, breakdown of muscle and adipose tissue feeds the liver, which exports glucose and ketone bodies required by the brain (Fig. 3).

Use of Metabolites Released by Autophagy

The breakdown products derived from autophagy have a dual role, providing substrates for both biosynthesis and energy generation (Fig. 1). In terms of biosynthesis, the abundance of ribosomal (relative to messenger) RNA makes transcriptome remodeling straightforward. In contrast, proteome remodeling demands copious amino acids, and a major role of autophagy is to provide them.

In addition to providing anabolic substrates, nucleosides and amino acids can be catabolized for energy generation. RNA breakdown yields nucleosides, which are degraded to ribose-phosphate. Six ribose-phosphate molecules are energetically equivalent to five glucose-phosphates, and, like glucose-phosphate derived by glycogen breakdown, they can yield adenosine triphosphate (ATP) either aerobically or anaerobically. In contrast, amino acids, like lipids, yield ATP only through oxidative phosphorylation (Fig. 1). The catastrophic effects of ischemia are a consequence of the relative paucity of nucleic acids and glycogen combined with the inefficiency of anaerobic glycolysis. Oxygen is the one nutrient that autophagy cannot provide.

In addition to being directly catabolized to yield energy, the liver can convert nucleosides, amino acids, and lipids into glucose and ketone bodies for distribution elsewhere in the body (Fig. 3). Ribose-phosphate from nucleosides can be converted to glucose through the non-oxidative pentose phosphate pathway (PPP). Amino acids feed into central metabolism at multiple points, including pyruvate, tricarboxylic acid cycle (TCA) cycle intermediates, and acetyl-coenzyme A (CoA) (Fig. 1). Pyruvate and TCA cycle intermediates are substrates for gluconeogenesis. In contrast, mammals cannot convert acetyl-CoA into glucose. Because lipid degradation yields mostly acetyl-CoA, ketone bodies are essential for feeding the brain and other vital tissues during prolonged starvation.

Autophagy as a Regulator of Metabolism

Autophagy is important for regulating cellular metabolic capabilities. A striking example comes from yeast capable of living off of methanol or fatty acids, substrates that are burned in peroxisomes. When more appealing forms of carbon become available, the peroxisomes are no longer required and are cleared by autophagy (22). The function of autophagy in removing unneeded peroxisomes is conserved in mammals. Peroxisomes are induced in liver by various hydrophobic chemicals, known collectively as peroxisome proliferators. Removal of peroxisome proliferators leads to restoration of normal peroxisome abundance through autophagy (22).

Autophagy also regulates the abundance of liver lipid droplets by their constitutive degradation (23). Defective autophagy in mice leads to larger and more plentiful lipid droplets, increased concentrations of hepatic triglycerides and cholesterol, and increased gross liver size. Lipophagy is selectively decreased by free fatty acids *in vitro* and by a high-fat diet (23). Thus, in addition to promoting lipid droplet growth, free fatty acids may impair lipid droplet breakdown. Because lipophagy releases free fatty acids, its suppression by them is a case of one of the most prevalent regulatory motifs in metabolism: feedback inhibition. But this feedback mechanism may backfire in the case of a chronic high-fat diet or obesity.

In contrast to the role of autophagy in clearing lipid droplets from the liver, autophagy is required for the production of the large lipid droplets characteristic of white adipose tissue (24,25). White adipose refers to the canonical fat storage tissue that expands in obesity; this is in contrast to brown adipose, a mitochondria-rich tissue that catabolizes glucose and lipids to generate heat rather than ATP. Brown adipose tissue contains uncoupling protein 1, which allows protons to leak across the inner mitochondrial membrane, short-circuiting oxidative phosphorylation. Inhibition of autophagy blocks white adipocyte differentiation, and adipose-specific knockout of *atg7* results in mice whose white adipocytes manifest features typical of brown adipose tissue. Consistent with the rapid energy burning of brown adipocytes, these mice are lean; however, they are not healthy—when fed either a regular or high-fat diet, they are at increased risk of early death (24).

Autophagy also contributes to both insulin secretion and physiological sensitivity to the hormone. It is essential for the health of pancreatic β cells and for the expansion of β -cell mass that occurs in response to a high-fat diet (26,27). In liver, defective autophagy leads to insulin resistance (28). For reasons that are not yet fully clear, hepatic autophagy is decreased in obese mice, and its restoration through retroviral expression of *atg7* ameliorates their insulin resistance.

Overall Energetic Impact of Autophagy

To maintain homeostasis, tissue degradation by autophagy must be balanced by new macromolecule synthesis, which is energetically expensive. Each peptide bond in protein costs four high-energy phosphate bonds, two for tRNA charging and two for ribosome peptide bond formation. Assuming a free energy of ATP hydrolysis of -50 kJ/mol under physiological conditions, synthesizing 1 g of protein consumes 1.8 kJ of energy. For a typical human, this means that rebuilding 10% of the body's protein content would consume at least 2000 kJ, or 20% of daily dietary energy intake. *In vitro* estimates of autophagic rates have generally been at or above the 10% per day level, for example, 1% of protein per hour for cultured hepatocytes (21). Accordingly, although *in vivo* rates of autophagy are presumably lower, rebuilding the structures degraded by autophagy may be a major contributor to mammalian caloric requirements. Consistent with this possibility, knockout of

p62, which brings cargo to autophagosomes, results in decreased calorie burning and eventually obesity (29). During aging, both autophagy and total caloric expenditures decrease in tandem (30). The possibility of a causative link, in which decreased autophagy leads to reduced energy burned for self-regeneration, is intriguing. Decreased autophagy in obesity may also contribute to the difficulty of losing weight (28).

Autophagy and Disease

Cellular garbage disposal by autophagy prevents the buildup of damaged proteins and organelles that cause chronic tissue damage and disease. Genetic inactivation of autophagy in mice revealed that the type of disease depends on the tissue type. In the brain, autophagy suppresses the accumulation of ubiquitinated proteins, disposes of aggregation-prone proteins and damaged organelles that cause Huntington's and Parkinson's diseases, and prevents neurodegeneration (31,32). In the liver, autophagy suppresses protein aggregate and lipid accumulation, oxidative stress, chronic cell death, inflammation, and cancer (4,33). In intestinal Paneth cells, it preserves cellular function, prevents expression of damage and inflammatory markers, and prevents the development of Crohn's disease (34). Although the cell-refreshing role of autophagy functions in preventing the above diseases, autophagy's metabolic role may also contribute by ensuring consistent availability of internal nutrients and enabling cells to survive periods of poor external nutrition in good health. Regardless of the underlying mechanism, autophagy stimulation is under consideration for disease prevention. In support of this concept, autophagy mediates the protective effects of dietary restriction on aging-related diseases in model systems (35), and autophagy suppression contributes to the deleterious consequences of obesity (28). Induction of autophagy may result in the fasting rituals common in many religions as well modern cleansing rituals, producing health benefits.

In contrast to normal cells in tissues, tumors often reside in an environment deprived of nutrients, growth factors, and oxygen as a result of insufficient or abnormal vascularization. Thus, the effects of autophagy in cancer are paradoxical: Although autophagy can prevent initiation of some cancers, it also may support tumor growth. Autophagy localizes to hypoxic tumor regions most distant from nutrient-supplying blood vessels, where it sustains tumor cell survival (36). Whether the primary role of autophagy in tumors is to provide metabolic substrates or prevent buildup of damaged components is not yet known. But either way, inhibition of autophagy may suppress the growth of established tumors (37).

Many of the pathways that control autophagy are deregulated in cancer (Fig. 2), and cancer therapeutics targeting these pathways activate autophagy. Some do so directly by inhibiting mTOR, whereas others inhibit upstream nutrient or signaling pathways. Cytotoxic cancer therapies activate autophagy, presumably by inflicting damage. The functional role of autophagy in these settings needs to be established. A particularly interesting possibility is that autophagy favors tumor cell survival. If this proves correct, then inhibition of autophagy might synergize with existing cancer treatments (37).

Conclusions

Autophagy is a major contributor to cellular metabolism. It provides internal nutrients when external ones are unavailable. It also provides an essential means of refreshing and remodeling cells. As such, it is required for normal development, including that of metabolic tissues such as adipose tissue and pancreatic β cells. In adults, autophagy promotes metabolic homeostasis and prevents degenerative disease and cancer. Once cancer occurs, however, autophagy may contribute to tumor resiliency. Thus, both activation and inhibition of autophagy hold promise for improved treatment of common, devastating diseases.

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Fig. 1.

Use of the products of autophagy. Multiple forms of stress activate autophagy (bottom right). Degradation of proteins, lipids, carbohydrates, and nucleic acids liberates amino acids, fatty acids, sugars, and nucleosides that are released into the cytoplasm for reutilization. Sugars (blue lines), including glucose released from glycogen granules by glycogenolysis or autophagy, are catabolized by glycolysis and the PPP to generate ATP, and pyruvate for subsequent TCA cycle metabolism. Nucleosides (green lines) are used for new nucleic acid synthesis and catabolized by the combined action of the PPP and glycolysis. Amino acids (purple lines) are used as building blocks for new protein synthesis, for ATP production by central carbon metabolism, and (in liver) as substrates for gluconeogenesis (Fig. 3). They also can be combined to yield citrate, which drives lipid synthesis and membrane biogenesis. Catabolism of amino acids yields ammonia, an activator of autophagy (dotted line). Fatty acids (yellow lines) from lipolysis or from autophagy of membranes or lipid droplets yield acetyl-CoA, which feeds the TCA cycle, supporting ATP production and citrate generation. OAA indicates oxaloacetate; α -KG, α -ketoglutarate; and ER, endoplasmic reticulum.

Fig. 2.

Signaling pathways that regulate autophagy. Common nutrient, growth factor, hormone, and stress signals that regulate autophagy. Purple lines depict events that positively regulate autophagy. Yellow lines depict those that negatively regulate autophagy. Many pathways converge on the AMPK-mTORC1 axis. Green lines depict pathways that are mTOR-independent. Note that all input signals are framed as autophagy activators; thus, they include limitation for growth factors and nutrients. IKK β , inhibitor of nuclear factor κ B kinase β ; PI3K, phosphatidylinositol-3 kinase; PTEN, phosphatase and tensin homolog; MAPK, mitogen-activated protein kinase; TSC1/2, tuberous sclerosis complexes 1 and 2; and EF, elongation factor.

Fig. 3.

Role of autophagy in adult mammalian starvation. Depicted pathways predominate after depletion of glycogen stores, typically ~12 hours into starvation. Autophagy in liver and heart (but not brain) generates fatty acids and amino acids, which are catabolized to yield energy. In the liver, this energy drives gluconeogenesis and ketogenesis. Amino acids are substrates for both ketogenesis and gluconeogenesis; acetyl-CoA from fatty acids is only for ketogenesis. As starvation continues, degradation of adipose and muscle play an increasing role in supplying substrates to the liver, which exports glucose and ketone bodies to feed the brain. The relative importance of ketone bodies increases in prolonged starvation. NADH, reduced form of nicotinamide adenine dinucleotide.