Review Article

Autophagy Role as a Double-Edged Sword in Anesthesiology and Critical Care

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Abstract

Autophagy is a conserved lysosomal degradation pathway that breaks down cytoplasmic components and is essential for host cellular immune response. The activity of autophagy at a basic rate is crucial for homeostasis. Autophagy has emerged in recent years as a major mechanism in many neurodegenerative diseases. The regulation of microbial infections and inflammatory responses can be significantly influenced by autophagic modulators. In this study, we explain the autophagy role as a double-edged sword in anesthesiology and critical care. Future studies should focus on investigating the molecular mechanism of interplay between pathogen-host-autophagy and on studying whether autophagy inducers/inhibitors can exert suitable modulatory immunomodulatory effects. Potential organ protection through autophagy pathways might be an advantage in patients undergoing anesthesia and/or needing critical care.

Keywords: Autophagy**,** Anesthesiology**,** Viral Infections

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Introduction

Autophagy is a conserved lysosomal degradation pathway that breaks down cytoplasmic components and is essential for host cellular immune response. It is also necessary for cellular survival, development, differentiation, and stability (1).

Three different pathways have been recognized for autophagy: macro, chaperon mediated autophagy (CMA), microautophagy (2). Autophagy is derived from the Greek words "auto" meaning self and "phagy" meaning eating and it extensively refers to cellular catabolic processes. In autophagy, cytoplasmic material is transported to lysosomes for degradation (3). Christian De Duve, who won the Nobel Prize for his work on lysosomes. The term autophagy was used for the first time in 1963. He used the word to describe phenomena in which vesicles with single or double-layer membranes contain the contents (cargo) of the cytoplasm, such as organelles for digestion. Thus, autophagy can be distinguished from heterophagy that cells destroy extracellular material (4).

1.1. Types of autophagy

a. Macroautophagy: macroautophagy is the best well-characterized pathway of autophagy in which the outer membrane of the autophagosome fuses with a lysosome to release its components into an autolysosome (2). Through activating of several regulatory molecules, macroautophagy induces the attraction of VP15Lc3 to the autophagosome membrane. These regulatory molecules are Beclin 1, Vps 34, Ambra1, and Atg 14 (5).

The selective attraction of mitochondria, which is called Mitophagy (a kind of macroautophagy), is complex of PTEN – include putative kinase1, P1NK1-Parkin, and Bcl2/ adenovirus EIB 19 KD interacting protein (Binp3) factor. Lysosomal destruction proteins like BAG3 are labeled by polyubiquitin chains and are delivered to autophagosome by PG2 scaffold protein (5).

More than 30 genes of ATGs have a role in producing materials to form autophagosomes and are the main components of the autophagy nucleus (6). These are divided into the following groups:

- Group A consists of ATG9 and its cycling system, which includes the ATG1/ULK1 kinase complex and ATG2, ATG18 that plays a regulatory role in forming autophagosome.
- Group B including the VPS34 complex
- Group C contains the ATG8/LC3 and ATG12 ubiquitin-like protein system, ATG7, ATG10 and ATG3, ATG4, ATG5, and ATG16.

ATG8 takes part in the extension of vesicles. ATG8 (ATG7-ATG4-ATG3) complex together with LC3 light chain, forms a complex which is necessary to form autophagosomes. By induction of autophagy, LC3 gets modified, LC3 in mammalian cells is a gold standard in autophagic mechanisms (6, 7).

b. Chaperon-Mediated Autophagy (CMA): after the damage caused by factors like ROS. Specific sequences of amino acids (KF3ZRQ) formed that are recognized by HSC70 (heat shock cognate protein70 KD) in collaboration with LAMP2A (Lysosome-associated membrane protein2) transports damaged proteins to the lysosome (8).

One of the distinct characteristics of CMA is that proteins degraded through this pathway are selected in a process, leading to their efficient distinguish from their normal neighbors within big protein complexes and degrading only the abnormal proteins (9).

Additionally, this selective mechanism allows a regulatory role for CMA in multicellular mechanisms through participation in the modification of intracellular levels of enzymes, replication factors, and cell survival proteins. CMA is a process with following multiple phases:

- Substrate recognition and lysosomal targeting
- Substrate binding and disassembly
- Substrate transportation
- Substrate degradation into the lysosomal lumen (9).

c. Microautophagy: the direct attraction of small proteins from the cytoplasm to a lysosome is called microautophagy. This degradation process is generally non-selective, lysosomal action and requires the direct uptake of cytoplasmic cargoes at a boundary membrane by autophagic tubes. The main function of microautophagy is to maintain the size of the organelles, membrane homeostasis, and cell survival in nitrogen scarcity (10).

The activity of autophagy at a basic rate is crucial for homeostasis. Intracellular stresses like viral infection trigger autophagy. Depending on the environmental conditions, cell type, and virus type, autophagy can play a proviral or antiviral role (10, 11).

During a viral infection, autophagy can detect and degrade viruses and their proteins. In autophagy, detecting different viruses is not based on a specific pattern. The main viral characteristics to detection are positive and negative-strand RNA viruses, DNA viruses, viral genotypes, viral life cycle, and pathogenesis. Cells use this method to prohibit viral replication (12, 13).

Some viruses have adapted approaches to escape degradation by lysosomes through autophagy. They interfere in the process of autophagy leading to their protection within immature lysosomes and use the autophagy pathway for their replication.

Thus, autophagy is a two-edged sword in viral infections. Controlling viral replication by regulating autophagy is a promising method in the arena of antiviral drug discovery (13).

2. Mechanism and role of autophagy in organisms

Autophagy is considered an important survival process that keeps the balance of energy sources at important stages in development following nutrient stress. It also has a role in removing damaged organelles and misfolded or accumulated proteins. There is suggesting evidence that selective autophagy plays an important role in neuropathies, cancer, and heart disease (14).

Autophagy organizes different aspects of cell responses to harmful stimuli like infection (15). Researches have shown that autophagy plays a vital role in the neonatal period by protecting cells from intracellular and extracellular nutrient deficiencies. Also, intracellular bacteria can be destroyed by autophagosomes. Furthermore, Beclin 1 and PKR signaling pathways carry out some of their antiviral effects by inducing autophagy. Cytokines responsible for intracellular responses to pathogens including IFNs and TNFs stimulate autophagy (16, 17).

3. The role of autophagy during the life

3.1. Fetus: eukaryotes have utilized autophagy as an evolutionarily conserved pathway to keep cellular homeostasis under environmental stress conditions. Autophagy plays an important role in the early stages of pregnancy including embryogenesis, implantation process. Autophagy provides to help extravillous trophoblasts which invade the decidua until the first third of uterine myometrium and migrate along the lumina of spiral arterioles under hypoxic conditions and low-level of nutrients in early pregnancy. Poor placentation is related to autophagy inhibition. Studies have shown that autophagy in the human placentas is not simple and it is a controversial process (18, 19). Within 4 hours after fertilization autophagy is extremely triggered in fertilized oocytes (20). Since oocytes without Atg5 are fertilized, autophagy seems to be not essential for folliculogenesis and oogenesis (21).

Along with oocyte-to-embryo transition, numerous maternal proteins that remained in oocytes are available to zygotes (fertilized embryos), but these proteins completely are degraded, and synthesized proteins are encoded via the zygotic genome again will be translated. Stimulation of autophagy is similarly detected in the inner cell mass, recognized as the pluralist or embryoblast that will evolutionally cause the perfect structure of the fetus (22).

3.2. Newborn: autophagy is activated soon after birth in neonatal tissues; neonatal tissues may be affected by other functions of autophagy. Autophagy can play a key role to supply amino acids in response to starvation. Besides, this process has a role in programmed cell remodeling, glycogen degradation, and response to oxidative stress at birth. In newborn animals, glucagon secreted during postnatal hypoglycemia induces the autophagy process, parenteral glucose and insulin can suppress this process, which abolishes glucagon secretion (23). At the time of birth, the extra-placental food source is suddenly lost; hence, neonates are facing starvation until the nutrient source can be altered to milk supply. The measurement of autophagy along with the embryogenesis is low; although after birth, autophagy will be upregulated in different tissues and will be at high levels for 3–12 h before downregulation to basal levels during 1–2 days (24). Animal models that lack Atg5 (Atg5, which is vital for autophagosome formation) appear to be normal from birth but die within a day of birth. These results suggest that the degradation of "native" proteins by the process of autophagy produces amino acids as an energy source, and thus autophagy helps maintain cell homeostasis (23).

3.3. Children: some neurological signs in children such as developmental delay and neurodegeneration may be caused by genetic disorders of autophagy during nervous system development in childhood-onset disorders. The pathological features of different childhood neurodegenerative diseases may be caused by defective autophagy as a key agent, which leads to the accumulation of abnormal protein and dysfunctional organelle (25). There is much evidence for the developing relationship between autophagy dysregulation and lysosomal storage syndromes including Lafora disease, Niemann–Pick type C, and leukodystrophies such as Alexander disease. Furthermore, studies are suggesting the role of genetically autophagy dysfunction in Vici syndrome. Interestingly knowing the particular mechanism that autophagy is linked to disease pathology can give us a novel therapeutic way to treat neurodegeneration (26).

3.4. Adult: the autophagy process has important roles in neurogenesis in several areas of the embryonic forebrain. Basal autophagy controls Notch and Wnt signaling that is required for adequate neuronal differentiation. The studies in the adult show that the autophagy-lysosomal pathway controls adult NSC maintenance, the activation of quiescent NSCs, the timing of their maturation, and the survival of the newly born neurons (27). In hematopoietic stem cells, losing the autophagy triggers the growth of mitochondria and a stimulated metabolic situation that enhances regenerative capacity with aging, myeloid differentiation, and self-renewal in damaged cells (28). There are many questions about NSC, including how the dynamics of metabolic pathways and mitochondria are closely related to various progressive steps in adult neurogenesis (29-31). In this regard, dysregulation of mitochondrial structure will be harmful to NSC self-renewal, with resulting age-dependent reduction and neurogenesis failings that happen by a ROS-mediated pathway (32).

4. The role of anesthetic drugs in autophagy

Anesthetic agents make patients feel comfortable and make better conditions for surgical and procedural interventions. These agents, both volatile and intravenous, are shown to modulate autophagic flux by recycling and degrading excess, aged, or dysfunctional proteins, maintains tissue homeostasis (33). Ethanol is recognized as containing both N-methyl- D-aspartate antagonist and γ-Aminobutyric acid agonist features as usual applied fugacious anesthetic agents. The latest evidence revealed that autophagy may decrease the progress of ethanol-stimulated neurotoxicity (34). However, it is not always clear, unlike apoptosis, whether upregulated autophagy is good or bad. Anesthetic autophagy modulation is useful in the vast majority of studies, including *in vitro* and *in vivo* studies. The only study where this was not the case was Kashiwagi's. In this study has been shown that general anesthesia can result in a long-term disorder of both synaptic transmission and mitochondrial morphogenesis in the growing rat brain and muscle-wasting conditions that are induced via facilitated autophagy. Autophagy can have a key part in general anesthetic-induced neurotoxicity (35).

In a study, Qiaoling et al reported that a protective effect against myocardial IRI is produced by sufentanil pretreatment via regulating miR-125a/DRAM2 signaling axis (36). In another study, it was shown that *in vivo* model, the creation of autolysosome and autophagosome is decreased by exposing rat or PC12 cells to propofol PC12 (37).

Cue et al showed that I/R-stimulated activation of autophagy is decreased by propofol. Propofol protects cells via blocking autophagy by microRNA expression induction (38). In 2016, Zho et al reported that sevoflurane can induce autophagy via endoplasmic reticulum stress in H4 cells (39). It also showed that autophagic flux can increase by local anesthetics which induce neurotoxicity (40). The proliferation of damaged cells by hypoxia-reoxygenation via remifentanil also can increase autophagy activity in human keratinocytes (33).

Xiong et al in a study (2019) indicated that the long noncoding RNA-miRNA-mRNA axes as potential therapies can affect the outcome of myocardial ischemia-reperfusion injury by regulating autophagy, apoptosis, oxidative stress, energy metabolism, and the inflammatory response (41).

5. The role of autophagy in critical care

In the severe stage of critical illness, autophagy appears to have a distinct function to produce vital nutrients to remain cellular integrity. Clinical trials show that nutritional support in early steps might inhibit the induction of autophagy in patients critically ill causing the development of organ failure. However, the regulation of autophagy by nutrients, in critical illness is not largely clear. Autophagy is a proteolytic process that can be activated by oxidative stress, which has the potential to either mitigate or exacerbate ventilator-induced diaphragmatic dysfunction. Weakness and atrophy of the diaphragm muscle are related to mechanical ventilation, which named ventilator-induced diaphragmatic dysfunction (VIDD). Some studies showed that mechanical ventilation can induce autophagy and this process cannot lead to diaphragmatic weakness. On the other hand, a study showed that an increase in the autophagy flux was

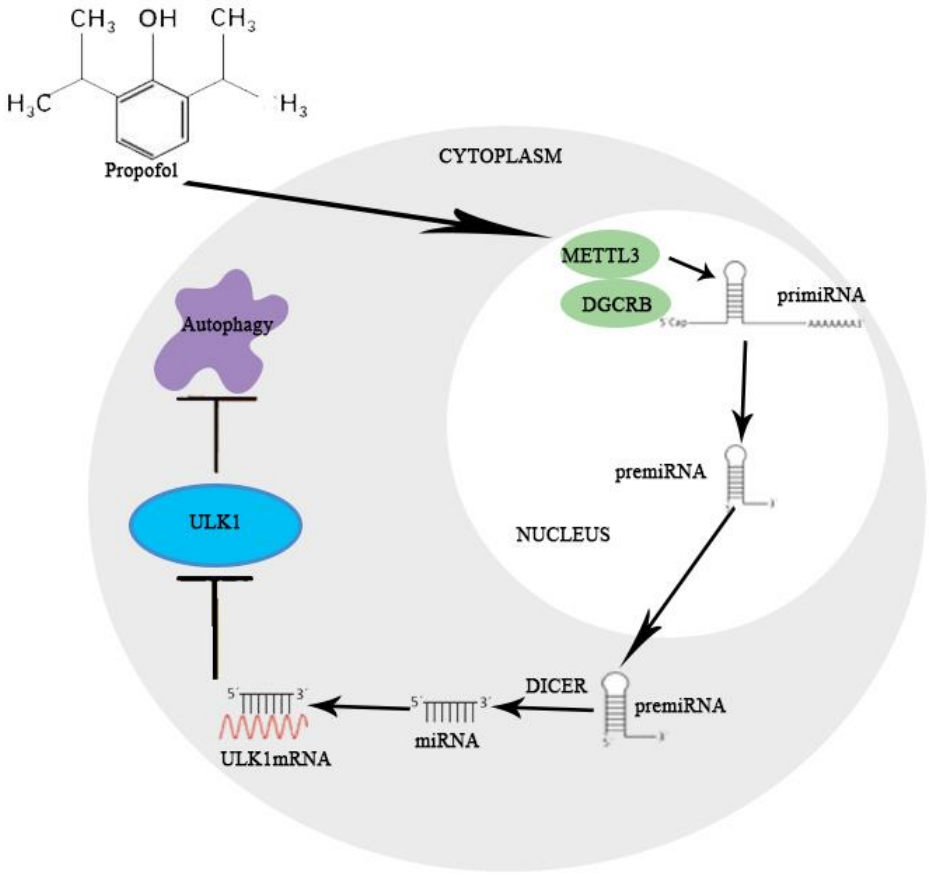

Figure 1. Propofol cytoprotective mechanisms via blocking autophagy by microRNA induction. mRNA: Messenger RNA, miRNA: microRNA, primiRNA: primary microRNA, premiRNA: precursor microRNA, METTL3: methyltransferase-like 3, DGCR8: DiGeorge critical region 8, ULK1: Unc-51-like kinase 1.

linked to lower serum levels of non-essential amino acids. Therefore, quick nutrition at the beginning of critical disease may not inhibit autophagy but can reduce the valuable influence of starvation on the reactivation of the autophagy mechanism. This can be of critical status in the patients, in which this pathway is suppressed through critical illness (42).

5.1. Autophagy and virus infection: depending on the species, viruses can either take over the autophagy for their replication or express certain proteins to suppress autophagy (43). Most of the negative-strand RNA (NS-RNA) viruses use autophagy for replication (44). Nevertheless, viral infections trigger autophagy and viral constituents are sequestered in autophagosomes. In addition to viral degrading, xenophagy indorses detection of the pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) which further results in IFN responses and production of proinflammatory cytokines (17).

a. Autophagy and HIV-1 infection: the virus genome inserts in host chromosomes are the main challenge for HIV-1 eradication and treatment of the disease. Human immunodeficiency virus (HIV) persistence occurs in long-lived cells including liver stem cells, CD4 + T memory cells, endocrine cells, and monocyte-macrophage cells such as microglial cells, which are the main HIV reservoirs in the central nervous system (CNS). Viral latency is usually able to reactivate viral infection. This ability is an important mechanism for the stability and escape of the virus from detection by the immune system (45).

Autophagy has multiple functions in immunity. In addition to its destructive function, the autophagy

pathway has a role in primary immunity; microbial and viral agents are delivered to the PRR receptor of the immune cells of macrophages and DCs by the autophagy pathway. Autophagy also regulates inflammation (46). For example, before inflammation, autophagy induces the secretion of IL-1B cytokine from macrophages. In T lymphocytes, autophagy contributes to present antigens by MHC type II of macrophages and DCs and affects the polarization of T cells (47). Recent studies have shown that autophagy, as an antiviral immune system is an important process in the HIV-1 infection cycle (48). HIV uses autophagy to facilitate the processing of viral proteins and the formation of the virus (48). Besides, autophagy is an intracellular degradation process and is responsible for clearing out the complex of proteins that cause neurodegenerative diseases such as Parkinson's and Alzheimer's (49). Therefore, non-regulated autophagy in HIV infection causes neurological disorders associated (HAND) with HIV. While autophagy is stimulated and continuously in CD4 +T uninfected cells, however, autophagy is effectively inhibited at the transcriptional level in infected cells by down regulated of BECLIN (48). Another study (2004) found that uninfected T cells died, due to HIV Env binding to co-receptor (50). This study proved that CXCR4 induces mTOR pathway activity, which subsequently causes phosphorylation and activation of p53. Expression of the Bax gene and the initiation of the mitochondria death pathway is activated by p53. This data suggests that HIV-1 uses different strategies to counteract the antiviral effects of autophagy during infection (50). For example, the viral protein Vif can inhibit autophagy in the early stages of infecting CD4 + T cells. Viral protein Nef (Negative Factor) is a protein that inhibits autophagy via its interaction with BECLIN1 and thus prevents the destruction of HIV-1 during the maturation stage of infected macrophage contamination (51). In dendritic cells, the HIV-1 Env protein is said to activate the mTOR pathway, thus inhibiting autophagy and transmitting the infection to CD4 + T cells (52).

The secreted form of the Tat proteins is detected and suppresses autophagy via Src, AKT, and STAT3 signaling pathways. Moreover, interleukin 10 (IL-10) is stimulated by Tat (53). IL-10 inhibits the initiation of autophagy in uninfected macrophages. IFN-γ signaling is dysregulated by Tat protein and suppresses autophagy in macrophages. Tat protein inhibits phosphorylation of STAT1 and decreases the upregulation of LC3B and autophagosome formation. Besides, HIV-Tat restricts mycobacteria capture by autophagosomes is restricted via HIV-Tat, so providing a suitable environment for opportunistic microbes in HIV-infected individuals (53).

b. Autophagy and Herpes simplex virus (HSV) infection: some reports show that double-stranded DNA of HSV can trigger autophagy independent of viral replication; however, it is dependent on the stimulator of interferon genes (54). Activation of STING also can induce an innate immune response to the infection (55-57).

HSV-1 has multiple mechanisms to ensure replication and prevent autophagy. The $\gamma_1$34.5 protein of HSV-1 plays an important role in the replication of the virus by preventing the formation of the autophagophore. This function is done by binding to Beclin-1 and by preventing the shutting down of the host translation (58-60). The virus also prevents autophagy by downregulating the major autophagy proteins, sequestome 1 (p62/SQSTm1), and optineurin. Furthermore, other ways of preventing autophagy have been suggested; Us11 expression can inhibit protein kinase R (PKR) and prevent shutting down of host translation(61, 62). Besides, protein kinase R-like endoplasmic reticulum kinase (PERK) is inhibited by glycoprotein B of the virus. Additionally, mechanisms that block the innate immune responses might inhibit autophagy indirectly (63, 64).

c. Autophagy and Influenza virus infection: autophagy is one of the essential steps in influenza virus replication. Influenza infection increases the formation of autophagosomes and the autophagy flux. Bafilomycin (Baf-A1) is one of the specific proton pump inhibitors (V-H + Vacuole), which probably affects on acidification of endosomes and ultimately has a key role in the replication of the influenza virus (59, 60). The use of Baf-A in low doses inhibits influenza viruses, which is done by stimulation of autophagy by increasing LC3-II. Autophagy can restrict virus replication, therefore; it can act as a primary immune mechanism. Autophagy suppression in viral infection can be a mechanism to escape from the immune system by influenza A virus. Ensuing the

disruption of the viral escape mechanism from the immune system, replication, and virulence of the virus decrease. Degradation of autophagosomes during viral infection can decrease the replication of the virus in the infected cells (65). Autophagy also acts as a key mechanism for inflammatory responses from H1N1 and H9N2. The protein EPG5 (Ectopic P-Granules Autophagy Protein 5 Homolog) is essential for autophagy and regulates the function of the ATG gene complex in the formation of autophagy and expression of multiple cytokines in the lung (66). The lacking EPG5 in myeloid cells in the lung causes increased IL-6, IL-1b, and IL-13 cytokine proteins in the lung macrophages, which results in favorable cytokine levels having protective effects on viral replication, and therefore increases the immune response to influenza. One study showed that the activation of the PI3K/AKT pathway associated with the autophagy process has a mutual effect on the replication of the influenza virus. Autophagy deficiency leads to impaired survival of memory CD8+ T cells during influenza virus infection. Secondary apoptosis and highly induced autophagy are observed in the influenza virus-infected cells (67).

d. Autophagy and Rabies Virus infection: in vitro studies have shown that rabies virus (RABV) infection can increase the amount of autophagy and the autophagosome buildup. It has also been suggested that RABV may prevent cell apoptosis in neuroblastoma cell lines (68-70). However, autophagy is not completed because of the inhibition of autophagy flux. One of the factors affecting this process is the viral phosphoprotein 5 (P5) that has multiple functions and is involved in viral transcription and replication. P5 binds to Becline1 (BECN1) and causes the reduction of caspase 2 and the stimulation of the AMP-activated protein kinase (AMPK)-AKT-mTOR and the AMPKmitogen-activated protein kinase pathways (68, 71).

It is suggested that the rhabdoviral glycoproteins can induce autophagy in vertebrate hosts after immunization. Autophagy in this case along with other immune responses can cause a long-lasting antiviral immune response. However, more research is needed to elucidate the role of viral glycoproteins in autophagy (72, 73).

e. Autophagy and Hepatitis C virus (HCV) infection: HCV RNA is transferred into the *endoplasmic reticulum* (ER). Non-structural proteins, NS4B and NS5A which are encoded by the HCV genome have a key role in viral replication and host cellular *immune response* modulation (74). Moreover, NS4B protein induces stress response and acts as a causative factor of autophagy. Although the formation of initial membranous webs to translate RNAs is inducted by autophagy, however, these structures are not essential for the initial replication of HCV RNA (75). There are many indications of indirect stimulation of autophagy by HCV infection. The accumulation of defective proteins in the *endoplasmic reticulum* (ER) stimulates the stress of the ER. Subsequently, stimulating ER stress activates three different signaling pathways within the cell.

1. IRE1 enzyme Pathway
2. ATF6 Pathway
3. PERK Pathway

These three pathways are used to deal with defective proteins by cells. This process is called "unfolded protein response". During this process, protein synthesis decreases in the ER, Protein folding is improved by increased regulation of the ER chaperone proteins, Increased protein degradation through autophagy, and ERAD6 pathway (degeneration is dependent on (ER)) (76). The apoptosis pathway can stimulate if the UPR pathway does not reduce ER stress. Also, ER calcium released through ER stress ER leads to deficiency in mitochondrial activity and increased production of oxygen free radical (ROS) (77).

HCV increases the expression of PINK1 and Parkin (ubiquitin-ligases (*E3*), Parkin recruits substrates to stimulate mitophagy. HCV can reduce apoptosis by stimulating mitophagy. PERK is the main stimulant of the ATG6 pathway, which increases the expression of ATG12 and LC3. Increased autophagy and mitophagy is required to maintain survival infected cell in chronic infection. Autophagy selectively reduces the receptor function of a *chain* of *type 1 interferon* (IFN-α) in response to chronic HCV infection, ENT1, and CNT1 Nucleoside analogs carriers expression reduced by activation of autophagy, Therefore, probably, autophagy is involved in a mechanism of resistance to HCV through the IFN-α + RBV complex (75, 78).

f. Autophagy and Hepatitis B virus (HBV) infection: Hepatitis B Virus (HBV) is an enveloped DNA virus and a member of the hepadnaviridae family. It can cause acute and chronic hepatitis in mammals (79). Worldwide, it is responsible for the majority of chronic hepatitis. Furthermore, chronic HBV infection is the major cause of hepatocellular carcinoma (HCC)(80).

HBV is known to induce autophagy through several mechanisms for promoting its replication. X protein (HBx) can give rise to autophagosome formation. One of the pathways responsible is the class 3 phosphatidylinositol 3-kinase (PI3KC3)/beclin1 complex dependent pathway (81). Another pathway is considered the increase in ROS production resulting in the activation of JNKs and stimulation of autophagosome formation (81, 82). The intracellular HBV small surface protein (SHB) has been shown to stimulate autophagy. Despite HBx it does not affect the expression of Beclin 1 and carries its effect by triggering ER stress and unfolding protein responses (UPR) (82, 83).

HBV-induced autophagy is known to have a strong correlation with hepatocellular carcinoma (HCC). An increase in autophagy can increase autophagic cell death, anti-tumor immune response, and the degradation of oncogenic microRNAs, thus weakening tumor progression. Besides, a considerable decrease in the amounts of beclin 1 mRNA has been seen in HBV-induced HCC cells compared with chronic hepatitis B infected cells (82).

g. Autophagy and Rotavirus infection: rotavirus infections are responsible for the majority of gastroenteritis in children less than 5 years of age. The infection can cause diarrhea, vomiting, malaise, and fever (84). The rotavirus is a none-enveloped virus and its genome consists of 11 segments of double-stranded RNA (dsRNA) (85, 86). Rotavirus is known to induce autophagy to the benefit of viral replication. The viral non-structural protein NSP4 is an endoplasmic reticulum (ER) transmembrane glycoprotein that acts as an ion channel and releases ER calcium into the host cell cytoplasm. The disruption of calcium homeostasis triggers a signaling pathway involving Ca2+l/calmodulin protein-dependent kinase kinase2 (CAMKK2) and the activation of adenosine monophosphate-activated protein kinase (AMPK) which induces autophagy (87, 88). Evidence suggests that the NSP4 molecule on the COPII vesicles interacts with autophagy protein LC3 and along with viral protein VP7 traffic to viroplasms, the immature virus particles then interact with NSP4 and bud through the membrane and form the infectious particles (89). Another mechanism affecting autophagy is used by rotaviruses in which cellular microRNAs are manipulated to induce autophagy; this is done by enhancing miR-99b expression and reducing let-7g expression (90). Besides, some of the rotaviruses encoded virus-like small RNA1755 triggers autophagy by inhibition of the PI3K/Akt/mTOR pathway; however, it eventually prevents autophagy maturation (91).

Conclusion

In the development and progression of neurodegenerative diseases, protein degradation pathways play a key role. Autophagy has emerged in recent years as a major mechanism in many neurodegenerative diseases. A greater understanding of the role of autophagy in many diseases, including common neurodegenerative diseases such as Alzheimer's or Parkinson's, has led to an interest in pharmacological-based or gene therapy approaches to modify autophagy. Besides, this system has some adventitious and pitfall in combat against viruses.

The pathway has raised many hopes as a therapeutic goal due to the essential role of autophagy in the immune response. The regulation of microbial infections and inflammatory responses can be significantly influenced by autophagic modulators. Future studies should focus on investigating the molecular mechanism of interplay between pathogen-host-autophagy and on studying whether autophagy inducers/inhibitors can exert suitable modulatory immunomodulatory effects. Also, to evaluate drug efficacy and kinetics in patients, accurate biomarkers for autophagy measurement are needed.

There may be some potential approaches to take advantage of autophagy pathways to reach therapeutic goals in the field of organ protection; these potential approaches might be beneficial for patients undergoing anesthesia and/or needing critical care.

Acknowledgment

None.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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