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Epigenetic regulation of autophagy in coronavirus disease 2019 (COVID-19)

Hamid Behrouj [a], Omid Vakili [b], Adel Sadeghdoust [c], Neda Aligolighasemabadi [d],
Parnian Khalili [f], Mozhdeh Zamani [f], Pooneh Mokarram [f,g,*]

[a] *Behbahan Faculty of Medical Sciences, Behbahan, Iran*
[b] *Department of Clinical Biochemistry, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran*
[c] *Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran*
[d] *Department of Internal Medicine, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*
[f] *Autophagy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[g] *Department of Biochemistry, School of Medicine, Shiraz University of Medical Sciences, Iran*

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has become the most serious global public health issue in the past two years, requiring effective therapeutic strategies. This viral infection is a contagious disease caused by new coronaviruses (nCoVs), also called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Autophagy, as a highly conserved catabolic recycling process, plays a significant role in the growth and replication of coronaviruses (CoVs). Therefore, there is great interest in understanding the mechanisms that underlie autophagy modulation. The modulation of autophagy is a very complex and multifactorial process, which includes different epigenetic alterations, such as histone modifications and DNA methylation. These mechanisms are also known to be involved in SARS-CoV-2 replication. Thus, molecular understanding of the epigenetic pathways linked with autophagy and COVID-19, could provide novel therapeutic targets for COVID-19 eradication. In this context, the current review highlights the role of epigenetic regulation of autophagy in controlling COVID-19, focusing on the potential therapeutic implications.

1. Introduction

The COVID-19 pandemic in China, and then all over the World, in late December 2019 took everyone by surprise. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared after the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 [1]. Unlike the previous two CoV-associated syndromes, the SARS-CoV-2 infection had a higher rate of human-to-human transmission [2]. As a result, the World Health Organization (WHO) finally declared the COVID-19 a global pandemic in March 2020, just a few months after it emerged [3]. SARS-CoV-2, as the causative pathogen for COVID-19, has led to almost 4,010,834 deaths as of July 9, 2021 [4].

SARS-CoV-2 belongs to the family *Coronaviridae* that are enveloped, positive-sense single-stranded RNA viruses (+ssRNA) [5]. Spike (S) is one of the key structural proteins encoded by almost all coronaviruses, including SARS-CoV-2. S glycoprotein consists of two subunits the N-terminal S1 domain, and the C-terminal S2 domain [6]. The receptor-binding domain (RBD), which is responsible for recognizing the angiotensin-converting enzyme 2 (ACE2) receptors on the target cells, is located on the S1 subunit, while the functional elements required for fusion, such as fusion peptide (FP), two heptad repeats (HR1 and HR2), and the transmembrane [7] domains are located on the S2 subunit [5,6]. The multibasic S1/S2 protease cleavage site is a vital characteristic of SARS-CoV-2 for its viral entry [8]. According to recent evaluations, ACE2, along with neuropilin-1 (NRP1), are the key receptors for the nCoV entry into the host cells [9,10]. After the binding of S proteins to the ACE2 receptors, S proteins need to undergo priming to be further processed and cleaved by the host cell's proteases, such as the human transmembrane protease serine 2 (TMPRSS2), to fuse the viral membrane with the host cell membrane [5]. Following this fusion, SARS-CoV-2 enters the cell by endocytosis. Inside the cytoplasm, the uncoating process results in the release of viral RNA. The genomic material of SARS-CoV-2 acts as a messenger RNA (mRNA), producing structural and nonstructural proteins (NSPs) with the assistance of host

Abbreviations:

COVID-19	coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
MERS-CoV	Middle East respiratory syndrome coronavirus
WHO	World Health Organization
RBD	receptor-binding domain
ACE2	angiotensin-converting enzyme 2
NRP1	neuropilin-1
TMPRSS2	transmembrane protease serine 2
NSPs	nonstructural proteins
ORFs	open reading frames
RdRp	RNA-dependent RNA polymerase
DMV	double-membrane vesicle
ER	endoplasmic reticulum
ARDS	Acute Respiratory Distress Syndrome
CVD	cardiovascular disease
DM	diabetes mellitus
DIC	disseminated intravascular coagulation
AKI	acute kidney injury
CMA	chaperone-mediated autophagy
Hsc70	heat shock cognate protein 70
LAMP-2AR	lysosomal-associated membrane protein 2A
Atg	autophagy-related genes
ULK1	unc-51-like autophagy activating kinase 1
PAS	phagophore assembly site
PI3K LC3B	phosphoinositide 3-kinase
microtubule-associated protein light chain 3	
PE	phosphatidylethanolamine
AMPK	AMP-activated protein kinase
mTORC1	mammalian target of rapamycin complex 1
Akt	protein kinase B
ERK	extracellular signal-regulated kinase
MAPK	mitogen-activated protein kinase
RTCs	replication/transcription complexes
PTMs	post-translational modifications
PKA	protein kinase A
UPR	unfolded protein response
HIF-1α	hypoxia inducible factor 1α
FoxO	forkhead box transcription factor class O
ncRNAs	non-coding RNAs
NOR1	nitro domain-containing protein 1
DAPK	death-associated protein kinase
SOX1	SRY-box transcription factor 1
DNMTs	DNA methyltransferases
ALL	acute lymphatic leukemia
ESCC	esophageal squamous cell carcinoma
H. pylori	*Helicobacter pylori*
Mtb	*Mycobacterium tuberculosis*
DRAM1	DNA damage-regulated autophagy modulator protein 1
HATs	histone acetylases
HDACs	histone deacetylases
SIRT	Sirtuin
HIV	human immunodeficiency virus
HMGB1	high-mobility group box 1
miRNAs	MicroRNAs
HCC	hepatocellular carcinoma
α-Syn	alpha-Synuclein
BCG	Bacillus Calmette-Guérin
MEG 3	Maternally expressed gene 3
siRNA	Small interfering RNA
USP22	ubiquitin-specific peptidase 22

ribosomes [11]. The 3′ end of the viral genome encodes four structural proteins, namely spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. The S protein is responsible for the attachment and fusion of the virus to the host cell receptors. The N protein encapsulates the RNA genome, keeping it stable within the envelope. The 5′ end of the RNA genome consists of two open reading frames (ORFs); ORF1a and ORF1b, which encodes 16 NSPs [5]. NSPs are vital components for viral RNA synthesis. The RNA-dependent RNA polymerase (RdRp) of the virus is the key enzyme of the replication/transcription complex (RTC), formed in a double-membrane vesicle (DMV) by NSPs [12]. For SARS-CoV-2 replication, full-length negative-sense genomic copies are initially created. Next, the aforementioned copies act as templates for the synthesis of the new positive-sense genomic RNA [5]. Finally, after the assembly of newly produced viral RNA and the structural proteins in the endoplasmic reticulum (ER) and Golgi apparatus, new viral particles are released from the infected cells through the exocytosis of secretory vesicles [13].

SARS-CoV-2 transmission is mostly through respiratory aerosols from an infectious person to others. Following the entrance of SARS-CoV-2 into the upper respiratory tract, the virus binds to the ACE-2 receptor, entering the host cell by endocytosis. Within the host cell, the virus goes through replication. Finally, the newly formed viruses are transported *via* exocytosis into the extracellular space, infecting the other cells [14]. The COVID-19 clinically varies from asymptomatic disease to critical infection. Mild symptoms following the involvement of the upper airways include anosmia, sore throat, dry cough, fever, malaise, and myalgias [15]. In most patients, the virus does not progress beyond the upper respiratory tract because of the sufficient performance of the immune system. However, lower respiratory tract involvement occurs in some individuals, leading to more severe manifestations, including ARDS (defined as Acute Respiratory Distress Syndrome),

lymphopenia, and acute cardiac, renal, and hepatic injuries. Furthermore, because of the highly expressed ACE-2 receptors inside the GI tract, especially the small intestine, some patients experience GI symptoms, such as abdominal pain, anorexia, nausea, vomiting, and diarrhea [16]. Complications mainly occurr in patients with severe or critical illness. Age, cardiovascular disease (CVD), chronic lung disease, diabetes mellitus (DM), immunosuppression, and obesity are considered as the major risk factors for COVID-19 complications. In this context, ARDS, acute respiratory failure, sepsis, disseminated intravascular coagulation (DIC), acute liver injury, acute kidney injury (AKI), and pulmonary embolism are some of the commonly seen complications [14].

At present, there is not a definitive cure for SARS-CoV-2 infection. Many clinical trials are trying to identify the most effective drug or combination therapy against the disease. Despite the presence of some suggested treatments to be administered for COVID-19 patients (Table 1), people are still dying from SARS-CoV-2 infection-related complications. Therefore, new therapeutic strategies are urgently needed for controlling the infection to avoid fatal outcomes. For their survival, viruses can manipulate some host cell processes, such as the autophagy machinery [17]. Autophagy is a cellular process that eliminates dysfunctional organelles, misfolded proteins, and intracellular pathogens [18]. Several investigations have attributed a key role in the growth and replication of nCoVs to the autophagic flux [3,19,20]. Additionally, increasing evidence suggests that autophagy has an essential role in the pathogenicity of SARS-CoV-2 [21]. Thus, identifying mechanisms that govern the regulation of autophagy could be therapeutically valuable. Recently, a significant number of studies have reported that epigenetic modifications may regulate the initiation of autophagy [22,23]. DNA methylation, histone modifications, and non-coding RNAs-dependent regulation are well-known epigenetic

Table 1
Potential drugs that have been suggested for SARS-CoV-2 infection.

Treatments	Mechanisms of Action	References
Remdesivir	Inhibits viral RNA polymerases	[26,27]
Lopinavir/Ritonavir	Inhibit proteases	[3]
Favipiravir	Inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses	[28]
Ivermectin	Inhibits the nuclear import of host and viral proteins	[29]
Hydroxychloroquine and Chloroquine	Prevent endosome trafficking and and viral fusion	[30,31]
Arbidol/lopinavir/ritonavir	Block the virus entry into the target cells	[32,33]
Prezcobix	HIV protease inhibitor	[34]
Oseltamivir	Neuraminidase inhibitor	[35]
Tocilizumab	Inhibits IL-6	[36,37]
Corticosteroids	Decreases inflammation	[38]

mechanisms that regulate cell cycle, cell apoptosis, and the autophagic flux [24]. Some epigenetic modifiers also contribute to the regulation of autophagy and potentiate the efficacy of traditional therapeutics [25]. Therefore, gaining an in-depth understanding of the role of epigenetic modifications in the process of autophagy may make it possible to develop potential therapeutic approaches for COVID-19 eradication.

Considering the lack of knowledge in the field of epigenetic modulation of autophagy during the SARS-CoV-2 infection, the present review will discuss recent findings on the epigenetics-autophagy interplay underlying COVID-19 to improve the understanding of involved mechanisms and identifying novel antiviral therapeutic targets.

2. Interplay between autophagy and COVID-19

2.1. Autophagy: definition and molecular mechanisms

The history of autophagy dates back to early 1960s, when a Belgian scientist, Christian de Duve, introduced the term "autophagy" at the Ciba Foundation Symposium on lysosomes, a discovery that culminated in the 1974 Nobel Prize in Physiology or Medicine [39]. Since then, the physiological and pathophysiological roles of autophagy have been widely investigated. Autophagy (as the programmed cell death type II) is now recognized as a lysosome-dependent controlled degradation process for eliminating unwanted or malfunctioning components [3,40]. In a regulated manner, it enables the breakdown and recycling of cellular components, a key feature of eukaryotic cells, enabling them to renew themselves [41,42]. Although autophagy was previously believed to be a primitive degradation mechanism that is activated to protect the cells from starvation, it has become evident that autophagy can also contribute to the homeostasis of non-starved cells [43]. Additionally, the autophagic flux affects aging, as well as different types of infectious and non-infectious diseases [44–46].

Macroautophagy, microautophagy, chaperone-mediated autophagy (CMA), and crinophagy are the four major subtypes of autophagia that can be differentiated based on the pattern of cytoplasmic components reaching the lysosomal degradative milieu [47]. The term "autophagy" usually refers to macroautophagy except where otherwise stated. Microautophagy sequesters small portions of cytoplasm containing proteins, mainly targeted by heat shock cognate protein 70 (Hsc70), and a small part of the bulk cytoplasm by direct invagination of the lysosomal membrane [48]. In CMA, targeted proteins carrying a specific pentapeptide motif (Lysine-Phenylalanine-Glutamate-Arginine-Glutamine (KFERQ)) are preferentially destroyed by direct transport into the lysosome in a complex with chaperones (e.g. Hsc-70) *via* the LAMP-2AR (so-called lysosomal-associated membrane protein 2A) [49]. During crinophagy, secretory granules containing excess or obsolete materials, directly combine with late endosomes or lysosomes to eliminate and

recycle the leftover secretory material from the cytoplasm [50].

When macroautophagy (hereafter referred to as autophagy) is triggered by intracellular or extracellular stimuli, a double-membrane autophagosome is formed to deliver various materials from the cytoplasm to the lysosome [10]. Autophagosome formation is a complicated process, divided into three consecutive steps, namely initiation, nucleation, and expansion (Fig. 1). This process is monitored by proteins encoded by evolutionarily conserved autophagy-related genes (Atg) [51]. About thirty-six Atg proteins (ATGs) have been identified so far as being critical for the autophagyic flux [52]. During the initiation step of autophagosome formation, the ATG13 binds unc-51-like autophagy activating kinase 1 (ULK1) at the phagophore assembly site (PAS) [53]. Other ATGs are subsequently added to this complex in order to build the ULK1/Atg1 activated unit which consists of ULK1, ATG13, FIP200 (focal adhesion kinase family interacting protein of 200 kD), and ATG101. Then (in nucleation step), ULK1/Atg1 unit activates a class III phosphoinositide 3-kinase (PI3K) complex (Beclin 1, ATG14, VPS15, VPS34) through attaching to the ATG13 [54]. ATG9A, as a transmembrane protein, plays a key role in this step by delivering lipids. ATG9A positive membrane vesicles, correlating with a ATG2-WIPI complex, are shuttled to the site of autophagosome initiation *via* interacting with the FIP200 [55]. Subsequently, membrane vesicles become fused at the PAS to create a pre-autophagosome structure called the isolation membrane. During the final step (i.e. expansion) of autophagosome formation, the recently created membrane constantly expands to surround and capture cytoplasm and various cellular components (referred to as phagophore) [56]. This step is mediated by two ubiquitin-like systems,: ATG5-ATG12 conjugation step and microtubule-associated protein light chain 3 (LC3B) processing step [57]. Atg4, which is known as a cysteine protease, generates LC3B–I by cleaving LC3B (a cytosolic protein expressed in different cells). LC3B–I is then activated and conjugated with the amino group of the phosphatidylethanolamine (PE) to form LC3B-II [10]. The ATG12–ATG5–ATG16 complex facilitates the recruitment of LC3B-II into both internal and external surfaces of the growing phagophore, where it participates in hemifusion and expansion of membranes, as well as selecting the suitable cargo for elimination [58]. Eventually, a closed bilayer membrane structure, referred to as mature autophagosome, is formed. At this time, the autophagosome will be transferred to the perinuclear region, where the recently formed lysosomes are usually located, to be merged with endosomes or lysosomes to form the autophagolysosome [59].

2.2. The paradoxical role of autophagy in viral infections

Autophagy has been reported to contribute to a vast array of diseases, including bacterial and viral infections, cancers, neurological disorders, and cardiovascular diseases [60,61]. In the last two decades, great efforts have been devoted to studying the complicated interplay between autophagy and CoV infections, and many hypotheses have been proposed to clarify the involved molecular mechanisms. Previous investigations have suggested that autophagy could be involved in direct and indirect antiviral responses such as the clearance of viruses, the presentation of their antigens, the decrease of hyperactive inflammatory responses [41]. In this context, xenophagy, which is also known as virophagy, refers to a kind of selective autophagy, in which specialized autophagy receptors capture the viruses, viral-derived antigens, and neosynthesized viral components [62]. However, viruses can suppress, escape, or utilize the autophagy machinery and ATG proteins of the host cells to replicate or to modify the autophagy to inhibit the cells' antiviral mechanisms [63,64]. Therefore, the autophagic flux is likely to be a "double-edged sword" in CoV-associated infections, especially the COVID-19. In this regard, the proviral and antiviral roles of autophagy in different viral diseases are summarized in Table 2.

2.2.1. Antiviral mechanisms of autophagy in COVID-19

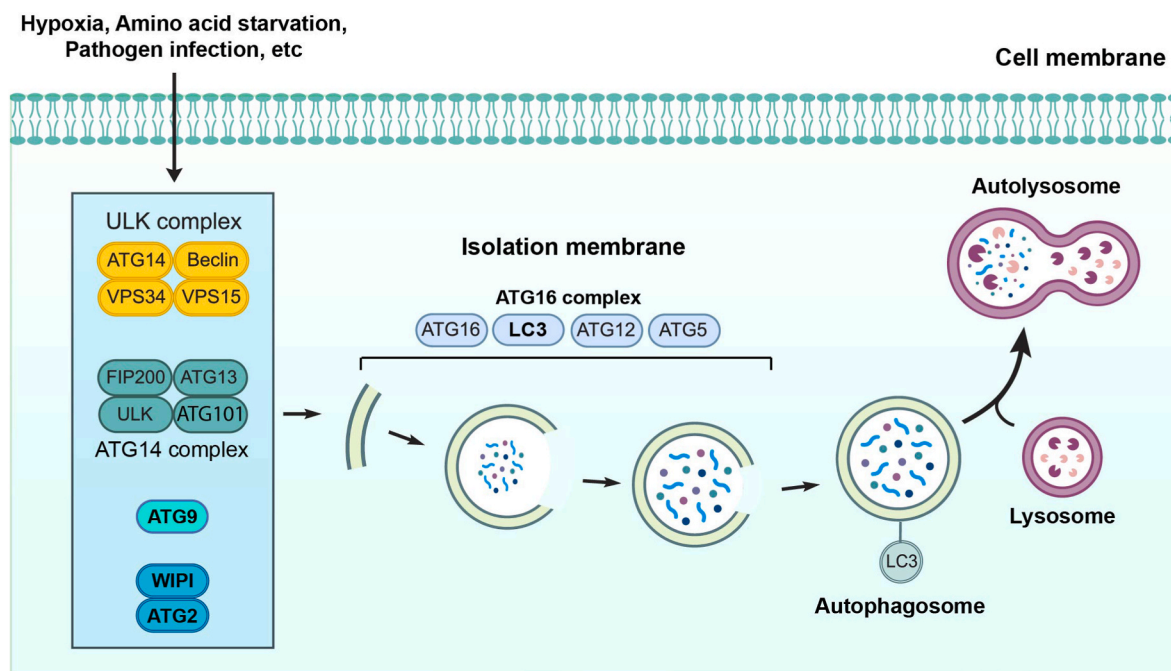During viral infections, AMP-activated protein kinase (AMPK)

Fig. 1. Schematic description of autophagy (macroautophagy). This process is triggered by several infectious and noninfectious stimuli. Autophagosome formation is divided into three main steps: initiation (ULK1 initiation complex), nucleation (Atg5–Atg12 conjugation, interaction with Atg16L and multi-merization at the phagophore), and expansion (LC3 processing and insertion into the extending phagophore membrane). Then, the autophagosome is fused with the lysosome, and the randomly or selectively captured targets are degraded by lysosomal proteases enzymes.

suppresses the mammalian target of rapamycin complex 1 (mTORC1) and alternatively triggers PI3K/protein kinase B (Akt1), resulting in autophagy initiation and virion encapsulation. Then, the formation of autolysosomes is activated by these downstream signaling pathways, which are subsequently joined with lysosomes to eliminate its viral contents [65]. However, like most other respiratory CoVs, SARS-CoV-2 might have particular mechanisms to escape the autophagy-triggered cellular clearance [66]. Thus, pharmacological targeting of escape mechanisms may mitigate the replication of the virus. Gassen et al. reported in a 2020 preprint that SARS-CoV-2 could inhibit the autophagic flux by interfering with multiple metabolic pathways, including the inhibition of glycolysis by suppressing AMPK and mTORC1 [67], which in turn, pro-autophagic compounds, such as spermidine can block the viral replication. The extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) and PI3K/Akt/mTOR, as two signaling responses with inhibitory effects on autophagy, were selectively activated in MERS-CoV-infected hepatocytes [68]. Interestingly, the pharmacological suppression of ERK/MAPK and PI3K/Akt/mTOR pathways led to inhibition of MERS-CoV replication *in vitro* [68]. Hoffmann et al. (2020) demonstrated that SARS-CoV-2, as well as SARS-CoV-1, used ACE2 as the entry receptor [69,70]. Indeed, ACE2 is a cellular receptor which can suppress cell apoptosis and inhibits autophagy inside the lungs [70]. The HMG-CoA reductase inhibitors, usually known as statins, are a group of drugs commonly used to lower serum cholesterol by reducing its synthesis in the liver [71]. In addition, its well-known lipid-lowering effects, statins have been postulated to possess pleiotropic beneficial actions by regulating numerous biological pathways implicated in antioxidant, anti-inflammatory, or anti-tumor cellular responses [71,72]. Some of the pleiotropic effects attributed to statins may related to their potential role regulating essential proteins involved in autophagy [72,73]. For example, it has been reported that Atorvastatin activated autophagy by upregulating Beclin1 and LC3-II gene and protein expression or via the AMPK/mTOR pathway [74,75]. Accordingly, our recent clinical study revealed that the use of statins in hospitalized COVID-19 patients was linked with a lower risk of death and reduced chance of being subjected to mechanical ventilation [76].

2.2.2. Proviral mechanisms of autophagy in COVID-19

The role of the autophagic flux in viral replication was hypothesized based on the discovery that the induction of double-membrane vesicles (DMVs) formation during the infection process of mouse hepatitis virus (MHV)-infected Vero cells was found to be associated with the LC3 and ATG12 protein, a key maker of autophagosomes formation [77]. Further investigations revealed the co-localization of replicase proteins to cytoplasmic complexes having markers for autophagosome membranes, including LC3, in SARS-CoVs-infected cells [78]. Additionally, it has been found that NSP6, as a key viral replicase protein of Avian CoV (formerly known as infectious bronchitis virus, IBV), is capable of inducing the generation of Atg5 and LC3II-positive autophagosome at the omegasome level [79]. Chen et al. (2014) discovered that the papain-like protease PLP2 (PLP2-TM) of COVs interacts with LC3 and Beclin-1, increasing the autophagosome concentration, preventing autophagosomes from attaching to lysosomes [80]. In another study, it was revealed that NSP6, which has been reported to be expressed in other CoVs, such as SARS-CoV-2, suppresses additional autophagosome expansion and disrupts the virus-to-lysosome transportations [81,82].

Nonetheless, a group of evaluations have challenged the theory of direct involvement of autophagy COVs replication. Consistently, the size of DMVs induced by mammalian CoVs, is reported to be smaller than cellular autophagosomes, and the replication of viruses in MHV-infected cells does not require ATG7 and ATG5, the essential ATGs in the control of autophagosome formation [79,83]. The co-localization of LC3 or green fluorescent protein (GFP)-LC3 with the replication/transcription complexes (RTCs) of SARS-CoV was not observed [84]. This lack of consensus is probably originated from the methodological and/or technical differences of such studies. Another reason for this inconsistency might be that some infectious diseases regulate autophagy in a biphasic, time-dependent manner. For example, Sneha A. Thomas et al. showed that during early infection—and via activation of the Akt pathway—Leishmania actively inhibits the induction of autophagy. However, by 24 h, Leishmania switched from being an inhibitor to an overall inducer of autophagy [85].

Table 2

Summary of the proviral/antiviral roles of autophagy in different viral infections.

Viral diseases	Proviral/Antiviral role of autophagy	References
Classical swine fever (CSF)	Pro-viral: Induction of autophagy to increase viral replication by activation of the PERK and IRE1 pathways	[86]
Crimean-Congo hemorrhagic fever orthonairovirus (CCHFV)	Pro-viral: Virus non-structural protein induces apoptosis by affecting mitochondrial membrane	[87]
Dengue virus (DENV)	Pro-viral: Enhancing autophagy through mTOR signaling molecule	[88]
Human immunodeficiency virus (HIV)	Anti-viral: Induction of autophagy by 1α, 25-dihydroxycholecalciferol leads to reduction of HIV replication	[89]
	Pro-viral: Nef (negative factor) prevents the autophagy process by connecting BECN1 to its inhibitor BCL2	[90]
Hepatitis C virus (HCV)	Pro-viral: Decrease in clearance of virus by IFN-α/RBV	[91]
Herpes simplex virus type 1 (HSV-1)	Anti-viral: MHC I presentation of viral antigen after HSV-1 infection	[92]
Human papillomavirus (HPV)	Pro-viral: Inhibition of autophagy by activation of PI3K/Akt/mTOR signaling lead to virus replication	[93]
Influenza A virus (IAV)	Anti-viral: Restriction of IAV infection through inhibiting fusion of virus with endosomes and activation of interferon by ATG16L1	[94]
	Pro-viral: IAV induces autophagy which contributes to IAV replication possibly through modulating virus-induced apoptosis	[95]
Vesicular stomatitis virus (VSV)	Anti-viral: Representing of viral antigens to Toll-like receptors (TLRs)	[96]
Respiratory syncytial virus (RSV)	Pro-viral: Non-structural protein (NS-1) causes viral replication through the mTOR pathway	[97]
Flavivirus	Pro-viral: Replication of virus by NS4A-induced autophagy	[98]
Foot-and-mouth disease virus (FMDV)	Anti-viral: Infection with the foot and mouth disease virus, Atg5-Atg12 boosts the NF–B and IRF3 pathways	[99]
Paramyxovirus	Anti-viral: Inhibiting of virus replication by IFN-induced TDRD7 (Tudor domain containing 7)	[100]
Severe acute respiratory syndrome-coronavirus (SARS-CoV)	Pro-viral: Receptor Interacting Protein 3 (Rip3) - mediated oligomerization of SARS causes death cells and promotes SARS CoV infection	[101]

3. Epigenetic control of autophagy

Like many other cellular processes, autophagy is regulated by multiple mechanisms. Different signaling pathways, transcriptional processes, post-translational modifications (PTMs), and epigenetic alterations are considered as the most important autophagy regulators [102]. In the case of signaling pathways, the target of rapamycin (TOR) [103] and Ras/cAMP/protein kinase A (PKA) pathways are central to nutrient deprivation-dependent induction of autophagy [104]. It has been demonstrated that TOR down-modulates the autophagic flux, just as the Ras/PKA pathway does [102,105]. Beyond the nutrient signaling, insulin/growth factor pathways [106], AMPK-dependent energy sensing [107], and different types of stress responses such as ER stress [108], oxidative stress [109], and hypoxia [110], which are moderated by unfolded protein response (UPR), antioxidant systems, and hypoxia inducible factor 1α (HIF-1α), respectively, are considered as the other

regulating signaling pathways. Yet, Atgs can be also modulated at a transcriptional level, especially when stress occurs. For instance, transcription of the Atg8/LC3, as an autophagosome marker, becomes up-modulated in yeasts and a group of mammalian cells under starvation conditions [102]. Although there is not enough information about the underlying transcriptional factors, forkhead box transcription factor class O (FoxO) is the first transcription factor indicated to be essential for the induction of autophagy according to studies performed on *Drosophila* larval fat body [111]. Consistent with the aforementioned regulating mechanisms, PTMs critically modulate autophagic flux through modifying a wide variety of ATGs [103,112]. In this context, phosphorylation of autophagy-related complexes, like the Atg1/ULK kinase [113], as well as the acetylation/deacetylation of major ATGs, including ATG5, ATG7, ATG8, and ATG12 [114], are the well-studied PTMs in correlation with autophagy. In spite of the importance of signaling-mediated, transcriptional, and post-transcriptional modulation of autophagy, epigenetic control of this vital process has recently attracted much attention in both physiological and pathological/infectious conditions [115]. DNA methylation/demethylation, histone modifications, and non-coding RNAs (ncRNAs)-mediated regulation are categorized as the most prominent epigenetic alterations, which are highlighted below.

3.1. DNA methylation/demethylation

DNA methylation is a dynamic process, in which methylated targets can be subsequently demethylated [116]. Several Atgs have been reported to be methylated and suppressed to block autophagy in particular pathological conditions. Atg1/ULK kinase, Beclin1/Atg6, LC3/Atg8, and lysosomal-associated membrane protein 2 (LAMP2) gene are some examples in this field [116–118]. Moreover, genes encoding autophagy regulatory molecules, such as nitro domain-containing protein 1 (NOR1), death-associated protein kinase (DAPK), and SRY-box transcription factor 1 (SOX1) can also be modified by DNA methylation [116].

DNA methylation generally takes place at three major levels: (i) loss of imprinting (LOI), (ii) hypomethylation, and (iii) hypermethylation, in which DNA hypermethylation has a more significant role in the regulation of autophagy than the two others [119,120]. In this context, DNA methyltransferases (DNMTs) have been reported to have vital roles in epigenetic control of autophagyic flux, in part because the improper methylation of Atgs, which results in changes in ATG expression levels, was found to be correlated with a variety of human diseases [121]. For example, children with acute lymphoblastic leukemia (ALL) were found to overexpress DNMT1 compared to healthy individuals, which is the main cause of hypermethylation of the ATG5 and LC3B gene promoters [122]. It was also revealed that improper methylation of LC3Av1, as a member of the LC3 gene family, could be in close association with suppressed autophagy in esophageal squamous cell carcinoma (ESCC) cells, as well as tumorigenesis [123]. Klotho (KL) and protocadherin 17 (PCDH17) tumor suppressor genes, expressed in colorectal and gastric cancer cells, respectively, are other genes that play a role in inducing autophagy. Interestingly, these genes can go under promoter methylation, and thus be employed as epigenetic diagnostic markers for the aforementioned tumors [124,125]. The overexpressed PCDH17 can stimulate autophagy, accompanied by the elevation of autophagy vacuoles and up-modulation of particular ATGs, such as ATG12 and ATG5 [124].

Beyond the cancers, DNA methylation can also orchestrate infectious circumstances. In this context, *Helicobacter pylori* (*H. pylori*)-induced DNA methylation has been reported to modulate several Atgs/ATGs in infected gastric mucosae [126,127]. MAP1LC3Av1 is one of these genes that become down-modulated following the hypermethylation in *H. pylori*-infected cancerous tissues, while it is not expressed in *H. pylori* negative tissues. Muhammad et al. interestingly showed that MAP1LC3Av1 suppression could disrupt the autophagic flux, resulting in an elevation in tumorigenicity of gastric epithelial cells [128].

Mycobacterium tuberculosis (Mtb) is another pathogen, which provokes its survival in host cells trough inhibiting the autophagy. Indeed, *Mtb* blocks autophagy in an mTOR-independent manner by triggering the hypermethylation of histones at the Atg5 and Atg7 promoters trough stimulation of p38-MAPK- and EHMT2 methyltransferase-dependent signaling cascades [129].

It should be noted that DNA demethylation can also contribute to the epigenetic control of autophagic flux. TET enzymes (identified as ten-eleven translocation family) are the key contributors to DNA demethylation [130]. Among all TETs, TET1 has been reported to be more often associated with autophagy, as it can exert its tumor suppressive effects. Further, CpG demethylase activities through operation of autophagy, especially at early stages [131]. TET1 can also modulate some Atgs, namely Atg13 and DRAM1 (defined as DNA damage-regulated autophagy modulator protein 1) in cancerous cells [132]. Nonetheless, other TETs may regulate autophagy as well. TET2 is a good example in this field, which can modulate autophagy by affecting the methylation of BECN1 promoter in atherosclerotic conditions [133]. In sum, more investigations should be performed to determine the exact interplay between TET enzymes and autophagic flux.

3.2. Histone acetylation/deacetylation

A group of evaluations have been recently focused on the role of histone acetylases (HATs), as well as histone deacetylases (HDACs) in the epigenetic modulation of autophagy [120,134]. Lysine acetyltransferases (KATs), such as KAT3A, KAT3B, and KAT5, are a major group of HATs, established in the control of autophagy. In addition, Sirtuin 1-3 (SIRT1-3), which are classified as key HDAC family members, are also involved in the modulation of autophagic flux [134]. The H4K16ac, a well-known acetylated histone, has a special effect on transcriptional modulation of Atgs and also stimulates a feedback route that regulates the induction of autophagy. Füllgrabe et al. demonstrated that SIRT1 and KAT8/human males, absent in the first (hMOF)/MYST1, affected the acetylation of H4K16, resulting in a histone shift and subsequent modulation of autophagy [135,136]. Down-modulation of *Drosophila* MOF and H4K16ac is also correlated with rapamycin/starvation-induced autophagy. More interestingly, SIRT1 can be considered as a limiting factor for autophagy inside the nucleus, where H4K16 deacetylation could repress different ATGs [22]. This fact is analogous to stimulating role of SIRT1 inside the cytoplasm, which deacetylates key ATGs (e.g. ATG5, ATG7, etc.) [22]. Accordingly, if H4K16ac deacetylation is suppressed as a result of SIRT1 deactivation or hMOF up-regulation, the autophagy might be triggered, and cell death would occur. Indeed, it is the H4K16 acetylation status that determines the autophagy-dependent cell death or survival [135,137].

In the case of infectious diseases, there is a well-studied crosstalk between HDAC-mediated regulation of autophagy and human immunodeficiency virus (HIV) infection [138]. Demonté et al. showed that HDAC inhibitors can trigger autophagy-mediated degradation of HIV particles; a valuable finding that reveals the therapeutic capacity of these inhibitors to ameliorate the HIV infection [139]. HDAC inhibition can also be involved in amplification of antimicrobial responses against *Mtb* by regulating the autophagic flux in a manner that is not fully understood [140,141]. Hepatitis B is another example in this field. HBx, a HBV X protein, is a key modulator of HBV-induced autophagy. Nonethelesss, the cytoplasmic high-mobility group box 1 (HMGB1) is an autophagy inducer, whose cytoplasmic translocation is strongly associated with its acetylation status [142]. Fu et al. demonstrated that HBx up-regulated the HMGB1 and stimulated its cytoplasmic translocation trough acetylation in order to accelerate autophagy. They also identified that nuclear HDAC could trigger HBx-induced hyperacetylation, leading to HMGB1 translocation, mediated by HDAC1 isoform [142]. Moreover, cytoplasmic HBx-to-HMGB1 attachment can initiate autophagy inside the hepatocytes [142]. However, further evaluations are definitely needed to reveal the exact interaction between histone acetylation/deacetylation and the process of autophagy in various infections.

3.3. Non-coding RNA-mediated modifications

In mammals, just like the other eukaryotes, the transcription process mostly results in the production of ncRNAs [120,143]. NcRNAs are believed to be responsible for a wide variety of biological functions. For instance, they can protect genomes during genome rearrangement or the process of DNA synthesis [144,145]. Recent evaluations have indicated that ncRNAs can also be involved in the modulation of autophagy, in which they contribute to the pathogenesis of multiple diseases [146].

MicroRNAs (miRNAs) are a major subgroup of ncRNAs, participating in the control of autophagy [120]. Indeed, miRNAs have been reported to be highly conserved molecules, which can epigenetically modulate the autophagic flux in multiple stages [147]. In this regard, miR-7, miR-101, miR-20a, miR-25, miR-106b, miR-199a, miR-17−5p, miR-595, miR-4487, and miR-409−3p are some examples of autophagy modulators [148]. The function of these miRNAs on autophagy is summarized in Table 3. MiR-7, as a tumor suppressor miRNA, has the ability to increase autophagy in hepatocellular carcinoma (HCC) cells; Wang et al. declared that miR-7-mediated induction of autophagy was a consequence of mTOR inhibition [149]. Furthermore, miR-101 has been demonstrated to be a potential autophagy inhibitor in HCC and breast cancer cells through targeting ATG4D, RAB5A, and stathmin1 [150]. In multiple system atrophy (MSA), miR-101 down-modulation can trigger the autophagic flux to mitigate the accumulation of oligodendroglial alpha-Synuclein (α-Syn) [151]. Further analyses on breast cancer cells revealed another miRNA as an autophagy regulator, miR-25, which modulates autophagy in correlation with cancer drug resistance. It has been confirmed that miR-25 silencing can stimulate autophagic cell death through increasing the expression of ULK1 [152]. Some of the aforementioned miRNAs can also regulate autophagy in infectious conditions [153]. For instance, miR-17-5p has been shown to be a positive modulator of autophagy in *Mtb* infection through interacting with Beclin-1 and Mcl-1 [154]. On the contrary, Bacillus Calmette-Guérin (BCG) infection-induced overexpression of miR-17-5p blocks the initiation of autophagy and increases the growth of *Mycobacteria* inside the cells [155]. MiR-106b is another miRNA in this field, which is reported to play a role in the operation of cathepsin S activity, as a crucial step in phagosomal acidification and the subsequent removal of bacteria [156]. However, miR-106b can also affect other autophagic markers such as ATG16L1 in conditions other than microbial infections [156,157].

In addition to miRNAs, long non-coding RNAs (lncRNAs) have also

Table 3
Autophagy-related microRNAs (miRNAs).

miRNAs	Effect on autophagy	References
miR-7	Activation: via mTOR inhibition	[173]
miR-101	Inhibition: through targeting ATG4D, RAB5A, and stathmin1	[150,174]
miR-20a	Inhibition: via targeting FIP200	[175]
miR-25	Inhibition: through targeting ULK1	[176]
miR-106b	Inhibition: through targeting ATG16L1	[177]
miR-199a	Inhibition: via targeting ATG7	[178]
miR-17−5p	Inhibition in cancer cells: via targeting BECN1	[179]
	Activation in *Mycobacterium tuberculosis* condition: through targeting Mcl-1 and STAT3	[154]
	Inhibition in Bacillus Calmette-Guérin (BCG) condition: through targeting ULK1	[155]
miR-595	Inhibition: through targeting ULK1	[180]
miR-4487	Inhibition: through targeting ULK1	[180]
miR-409−3p	Inhibition: through targeting BECN1	[181]

been reported to interact with autophagy as unusual modulators [120]. LncRNAs affect the autophagy process through mediation of Atg expression levels, as well as interfering with DNA, RNA, and/or protein molecules [145,158,159]. Maternally expressed gene 3 (MEG 3), which is a tumor suppressor lncRNA, is inversely correlated with the autophagosome marker MAP1A/MAP1B-LC3/ATG8. Small interfering RNA (siRNA)-mediated inhibition of MEG3 was indicated to contribute to autophagy initiation, cell proliferation, and repression of apoptotic flux in bladder cancer cells [160]. Furthermore, the suppressed MEG3 in BCG-infected macrophages, accelerates the clearance of *Mycobacterium bovis* BCG through stimulation of autophagy [161]. HULC, as another lncRNA overexpressed in HCC, can indirectly induce the process of autophagy through up-regulating the ubiquitin-specific peptidase 22 (USP22) following the suppression of miR-6886−3p, miR-6825−5p, and miR-6845−5p. Xiong et al. declared that USP22 actually restored SIRT1, and inhibited the ATG5/ATG7 acetylation to trigger the autophagic flux [162].

Circular RNAs (circRNAs) are another form of noncoding RNAs that are usually expressed in tissues and body fluids [163]. The circRNAs are reported to have diverse functions in mammals and plants. They can act as microRNA (miRNA) sponges to regulate the function of mRNA [164]. CircRNAs can also play a role in RNA-binding protein (RBP) assembly or allosteric regulation by RBPs to affect biological functions [164]. The circRNAs play essential roles in human diseases and are considered to be ideal biomarkers of these diseases due to their high stability [165]. Evidence has shown that circRNAs influence the course of a disease by regulating autophagy [166]. For example, following binding with MIR139-5p, circEIF3K inhibits the functions of MIR139-5p, the phosphorylation of MAPK/Erk, and the expression of BCL2, which promotes the autophagy in somatic inflammatory cells of patients with tubal inflammation, thereby inhibiting cell vitality and promoting apoptosis [167]. circCDK8 enhances autophagy in periodontal ligament stem cells during hypoxia via upregulation of ATG5 [168]. mmu_circ_0000250 promotes autophagy in endothelial progenitor cells through upregulation of SIRT1 expression [3]. Furthermore, mmu_circ_0000623 inhibits liver fibrosis via activation of cell autophagy [169]. In lung fibroblasts, circ012091 inhibits the expression of the autophagy-associated protein LC3-II by inhibiting the expression of PPP1R13B, a major pro-apoptotic protein of the TP53 family, thus inhibiting autophagy in the cells [170]. During inflammatory bowel disease, circPabpn1 attenuates autophagy in intestinal epithelial cells via downregulation of Atg16l1 gene [171]. Additionally, Virus-derived circRNAs and/or differentially-expressed host circular RNAs have been observed following various virus infections. For instance, following infection with influenza Virus, circGATAD2A increases viral replication by inhibiting autophagy [172]. Although, the role of circRNAs in autophagy regulation has been investigated in various diseases, currently, there is no study about the modulation of autophagy by circRNAs in COVID-19 cases. Therefore, future studies should focus on identifying circRNAs that regulate autophagy in COVID-19 patients because they could be useful in understanding, detecting, and treating COVID-19.

In sum, these findings show that epigenetic modifications play an important role in the control of autophagy during various diseases.

4. Targeting autophagy through epigenetic modulations as a novel therapeutic strategy against COVID-19

Given the important role of autophagy in COVID-19 exacerbations and also regarding the essential role of epigenetic mechanisms in autophagy regulation, epigenetic therapeutics are promising strategies to modify autophagy during the COVID-19. As mentioned above, the histone modification and DNA methylation are commonly evaluated and broadly occurring molecular mechanisms that control the autophagic flux. Relevant analyses in this regard have focused on the significance of inhibitors of these epigenetic alterations to modulate the autophagy. To date, FDA has approved multiple DNMT and HDAC inhibitors for

therapeutic purposes. 5-Azacytidine and 5-aza-2′-deoxycytidine (decitabine) are frequently used medications to stimulate DNA demethylation by incorporation into DNA. Vorinostat (SAHA), Belinostat, romidepsin, trichostatin A (TSA), and Panobinostat are commonly used drugs for HDAC inhibition. Some of these drugs are already used for the treatment of several cancers through autophagy modulation (Table 4). For instance, 5-Azacytidine and decitabine activate autophagy in leukemic T cells through enhancement of the ROS generation, as well as the up-regulation of ATGs [182,183]. Similarly, SAHA induces autophagy in MDA-MB-231, DLD1, T cell lymphoma HUT78, and colorectal cancer cells *via* p53 degradation and up-regulation of LC3-II and ATG5 [184–186]. Nevertheless, it was reported that SAHA suppresses autophagy in MCF7 breast cancer cells through down-regulation of p62 and overexpression of LC3-II and Beclin-1 [187]. Romidepsin has been shown to be capable of inducing the autophagy in gastric tumor cells through the activation of MAPK pathway and increasing the ROS levels [188,189]. Furthermore, TSA activates the autophagic flux in HCT116 and HepG2 cancer cells by inhibiting mTOR and inducing FOXO1 transcription factor [155]. Panobinostat also up-regulates autophagy in Human pre-B ALL Nalm-6 cells *via* the activation of FOXO3 and FOXO4 transcription factors [190]. In addition to anti-cancer effects, several studies reported that epigenetic medications, such as DNMT1 and HDAC inhibitors, potentially inhibit SARS-CoV-2 activities [191]. For example, SAHA was reported to be responsible for decreasing the replication of initiating genes, as well as the stimulation of cellular proteins in charge of viral inhibition [192]. VPA was demonstrated to be involved in minimal modulation of SARS-CoV-2 growth [193]. Therefore, common antiviral drugs, e.g., remdesivir, ribavirin, favipiravir, and galidesivir, could be preferentially used in combination with DNMT inhibitors, such as decitabine, and azacitidine, or HDAC inhibitors like vorinostat, belinostat, panobinostat, and TSA. Nonetheless, more preclinical analyses, as well as clinical trials are needed to confirm the clinical benefits of the corresponding combined candidates.

5. Conclusion and future perspective

As it is highlighted in the current review, autophagy has been markedly implicated in SARS-CoV-2 infection. Today, we know that epigenetic control of autophagy is an important regulatory step in various physiological and pathological conditions, as epigenetic dysregulation of Atg/ATGs is significantly involved in the etiology of different infectious and non-infectious diseases (e.g., cancers, metabolic disorders, and neurodegenerative diseases). However, epigenetic regulation of autophagy in COVID-19 has not significantly been reported. It is therefore imperative to understand the role of epigenetic mechanisms in the regulation of autophagy in COVID-19 because the application of epigenetic modulators, such as demethylating agents or HDAC inhibitors, not only aims to normalize atypical epigenetic patterns on DNA sequences or histones but also provides a newer therapeutic opportunity

Table 4
Epigenetic regulators associated with autophagy.

Inhibitors	Effect on autophagy	References
5-Azacytidine	Up-regulation	[182]
decitabine	Up-regulation	[183]
Zebularine	Up-regulation	[194]
Vorinostat (SAHA)	Up-regulation	[184–186]
Romidepsin	Up-regulation	[188,189]
Trichostatin A (TSA)	Up-regulation	[155]
Tucidinostat	Down-regulation	[195]
Panobinostat	Up-regulation	[190]
Givinostat	Down-regulation	[196]
Mocetinostat	Down-regulation	[197]

to regulate autophagy in COVID-19 patients.

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Declaration of competing interest

All authors have no conflicts of interest to declare.

Data availability

Data will be made available on request.

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