Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

Targeting autophagy regulation in NLRP3 inflammasome-mediated lung inflammation in COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Emerging evidence indicates that the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome is activated, which results in a cytokine storm at the late stage of COVID-19. Autophagy regulation is involved in the infection and replication of SARS-CoV-2 at the early stage and the inhibition of NLRP3 inflammasome-mediated lung inflammation at the late stage of COVID-19. Here, we discuss the autophagy regulation at different stages of COVID-19. Specifically, we highlight the therapeutic potential of autophagy activators in COVID-19 by inhibiting the NLRP3 inflammasome, thereby avoiding the cytokine storm. We hope this review provides enlightenment for the use of autophagy activators targeting the inhibition of the NLRP3 inflammasome, specifically the combinational therapy of autophagy modulators with the inhibitors of the NLRP3 inflammasome, antiviral drugs, or anti-inflammatory drugs in the fight against COVID-19.

1. Introduction

Since December 2019, the coronavirus disease 2019 (COVID-19) outbreak that first occurred in Wuhan city, Hubei Province, China has spread globally. In 2020, the World Health Organization (WHO) named the disease COVID-19, and the International Committee on Taxonomy of Viruses (ICTV) named the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The same year in March, the WHO declared that COVID-19 was a pandemic. Over the past three years, variants of SARS-CoV-2 have appeared successively, mainly including the Delta variant and recent rapidly increasing Omicron variant. For the prevention and treatment of COVID-19, a total of 367 vaccine candidates have been developed up to 19 July 2022, and drugs such as Coronavir, Sinopharm, and Molnupiravir have been proven. However, a large number of drugs and vaccines are still in preclinical trials, and more studies are needed to confirm their efficacy in the clinic. As of 19 July 2022, the WHO has reported 561,156,416 confirmed cumulative cases of COVID-19, including 6,365,510 cumulative deaths. These confirmed cases are mainly distributed in countries in Europe, the Americas, and the Western Pacific. Among them, countries and regions with over 5,000,000 cumulative cases include the United States, India, Brazil, and so on (Fig. 1).

Therefore, COVID-19 poses a serious threat to public health and imposes heavy burdens on the social economy and the people's spirit. Clinically, COVID-19 patients manifest varying degrees of difficulty in the respiratory system. For example, mild cases present the symptoms of upper respiratory tract infection, and severe cases have lung edema, acute lung injury (ALI), hypoxemia, and respiratory failure. In the initial

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stage of COVID-19 infection, SARS-CoV-2 binds to epithelial cells of the upper respiratory tract and propagates locally with a low viral burden and limited immune response [1]. Then, increasing viruses spread down to the pulmonary alveoli and propagate within alveolar type II cells, resulting in the apoptosis and death of cells [2]. Meanwhile, activated alveolar macrophages and pulmonary epithelial cells release proinflammatory cytokines, causing cytokine storms and lung injury, and the NLR family pyrin domain containing 3 (NLRP3) inflammasome, a critical component of the innate immune system, is activated in COVID-19 [3], which promotes the production of proinflammatory cytokines, resulting in cytokine storms and acute respiratory distress syndrome (ARDS) [4,5], and ultimately lung and multiorgan injury. The NLRP3 inflammasome is composed of a sensor, the adaptor apoptosis-associated speck-like protein containing a caspase-1 recruitment domain (ASC) and the effector caspase-1. Most inflammasome sensors belong to the NLR protein family, including NLRP1, NLRP3, and NLRC4 (NOD-, LRR- and consist of a caspase recruitment domain (CARD)-containing 4; also known as IPAF), NLRP6, NLRP7, and NLRP12. [6]. The NLRP3 protein, the sensor, is composed of a leucine-rich repeat domain (LRR), a pyrin domain (PYD), and a nucleotide-binding and oligomerization domain. PYCARD, the receptor, CARD and PYD [7,8]. Autophagy, a highly conserved eukaryotic cell recycling process, is the main intracellular degradation system [9]. Autophagy begins with the formation of a sequestering compartment, known as a phagophore, with a double membrane, which engulfs damaged or unnecessary components in the cytoplasm; the phagophore matures into an autophagosome, which transports the cargo to lysosomes for degradation [10]. The generated amino acids and other degraded byproducts are released back to the cytoplasm to provide energy for cell metabolism and survival [11]. Emerging evidence indicates the critical role of autophagy in various

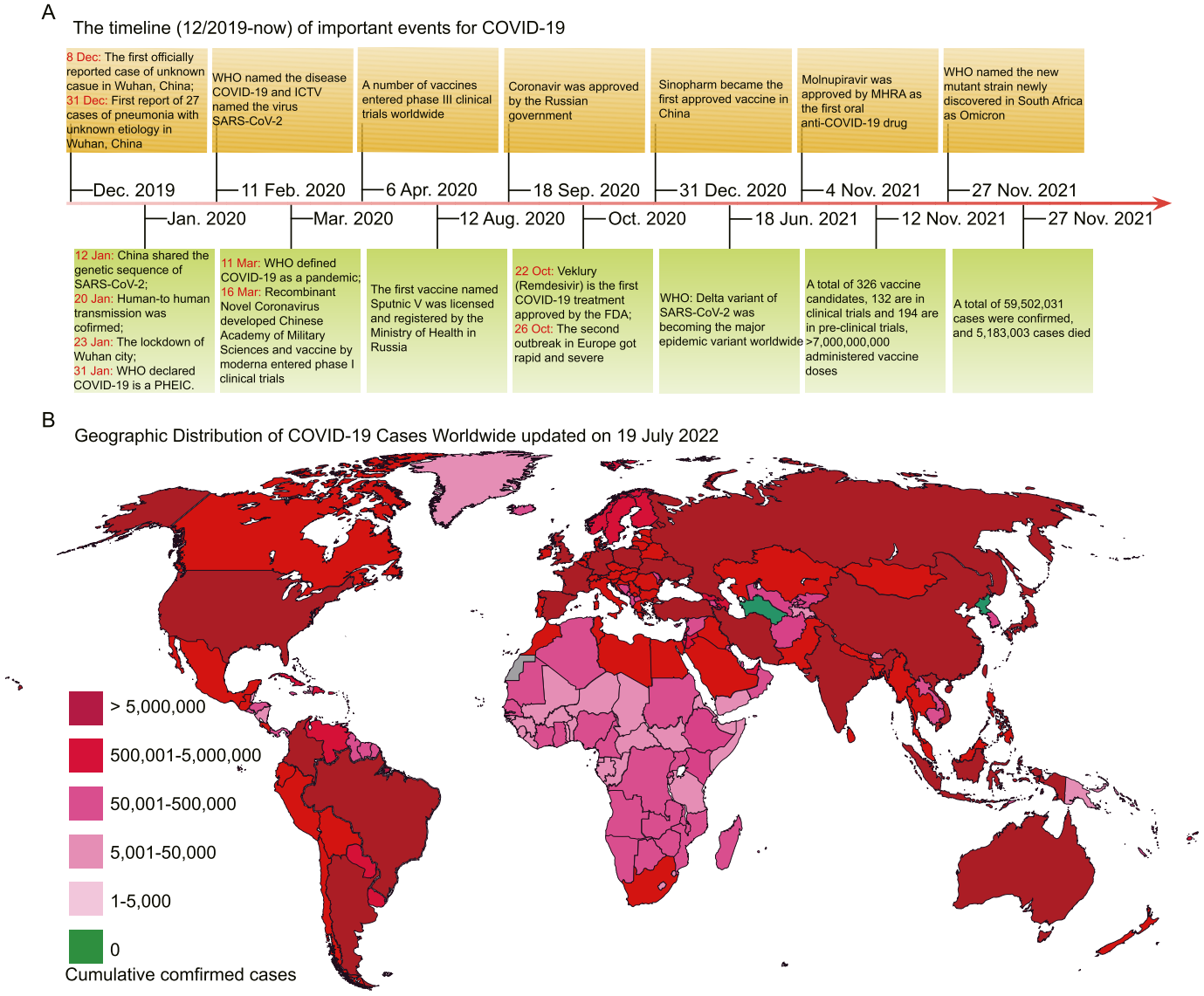

Fig. 1. The important events and cumulative cases of COVID-19 worldwide.
(A) The timeline of important events of COVID-19 from 12/2019 to the present. Critical events mainly include the following: (1) COVID-19 first broke out in Wuhan, China, in Dec. 2019. (2) The WHO declared COVID-19 a PHEIC on 31 Jan. 2020. (3) The WHO named the disease COVID-19, and ICTV named the virus SARS-CoV-2 on 11 Feb. 2020. (4) Veklury (remdesivir) is the first COVID-19 treatment approved by the FDA in Oct. 2020. (5) The WHO declared that the Delta variant of SARS-CoV-2 was becoming the major epidemic variant worldwide on 18 June 2021. (6) The WHO named the new mutant strain in South Africa Omicron on 27 Nov. 2021. (B) The geographic distribution of cumulative confirmed COVID-19 cases worldwide updated on 19 July 2022. The confirmed cases are mainly distributed in countries in Europe, the Americas, and the Western Pacific. Among them, countries and regions with over 5,000,000 cumulative cases include the United States, India, Brazil, and so on. PHEIC, public health emergency of international concern; MHRA, Medicines and Healthcare Products Regulatory Agency.

human diseases, including cancer, neurodegenerative diseases, diabetes, and cardiovascular disease [12]. In this review, we mainly focus on the role of autophagy, commonly referred to as macroautophagy, in COVID-19. Autophagy plays a dual role in the development of COVID-19. In the first stage of COVID-19 infection, SARS-CoV-2 escapes the body's antiviral immune response by activating autophagy [13]. In addition, GU-rich RNA-induced interleukin (IL)-1β secretion is dependent on autophagy, whereas treatment with siAtg5 decreases the secretion of IL-18. Thus, genetic and pharmacological inhibition using autophagy inhibitors such as hydroxychloroquine (HCQ) and chloroquine (CQ) can effectively reduce virus replication and inhibit the development of COVID-19 [14,15]. However, in the late stage of COVID-19, increasing SARS-CoV-2 levels destroy mitochondrial structure and function, resulting in increased levels of reactive oxygen species (ROS) and the subsequent activation of the NLRP3 inflammasome and the generation of the proinflammatory cytokines IL-1β and IL-18. In this stage, autophagy, as a negative regulator of the NLRP3 inflammasome-mediated inflammation, can clear damaged mitochondria and ROS and degrade the NLRP3 inflammasome and its key components, including NLRP3, PYD and CARD domain containing (PYCARD/ASC), and caspase -1 (CASP-1). Therefore, autophagy activators such as rapamycin and trehalose are recognized as potential drugs for the treatment of COVID-19 by ameliorating the NLRP3 inflammasome-mediated acute lung inflammation. In this review, we comprehensively discuss the pathogenesis, clinical manifestations, and mechanism of COVID-19 infection by SARS-CoV-2, as well as the role of the NLRP3 inflammasome-mediated lung inflammation and the regulation of autophagy in different stages of COVID-19. Meanwhile, we summarized the inhibitors of the NLRP3 inflammasome and the modulators of autophagy in the treatment of COVID-19. Moreover, we highlighted the therapeutic potential of autophagy activators in inhibiting the activation of the NLRP3 inflammasome, thereby avoiding cytokine storms at the late stage of COVID-19. Finally, we hope this review provides novel insight into the prevention and treatment of COVID-19 targeting the regulation of autophagy for the NLRP3 inflammasome in the future.

2. COVID-19 and SARS-CoV-2

The new coronavirus that emerged in 2019 is previously unknown to humans. It is classified as a β-coronavirus in group 2B and causes serious life-threatening diseases [16], and the ICTV named it SARS-CoV-2 [17]. Accumulating evidence shows that the transmission methods of SARS-CoV-2 mainly include respiratory transmission, fecal-oral transmission, and indirect contact transmission [18,19]. In general, the incubation period of COVID-19 is mostly within 14 days and the median is 5.1 days [20]. The genus coronaviruses have been known to cause severe diseases, including SARS and the Middle East respiratory syndrome (MERS) [21]. COVID-19 has been reported to affect the normal function of the lung, cardiovascular system [22], gastrointestinal system [23], central nervous system [24], liver [25], and kidney [26], thus causing serious clinical symptoms including, fever, dry cough, sore throat, lymphopenia, dyspnea, fatigue/myalgia, anosmia, headache, abdominal pain, diarrhea, nausea, and vomiting [27–29]. ARDS is the most common complication of COVID-19, followed by anemia, acute cardiac injury, subsequent infections, thromboembolism, and stroke [30,31]. In addition, emerging studies have shown that many patients who die from COVID-19 have impaired metabolic health [32], and they commonly have hypertension, dyslipidemia, and hyperglycemia [33]. Moreover, nearly two-thirds of confirmed coronavirus patients have cardiovascular disease and diabetes [33]. Metabolic syndrome is a common metabolic disorder consisting of diabetes, hypertension, etc., caused by the increased prevalence of obesity [34]. Mounting evidence indicates that metabolic syndrome leads to the worsening of COVID-19 [33,35–38]. For example, COVID-19 patients with obesity, diabetes, or hypertension have a worse prognosis and higher in-hospital mortality [35,36]. In addition, the expression of angiotensin converting enzyme 2 (ACE2), the cell entry receptor for SARS-CoV-2, is found to be enhanced in obese individuals, which results in more SARS-CoV-2 infection and distribution and ultimately the exacerbation of COVID-19 [33,39]. With the development of COVID-19, the diseases associated with metabolic syndrome are exacerbated, and mortality is increased. For example, the proinflammatory milieu and increased levels of IL-6, IL-1β, tumor necrosis factor (TNF/TNF-α), monocyte chemoattractant protein (CCL2/MCP1), and C-X-C motif chemokine ligand 10 (CXCL10) in COVID-19 decrease insulin sensitivity [33]. Therefore, metabolic syndrome and COVID-19 are a vicious cycle of each other. The global pandemic of COVID-19 is not merely a health problem but also affects the environment and economy in diverse ways worldwide. Modern transportation, high-density population and frequent population mobility make COVID-19 easily spread among countries and regions [40]. In turn, the disease has caused severe damage to the social and economic system, limiting production and development and increasing the medical burden, which may remain long after the pandemic. For individuals, COVID-19 poses a severe threat to people's lives, and its sequelae also affect people's quality of life both physically and mentally [41]. In addition, during a time of ongoing global conflict, COVID-19 poses challenges and threats to the military and public health personnel, which has also attracted more attention [42]. From the outbreak to the present, researchers are trying their best to develop vaccines and drugs for the prevention and treatment of COVID-19. For example, the discovery of inhibitors targeting the SARS-CoV-2 main protease or 3C-like protease (Mpro or 3CLpro) to inhibit viral replication and maturation provides hope for the treatment of COVID-19 [43]. In addition to vaccines and commonly used drugs, other treatments such as mesenchymal stem cell therapy [44], transfusion of convalescent plasma [45], monoclonal antibodies such as tocilizumab, inhaled nanobodies [46], thromboprophylaxis and fibrinolysis [47], and probiotics [48], are under trial. Although the propagation of the virus and the fatality rate of COVID-19 have been relieved to a certain extent, it still seriously affects the economic development and daily life of people owing to the constant appearance of SARS-CoV-2 variants.

The literature shows that SARS-CoV-2 shares ~80% RNA sequence identity with SARS-CoV [17]. Structurally, SARS-CoV-2 is an enveloped, nonsegmented positive-sense, and single-stranded ~30 kb RNA β-coronavirus [49] consisting of structural proteins and nonstructural proteins (NSPs). Structural proteins of the virus include spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins [50,51]. The S protein has two major subunits, S1 and S2. Among them, S1 is responsible for receptor recognition and binding, while membrane-anchored S2 is responsible for membrane fusion [52,53]. The receptor-binding domain (RBD) in the S protein recognizes and combines with the ACE2 receptor of target cells, and the transmembrane protease serine 2 (TMPRSS2) cleaves the S protein at S1/S2 and S2 to initiate the protein S. The two processes enable the entry of SARS-CoV-2 into host cells [54,55]. M and E are conserved proteins in β-coronavirus and play a key role in the regulation of virus assembly [56] (Fig. 2). In addition, SARS-CoV-2 also encodes accessory proteins, including open reading frame 3a (ORF3a), ORF6, ORF7a, ORF7b, ORF8, ORF9, and ORF10 [57]. Among them, ORF3a and ORF8, two ion-channel proteins, are the most widely studied thus far [58]. ORF3a is a conserved viroporin related to virulence, infectivity, and virus release [59], that has also been demonstrated to regulate the NLRP3 inflammasome and autophagy in COVID-19. For example, ORF3a has a TNF receptor-associated factor 3-binding motif that activates the NLRP3 inflammasome [60]. Additionally, ORF3a prevents the fusion between autophagosomes and lysosomes to block autophagic degradation, enabling the virus to escape clearance by host cells [61]. ORF8 is a highly mutating region that downregulates the major histocompatibility complex class I (MHC-I) levels of infected cells through the autophagy-lysosomal degradation pathway or direct binding [62]. Additionally, ORF8 simulates immune molecules such as IL-1β to activate inhibitory molecules from macrophages, $CD8^+$ T lymphocytes, and NK cells [63]. The life cycle of SARS-CoV-2 mainly includes

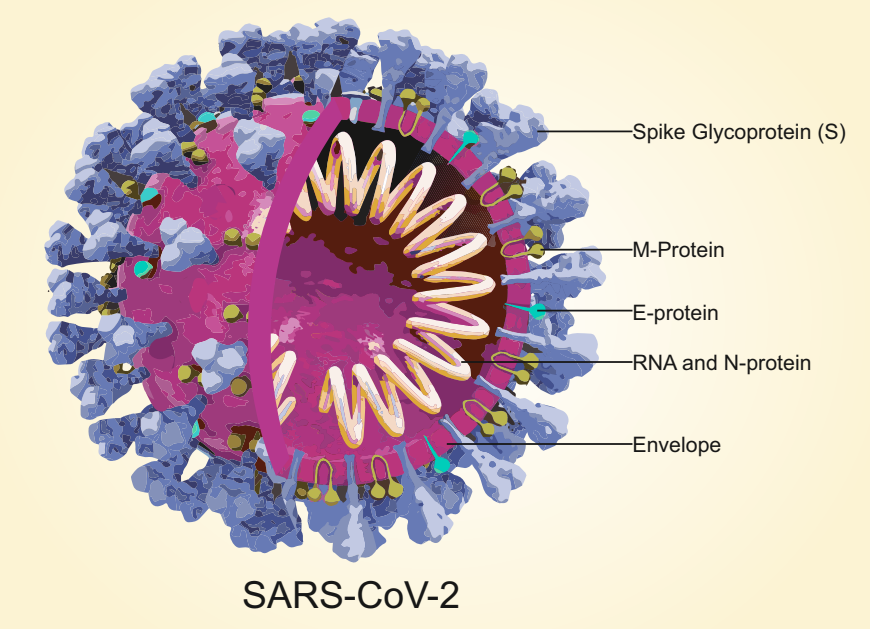

Fig. 2. The structure of SARS-CoV-2. SARS-CoV-2 is an enveloped, nonsegmented positive-sense, and single-stranded RNA virus of the genus β-coronavirus. It encodes four structural proteins, including spike glycoprotein (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, and several nonstructural proteins. S, E, and M proteins are transmembrane proteins incorporated into the virus bilayer lipid envelope. The S protein is responsible for the entry of the virus into target cells. M and E proteins play a key role in the regulation of virus assembly. The inside of the virus is a nucleoprotein core with a spiral structure composed of RNA and N protein. The N protein protects the viral RNA genome and helps package it into a ribonucleoprotein complex.

the following stages: (1) Entry: the S1 subunit binds to the ACE2 receptor, and the S2 subunit promotes the fusion of the virus and the host cell membrane. (2) Replication: SARS-CoV-2 genome RNA is released and translated into two large open reading frames, ORF1a and ORF1b, and then forms the replicase and transcriptase complex. (3) Assembly: Structural proteins, including S, E, and M, are translated and delivered to the endoplasmic reticulum (ER) to be processed and then transported into the ER-Golgi intermediate compartment, where they are packaged with the N protein. (4) Release: The mature virions are transported by the secretory vesicle chamber lumen and released via exocytosis [64–66].

3. The NLRP3 inflammasome-mediated lung inflammation in COVID-19

In COVID-19, the lung is the most severely affected organ. Clinical data show that the pathological changes in the lungs of COVID-19 patients include sequential alveolar damage, hyaline membrane formation, capillary damage, focal capillary microthrombus formation, alveolar septal fibrosis proliferation, and pulmonary parenchyma [2,67,68]. Emerging evidence indicates that the inflammatory cytokine storm is an important mechanism that leads to the abovementioned pathological changes, especially for COVID-19 patients at the critical and deceased stages [69]. The course of COVID-19 is divided into three stages. When the virus transmits down the respiratory tract to the lungs, T cells, pulmonary macrophages, NK cells, monocytes, dendritic cells, and/or neutrophils are rapidly proliferated and hyperactivated if body immunity cannot eliminate the increasingly invasive virus; then, the COVID-19 patients will enter the severe, critical, and deceased stages. At this stage, an abnormal and uncontrolled systemic inflammatory response is induced and characterized by the release of large amounts of proinflammatory cytokines (IL-6, IL-1β, IL-18, IL-10, TNF, CXCL10, *etc.*), which results in the formation of an inflammatory cytokine storm [70–72]. In addition, the upregulation of vascular endothelial growth factor (VEGF) and endothelial cell adhesion molecules (CAMs), such as vascular cell adhesion molecule 1, intercellular adhesion molecule, von Willebrand factor, and angiopoietin 2, increases the permeability of the pulmonary endothelium and reduces barrier protection function, enhancing the infiltration of neutrophils and inflammatory monocytes to produce oxygen radicals and lipid mediators [73,74]. The cytokine storm and the resulting ARDS, systematic inflammatory response syndrome, respiratory failure, coagulopathy, and multiple organ dysfunction syndrome (MODS), upon SARS-CoV-2 infection, are responsible for the severity and mortality of COVID-19 [75] (Fig. 3). Therefore, suppression of the proinflammatory responses and management of the symptoms at the late stage are very important for the treatment of COVID-19 [76].

The inflammasome is a large multimolecular complex formed in the cytosol that promotes the innate immune system to recognize pathogens, including infectious microbes and molecules from host proteins. They have been implicated in various inflammatory-related diseases, including cancers, neurodegenerative diseases, and diabetes [77–79]. NLR family inflammasomes have been widely recognized, and non-NLR family inflammasomes have also been reported, including absent in melanoma 2 (AIM2), CARD8, and PYRIN [6]. NLRP1, NLRP3, NLRP6, NLRP7, NLRP12 and AIM 2 need ASC for the engagement of caspase-1, while NLRC4 and NLRP1 can directly interact with caspase-1 through their CARDs without recruiting ASC [80]. NLRP6 has a wide range of functions in innate immune signaling and is highly expressed in liver and intestine cells [81]. NLRP7 is linked to innate immune signaling, and its precise role in inflammasome responses is still controversial [82]. NLRP12 is reported to play a crucial role in controlling overt inflammation, colitis and colitis-associated tumorigenesis [83]. AIM2 can sense microbial DNA and recognize self-DNA in the context of neoplasms and autoinflammatory and autoimmune diseases [84]. CARD8 is an inflammasome sensor that is unique to humans and other primates [85]. NLRP3, NLRC4, NLRP6, and AIM2 have also been reported to interact with autophagy. Among them, the NLRP3 inflammasome is the most extensively investigated thus far [86]. The literature shows that the NLRP3 inflammasome complex consists of three key components, including the NLRP3 protein, PYCARD/ASC, and the cysteine protease pro-CASP1 [87]. The activation of the NLRP3 inflammasome is a two-step process, including priming and activation. In the first step, priming is mediated by a variety of molecular and cellular events, including pathogen-associated molecular patterns (PAMPs) obtained from microbial infection and danger/damage-associated molecular patterns (DAMPs) driven by endogenous danger signals released from damaged or dying cells [88–91]. PAMPs and DAMPs are recognized by pattern recognition receptors (PRRs), such as nucleotide binding oligomerization domain containing 2 and toll-like receptors, thereby activating the

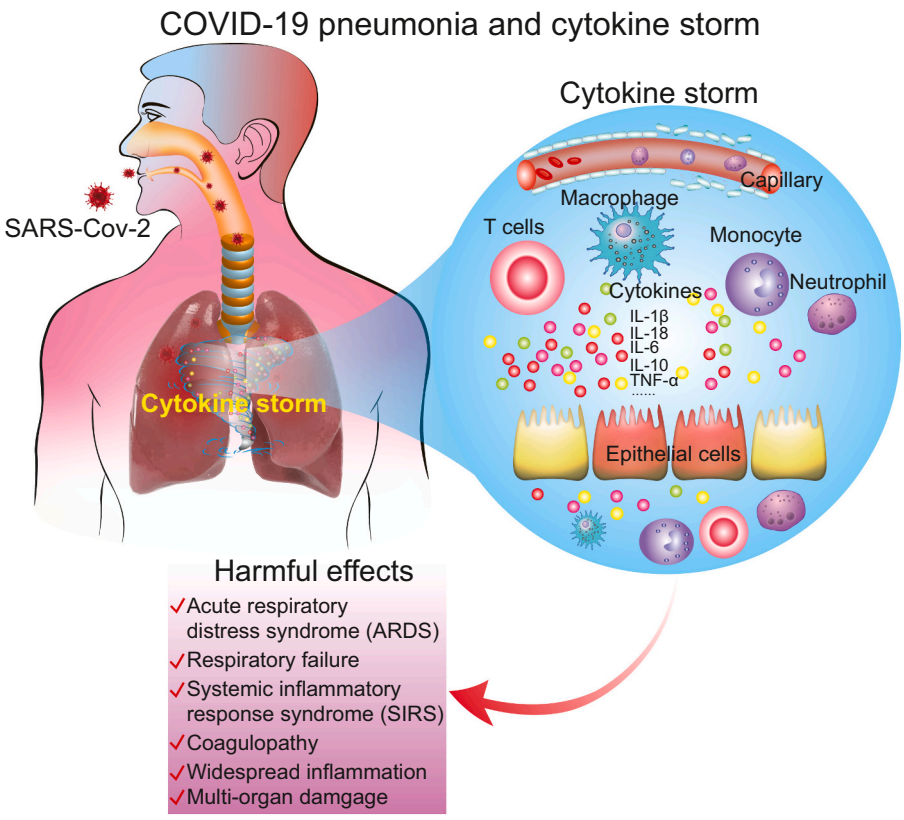

Fig. 3. Cytokine storm and its harmful effects on the human body in COVID-19. Once SARS-CoV-2 is transmitted to the lungs through the respiratory system, alveolar macrophages and pulmonary epithelial cells are activated to produce many proinflammatory cytokines, including IL-1β, IL-18, IL-6, IL-10, and TNF-α. These cytokines increase the permeability of the pulmonary capillary endothelium and lead to the exudation of T cells, monocytes, macrophages, and neutrophils, which further promote the release of cytokines and induce a series of harmful effects, including ARDS, respiratory failure, systemic inflammatory response syndrome, coagulopathy, widespread inflammation, and multiorgan damage.

NF-κB-mediated signaling and promoting the expression of active NLRP3 [92]. The second step can be triggered by viral RNA, ATP, pore-forming toxins, and other molecules, such as crystalline substances and misfolded protein aggregates [92]. In COVID-19, SARS-CoV-2 enters host cells by binding to the ACE2 receptor on the cell membrane and releasing its RNA. Viral RNA causes lysosomal dysfunction, mitochondrial damage and generated dsDNA and ROS, thereby activating the NLRP3 protein [93–96]. In addition, multiple cellular events, including ion fluxes (K^+ efflux, Ca^{2+} influx, and Cl^- efflux), are also involved in the activation of the NLRP3 inflammasome. For example, K^+ efflux is mediated by ORF3a, an ion-channel protein of SARS-CoV-2, and Ca^{2+} influx is controlled by the viroporin-E protein on the Golgi intermediate chamber (ERGIC) [97–101]. Then, the NLRP3 protein, ASC, and pro-CASP1 assemble into a complex, followed by the autoproteolytic activation of pro-CASP1 to produce active CASP-1. The activated CASP-1 then cleaves pro-IL-1β and pro-IL-18, as well as gasdermin D (GSDMD), into the mature forms of IL-1β, IL-18, and GSDMD-NT. In addition, the activated CASP4-CASP5-SCAF11/CASP11 associated with the noncanonical inflammasome in human cells and mice also cleaves GSDMD into GSDMD-NT. Finally, the GSDMD pore is formed on the cell membrane, facilitating the secretion of IL-1β and IL-18 and triggering the inflammatory response [102,103] (Fig. 4).

In the last two years, studies have demonstrated a crucial role for the NLRP3 inflammasome in the development of lung inflammation and fibrosis owing to SARS-CoV-2 infection [104,105]. There is a study demonstrating that the NLRP3 inflammasome is activated in peripheral blood mononuclear cells (PBMCs) in COVID-19 patients [106]. The researchers further evaluated the activation of inflammasomes in the lung tissue obtained from the autopsy of deceased COVID-19 patients. They found that there are active inflammasomes in fatal COVID-19 cases and that the NLRP3 inflammasome is activated in the postmortem tissues of COVID-19 patients [106]. Moreover, the pathological activation of the NLRP3 inflammasome and its resultant cytokine storm and cell pyroptosis in alveolar macrophages and recruited monocyte-derived macrophages have been found in COVID-19 subjects [3,7,107]. Therefore, the activation of the NLRP3 inflammasome may be an important mechanism in lung inflammation in COVID-19.

As SARS-CoV-2 is inhaled into the airway, it mediates the activation of the purinergic receptor P2X 7 (P2RX7) receptor by releasing extracellular ATP. The P2RX7 signal then leads to NLRP3 activation through direct or indirect activation of macrophages [3]. In SARS-CoV-2-infected individuals, impaired type II alveolar epithelial cells expressing ACE2 receptor can activate the NLRP3 inflammasome. The acute immune response to SARS-CoV-2 infection is mainly driven by inflammatory alveolar and monocyte-derived macrophages [108]. These macrophages are activated by PAMPs/DAMPs which are released by SARS-CoV-2-infected lung cells [109–112]. TNF-α and IL-1β secreted by alveolar macrophages initiate an acute proinflammatory cascade immediately after infection [3]. The secretion of these cytokines induces cell damage or even death, PAMP/DAMP production, immune cell recruitment, and extensive NLRP3 activation, establishing a proinflammatory positive feedback cascade [109,110,112–114]. During the incubation, early, and mild stages, a specific adaptive immune response is activated to eliminate the virus and prevent the disease from progressing to a more severe stage. In this stage, inflammation plays a protective role in promoting the development of adaptive immunity by recruiting immune cells to the sites of infection to activate their expansion and protective functions [115]. For example, the NLRP3 protein recognizes multiple PAMPs and DAMPs that are produced during viral replication, thereby triggering NLRP3 inflammasome-dependent antiviral immune responses and promoting viral eradication [116]. In addition, CASP-1 activated by the NLRP3 inflammasome mediates the proteolysis of pro-IL-1β, pro-IL-18, and GSDMD [117–119]. GSDMD forms pores in the membrane of infected cells and promotes IL-1β and IL-18 secretion [120]. Then, the secretion of IL-1β recruits neutrophils to sites of inflammation to help eliminate invading viruses [121]. Furthermore, appropriate levels of IL-1β and IL-18 induce adaptive immune responses [122,123]. Moreover, NLRP3 activation is strongly downregulated after the initial

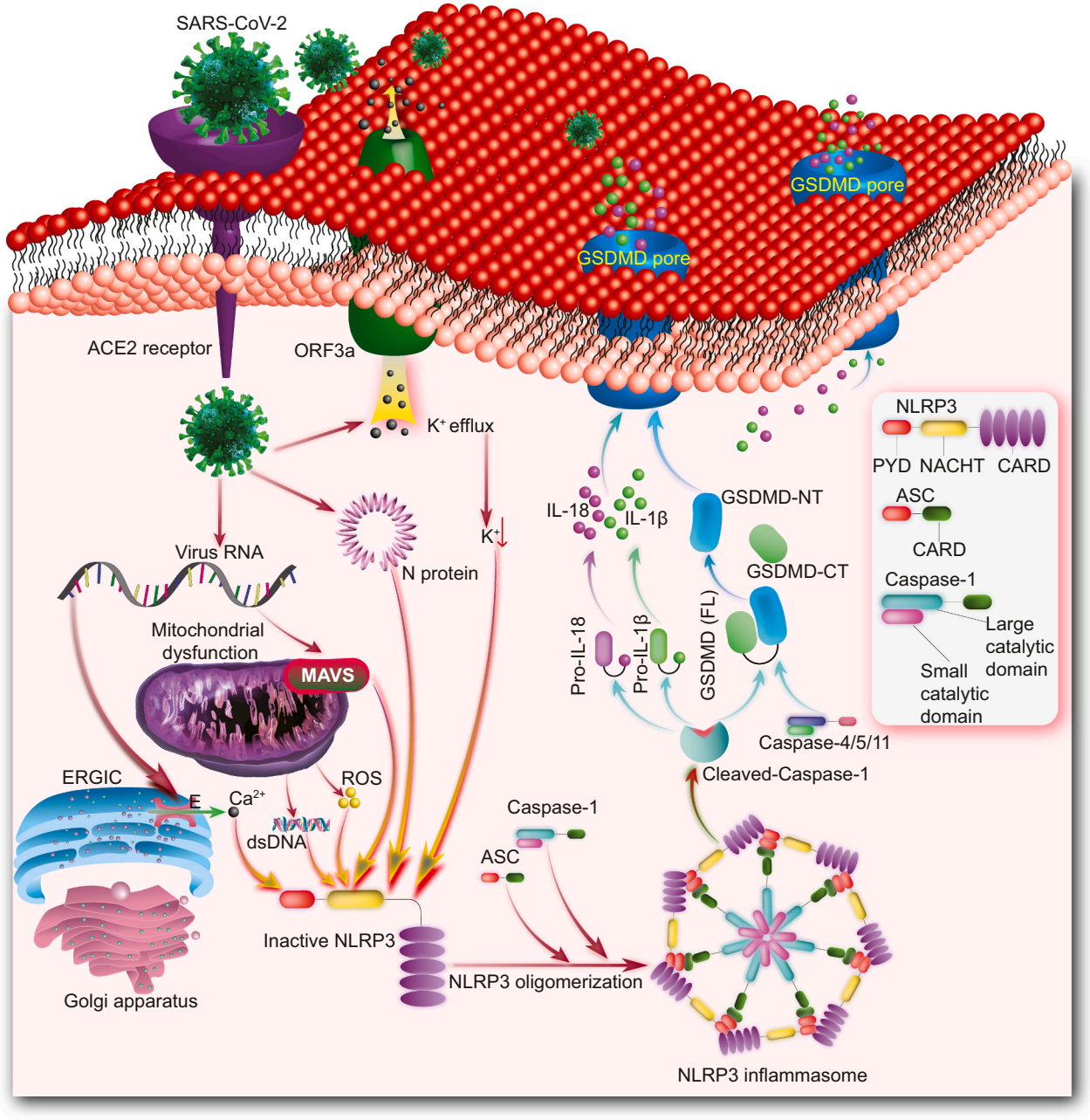

Fig. 4. Activation of the NLRP3 inflammasome in COVID-19. SARS-CoV-2 enters host cells through S protein binding to ACE2. After the release and translation of the viral genome, the viroporins ORF3a and E induce K^+ efflux or Ca^{2+} influx to activate the NLRP3 protein. In addition, the viral N protein also binds directly to the NLRP3 protein, leading to NLRP3 inflammasome activation. Viral RNA activates the NLRP3 protein via mitochondrial antiviral signaling (MAVS) on the mitochondrial outer membrane. The generated cytosolic double-stranded DNA (dsDNA) and ROS levels from the damaged mitochondria activate the NLRP3 protein. Then, the active NLRP3 protein interacts with ASC through the PYD, followed by the recruitment of pro-CASP1 via its CARD domain to activate the effector CASP through proteolytic cleavage. Activated CASP-1 cleaves the proinflammatory cytokines pro-IL-1β and pro-IL-18, as well as gasdermin-D (GSDMD), into the mature forms of IL-1β, IL-18, and GSDMD-NT. In addition, the activated CASP-4/5/11 associated with the noncanonical inflammasome in human cells and mice also cleaves GSDMD into GSDMD-NT. Finally, the GSDMD pore is formed on the cell membrane, facilitating the secretion of IL-1β and IL-18 and triggering the inflammatory cytokine storm.

costimulation required for antigen-presenting cell activation (APC), followed by a sufficient adaptive response and the production of antibodies against the virus [124]. Therefore, the optimal activation of the NLRP3 inflammasome contributes to the establishment of a host antiviral state, and the virus can be resisted by appropriate activation of the NLRP3 inflammasome at the early stage of COVID-19. However, the process of virus replication leads to the death of lysed cells and subsequent potassium efflux, which provides a second signal for the activation of the NLRP3 inflammasome. Meanwhile, viral infection changes the integrity of the plasma membrane and ion efflux, which may lead to programmed cell death and induce secondary activation of the NLRP3 inflammasome [116,125]. Most importantly, SARS-CoV-2 also directly activates the NLRP3 inflammasome through ORF3a [126]. This local inflammatory cell death extends to the vasculature, leading to the leakage, edema, and pneumonia characteristics of COVID-19 [109,112,113]. In the second stage, the sustained NLRP3-dependent inflammatory response leads to severe clinical symptoms, necrosis, DAMP release, and severe lung inflammation [127]. Emerging evidence

indicates that the critical stage of COVID-19 is characterized by an uncontrolled inflammatory response [128]. During this stage, the innate response cannot clear the virus infection, which leads to increased DAMP invasion and stimulation and is followed by the overactivation of NLRP3 inflammasomes and the production of proinflammatory cytokines [76,129]. Reports from patients with severe COVID-19 indicate that increased levels of IL-1β and IL-6 are associated with increased immune failure and decreased T-cell functional diversity [130]. In contrast, patients with mild COVID-19 have lower levels of IL-6, as well as activated T lymphocytes and IgM SARS-CoV-2 binding antibodies [131]. In addition, accumulating studies show that the moderate activation of the NLRP3 inflammasome serves critical functions in pathogen defense by stimulating the adaptive immune response and removing damaged or transformed host cells [132–134]. Moreover, an increasing number of studies have shown that a low inflammatory cytokine response may be related to an adaptive response that is conducive to the regression of disease, while a strong inflammatory cytokine response promotes or aggravates the development of COVID-19 [3,135–142]. Therefore, targeting the modulation of NLRP3 inflammasome-mediated inflammatory responses is a promising therapeutic strategy for COVID-19.

The rapid decline in COVID-19 patients coincides with the sudden transition of the NLRP3 cytokine storm to a compensatory immunosuppressive state [111,143]. This repair and recovery-oriented phase are characterized by the production of IL-10, the polarization of macrophages to the anti-inflammatory M2 state, the inhibition of NLRP3, and the recruitment of fibroblasts and platelets [109,112,144]. Therefore, targeting the inhibition of NLRP3 inflammasome activation has become a promising strategy for the treatment of various inflammatory-related diseases, such as COVID-19. In this review, we summarized drugs that directly or indirectly inhibit the activation of NLRP3 inflammasomes in the study of COVID-19 (Table 1). Canakinumab targets IL-1β to control cytokine storms. This mechanism reduces the likelihood of excessive inflammation throughout the patient's body. Studies have shown that canakinumab may have prognostic benefits in patients with COVID-19 infection [145]. In the results of a cohort study on anakinra, researchers found that anakinra not only reduces the need for invasive mechanical ventilation in the intensive care unit but also reduces the mortality rate of patients with severe COVID-19. Most importantly, although there are no serious side effects found, the confirmation of its effectiveness requires more controlled trials [146]. In addition, MCC950, an NLRP3 inhibitor, was reported to reduce the activation of CASP-1 and the secretion of IL-1β in primary human monocytes infected with SARS-CoV-2 in vitro [106]. Meanwhile, glibenclamide, another inhibitor of NLRP3 widely used for diabetes, was demonstrated to reduce the secretion of IL-6 in SARS-CoV-2-infected human monocytes [147]. In patients with moderate to severe COVID-19, colchicine could reduce oxygen demand and hospitalization rate, which is associated with indirect inhibition of the NLRP3 inflammasome [148]. In addition, metformin, a drug widely used for diabetes, was reported to indirectly inhibit the NLRP3 inflammasome via the regulation of the mechanistic target of rapamycin mechanistic target of rapamycin kinase (mTOR) protein, which is related to the reduction in the mortality of COVID-19 and type 2 diabetes mellitus (T2DM) patients [149]. In SARS-CoV-2-infected mice, metformin has also been shown to inhibit the activation of the NLRP3 inflammasome and its-mediated lung inflammation [149]. Therefore, although these inhibitors targeting the NLRP3 inflammasome are in the clinical effectiveness evaluation stage, they still bring new hope for the prevention and treatment of COVID-19 in the future.

4. The inhibition of autophagy in COVID-19

Autophagy occurs in response to different forms of stress. Under the conditions of starvation, oxidative stress, and pathogen attack, autophagy can be highly induced, and the number of autophagosomes increases rapidly [167]. Studies have shown that the restoration of amino acid levels in cells can reactivate the serine/threonine-protein kinase mTOR complex 1 (mTORC1) and inhibit autophagy. Therefore, autophagy constitutes a negative feedback loop in response to starvation [168,169]. Regulation of autophagy involves multiple signaling pathways. The induction or initial phase of autophagy is controlled by mTORC1 and the Unc-51-like kinase 1 (ULK1/unc-51)-like autophagy activating kinase 1 (Atg1) complex. Under adequate nutrition, mTORC1 binds to the ULK1 kinase complex and phosphorylates ULK1-ULK2 and Atg13 [170]. Under the starvation condition, mTORC1 separates from the complex, resulting in the alternative (activating) phosphorylation of ULK1-ULK2 with Atg13, thereby activating autophagy [171,172]. Then, the nucleation and expansion phases are mediated by the Atg14-containing class III phosphatidylinositol 3-kinase (PtdIns3K) complex and two conjugation systems involving ubiquitin-like proteins (UBLs) (the Atg12–Atg5-Atg16L1 complex and Atg8-family proteins including microtubule associated protein 1 light chain 3 (MAP1LC3/LC3) and GABARAP) [173]. Studies have shown that the PtdIns3K complex mainly regulates autophagy by interacting with Beclin1 (BECN1) and participates in the recruitment of PtdIns3P binding proteins to the phagophore assembly site (PAS). The Atg12–Atg5-Atg16L1 complex and Atg8-family proteins mainly positively regulate the expansion of phagophores [174]. The expanded phagophore finally matures and forms complete autophagosomes, which are then transported to endosomes or lysosomes by microtubule transport [175] and are fused with them to form autolysosomes (ALs) and degrade their contents. The fusion process mainly involves the protein VTI1B [176,177]. In short, autophagy is a very complex process of self-degradation that is regulated by multiple proteins and signaling pathways.

Table 1
Direct or indirect inhibitors of the NLRP3 inflammasome in the study of COVID-19.

Drug	Mechanism of action	The possible effects on COVID-19	Reference(s)
Melatonin	Inhibition of the NLRP3 inflammasome	Improvement of breathing, cough, fatigue, and other symptoms	[150]
Statins	Inhibition of the NLRP3 inflammasome	Inhibition of release of SARS-CoV particles	[150]
IFN	Inhibition of the NLRP3 inflammasome	Enhancement of virus clearance	[150]
Dapansutrile (OLT1177)	Inhibition of the NLRP3 inflammasome	Inhibition of cytokine storm	[151,152]
Canakinumab	Inhibition of IL-1β cytokines	Rapid return to normal oxygen status and reduction of mechanical ventilation	[145,153–155]
Anakinra	Inhibition of the IL-1 receptors	Improvement of breathing function	[156–159]
Baricitinib	Inhibition of the NLRP3 inflammasome	Inhibition of SARS-CoV-2 entry into target cells	[160]
Azithromycin	Inhibition of the NLRP3 inflammasome	Hindering the entry, replication and spreading of the virus	[161]
MCC950	Selective inhibition of the NLRP3 inflammasome	Suppressing cytokine storm; inhibiting the expression of pro-inflammatory cytokines	[106,111,162]
Sulfonylurea drug glibenclamide	Inhibition of the secretion of IL-6	May increase viral entry and protect against cytokine storm	[163]
Colchicine	Indirect inhibition of the NLRP3 inflammasome formation	Slowing down cell virus infection, reducing duration of supplemental oxygen therapy and hospital stay and increasing clinical improvement	[148,164,165]
Metformin	Indirect inhibition of NLRP3 by regulation of mTOR	May enhance clearance of SARS-CoV-2	[149,166]

Interestingly, many current studies have shown that autophagy also plays a very important role in the development of COVID-19. In 2004, researchers determined the colocalization of SARS-CoV replicase NSP8 with LC3, and they found that SARS-CoV might interact with autophagy-related proteins [178]. Subsequently, the mouse hepatitis virus (MHV) replication complex has also been demonstrated to colocalize with autophagy proteins, including LC3 and Atg12 [178]. Meanwhile, MHV induces the ER and the Golgi apparatus to form double-membrane vesicles (DMVs), which serve as sites for viral RNA replication, further supporting the role of autophagy in MHV infection [179]. In addition, Sourish Ghosh et al. found that β-coronavirus spread through the lysosomal pathway instead of the more common biosynthetic secretion pathways of other enveloped viruses [180]. In recent years, SARS-CoV-2 virus particles have also been found in the secretory vesicles of respiratory epithelial cells and autophagosomes of lung cells of COVID-19 patients [181], and then the SARS-CoV-2 virus is released from lung cells through lysosomal exocytosis. These observations indicate that the autophagy-lysosomal pathway plays an important role in the process of SARS-CoV-2 infection. Mitochondria are intracellular energy production factories that generate ATP through oxidative phosphorylation and participate in a variety of cellular processes, such as ROS generation, autophagy, and apoptosis [182]. Emerging evidence indicates that mitochondria also play an important role in COVID-19 by regulating innate and adaptive immunity and virus replication [183]. For example, SARS-CoV-2 binds to the translocase of outer mitochondrial membrane 70 and impairs the type I interferon response of host cells, thereby facilitating virus replication [184]. Additionally, SARS-CoV-2 also hijacks host mitochondria to suppress host immunity by regulating mitochondrial dynamics, mitochondrial function, mitochondrial respiration, and mitochondrial DNA release, thereby enabling them to evade host innate immunity [185–190]. Furthermore, viruses interact with mitochondrial membranes and components, which leads to increased ROS production. These increased mitochondrial ROS benefit viral replication by regulating host pathways and covalent changes in viral components [191,192]. Therefore, viruses control the oxidative status of the host cell to ingitate virus replication via moderately increasing mitochondrial ROS levels, and antioxidant treatments have emerged as a promising antiviral strategy [182]. However, mitochondria are impaired and excessive ROS are generated under the condition of acute viral infections, which inevitably induces injury or even death of host cells [192]. In response to virus-induced mitochondrial damage, host cells trigger mitophagy through the PINK1-PRKN pathway to maintain mitochondrial homeostasis and degrade viral RNA [193]. However, SARS-CoV-2 blocks the occurrence of mitophagy by inhibiting the binding of p62 to the LC3 protein [193]. Therefore, combining antioxidants with mitophagy activators and antiviral drugs instead may represent a promising therapeutic approach for COVID-19 during acute viral infections. Specifically, in the first stage of viral infection, the virus uses autophagosomes as a means to escape the host's antiviral response [194]. Under normal conditions, SARS-CoV-2 enters endosomes or autophagosomes through endocytosis under the action of TMPRSS2 and ACE2, and endosomes combine with autophagosomes to form amphipathic bodies [54,195,196]. Amphisomes or autophagosomes that encapsulate virus particles bind to lysosomes, thereby transporting the virus to lysosomes for degradation. However, SARS-CoV-2 can evade lysosomal degradation through various pathways to inhibit autophagy. For example, a study in three cell lines, HEK293T, HeLa and MCF-7, showed that coronavirus papain-like protease induces incomplete autophagy through its interaction with BECN1, thereby escaping the host antiviral innate immune response and creating favorable conditions for its replication [197]. In Vero cells, NSP6 has been shown to activate autophagosome formation, inducing vesicles containing Atg5 and LC3-II [198,199]; however, the size of autophagosomes formed by NSP6 is smaller than that induced by starvation, suggesting that NSP6 may also inhibit autophagosome expansion [200]. In addition, NSP6 and NSP3 bind to the ER [13] and induce the characteristic rearrangement of the ER membrane or Golgi apparatus to produce DMVs or smooth vesicles containing newly assembled virions, which are eventually released by exocytosis. Moreover, in HeLa and A549 cells, ORF3a of SARS-CoV-2 inhibits autophagic flux by blocking AL fusion [61]. Likewise, in SARS-CoV-2-infected VeroFM cells, SARS-CoV-2 infection can limit autophagic flux by reducing BECN1/Atg14-dependent AL fusion [201]. In Vero E6 and Huh-7 cells, SARS-CoV-2 induces autophagosome formation, but it blocks AL fusion. Modulation of autophagy elements, including the VPS34 complex and Atg14, but not Atg5, inhibits SARS-CoV-2 replication [202]. In HeLa-GFP-LC3B cells, ORF7a reduced autophagosome degradation by reducing the acidity of lysosomes [32]. ORF3a of SARS-CoV-2 inhibits autophagy by blocking the fusion of autophagosomes or amphisomes with lysosomes [203]. Therefore, inhibiting autophagy at this stage can weaken the replication and release of SARS-CoV-2 to a certain extent. For example, in vitro studies found that blocking autophagy with autophagy inhibitors (3-methyladenine (3-MA) and wortmannin) inhibited viral replication in SGFP-LC3-transfected Vero-E6 cells [204]. In the second stage, autophagy is in a moderately activated state. Studies have shown that in HEK293T-hACE2, Vero E6, 16HBE and HMEC-1 cells infected with SARS-CoV-2 spike pseudovirions or treated with recombinant spike virus, the autophagosome marker LC3-II is increased, and the expression of p62 is decreased, indicating that the SARS-CoV-2 spike induces an autophagic response in infected cells [205]. Further mechanistic studies revealed that SARS-CoV-2 inhibited the PI3K/AKT/mTOR pathway by upregulating intracellular ROS levels, thereby promoting autophagy. Furthermore, the expression levels of most autophagy-promoting genes were significantly increased in HEK293T-hACE2 and Vero E6 cells infected with SARS-CoV-2 spike pseudovirions [205]. Similarly, another study found that SARS-CoV-2 infection induced autophagy in Vero-E6 cells, Huh7.0 cells, and Caco-2 cells [204]. However, once the disease progresses to the third stage, severe inflammatory responses inhibit the activation of autophagy [194] (Fig. 5).

During the early stages of infection, amphisomal/endosomal structures contain SARS-CoV-2 virions, demonstrating that SARS-CoV-2 can enter host cells by endocytosis [203]. Recent studies have found that nucleotide-binding leucine-rich repeat proteins (NLRs) interact with autophagy proteins [206]. For example, Mengyu Lai et al. found that the NLRP3 inflammasome in BV-2 cells cleaves TIR domain-containing adaptor molecule 1 by activating CASP-1 to attenuate autophagy [207]. In addition, the inactive NLRP3 protein under high glucose conditions can restore podocyte autophagy and reduce podocyte damage [208]. Accordingly, NLRP3 inflammasome-mediated inflammatory responses may negatively regulate autophagy. Therefore, targeting the modulation of autophagy at different stages of COVID-9 may be a promising strategy for the treatment of COVID-19. At present, many compounds have been identified to modulate autophagy. In the initial stage of COVID-19, the SARS-CoV-2 virus evades the host cell's antiviral response by hijacking autophagosomes or inducing incomplete autophagy [194]. Therefore, the use of autophagy inhibitors at this stage may be a feasible way to prevent the replication and spread of the virus and restore the body's immune response. At present, two antimalarial drugs, HCQ and CQ, widely used to inhibit the fusion of autophagosomes and lysosomes, have been shown to have potential anti-SARS-CoV-2 activity and have achieved promising results in the clinical treatment of COVID-19 patients. In a multicenter clinical trial conducted in China, CQ exhibited significant efficacy and acceptable safety in COVID-19-related pneumonia [209,210]. Mechanistic studies have demonstrated that CQ destroys the endolysosome system, thereby disrupting the stability of the lysosomal membrane and leading to the intracellular release of lysosomal enzymes and an obstacle to AL fusion [211,212]. At the same time, they interfere with endosomal toll-like receptor (TLR) signal transduction and nucleic acid cytoplasmic sensors, resulting in the decreased activation of macrophages and decreased secretion of type I interferons and inflammatory cytokines [213]. However, CQ/HCQ therapy, especially high-dose therapy, may be complicated by heart

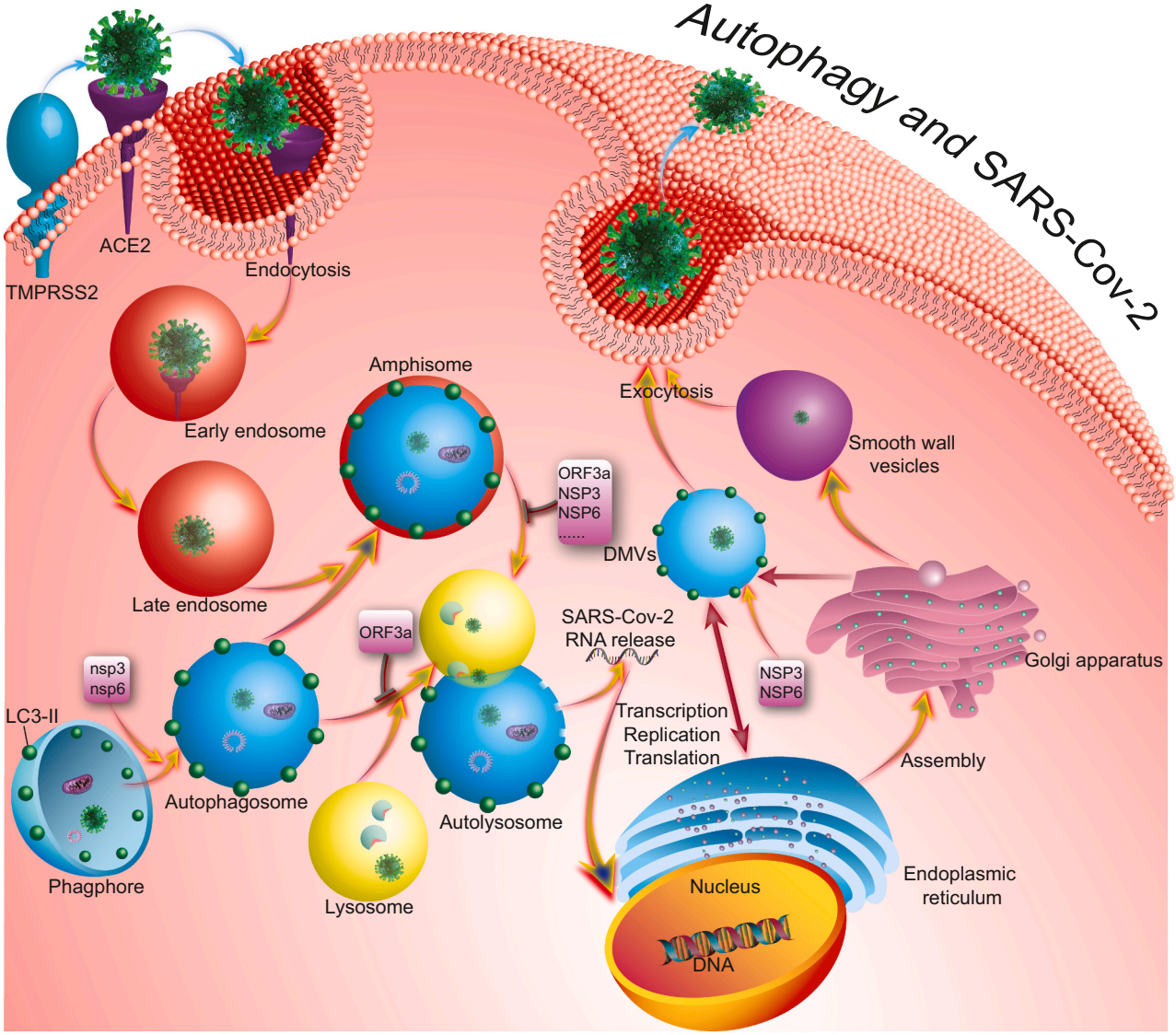

Fig. 5. The role of autophagy in SARS-CoV-2 infection. SARS-CoV-2 is hydrolyzed and activated under the action of TMPRSS2 protein to bind to ACE2 and enter the early endosome of the host cells through endocytosis. SARS-CoV-2 virus NSP6 can activate autophagosome formation and induce LC3-II-containing vesicles; however, the size of autophagosomes formed by NSP6 is smaller than that induced by starvation. Expansion of the phagophore through membrane addition sequesters some of some SARS-COV-2 virions, and upon closure, autophagosomes form. The autophagosomes fuse with endolysosomal vesicles such as late endosomes/lysosomes to form amphisomes, a process known as autophagosome maturation, which eventually leads to the formation of degradative ALs, which degrade SARS-CoV-2 virus particles. However, the SARS-CoV-2 virus can use autophagosomes and evade lysosome degradation by preventing the complete autophagy pathway through the corresponding viral protein. The late endosomal/lysosomal-localized viral ORF3a protein sequestrates the HOPS complex component VPS39, preventing its interaction with the autophagosomal SNARE protein STX17, thereby blocking the fusion of autophagosomes and amphisomes with lysosomes to inhibit autophagic activity. ORF7a can reduce the acidity of lysosomes. Subsequently, SARS-CoV-2 RNA is released from the AL and undergoes extensive transcription, replication, and translation in the ER. In addition, NSP6 and NSP3 induce the characteristic rearrangement of the ER membrane or Golgi apparatus to produce DMVs or smooth vesicles containing newly assembled virions, which are eventually released by exocytosis.

failure or irreversible conduction disorders [214]. In addition, corticosteroids, commonly used for anti-inflammatory, anti-allergic, and immune response suppression, also inhibit SARS-CoV-2 infection and decrease autophagy activity by blocking LC3 recruitment. For example, the administration of methylprednisolone, a representative corticosteroid, can reduce the mortality of patients with severe diseases [215,216]. Therefore, corticosteroids exert an anti-SARS-CoV-2 effect via the inhibition of autophagy. Furthermore, recent studies have shown that the class III PI3 kinase inhibitor VPS34-IN1 and its bioavailable analog VVPS34-IN1 can effectively inhibit SARS-CoV-2 infection in isolated human lung tissue cultures at the nanomolar level [217–219], suggesting that the inhibition of the initiation process of autophagy can effectively inhibit SARS-CoV-2 [218]. Eugenol, also called clove oil, was reported to interfere with autophagy by avoiding the dissociation of BECN1-BCL2. Meanwhile, eugenol also reduces the SARS-CoV-2 spike S1-induced activation of NF-κB and the subsequent expression of proinflammatory cytokines, including IL-6, IL-1β, and TNF-α, in human A549 lung cells [220]. In SARS-CoV-2 S1-infected mice, oral treatment with eugenol reduces lung inflammation, alleviates fever, improves heart function, and enhances sports activity [220,221]. Therefore, the selective intervention of autophagy by eugenol to inhibit SARS-CoV-2 and its induced proinflammatory responses may be beneficial for COVID-19 treatment. Moreover, compound 2d, a derivative of berberine, has been reported to inhibit both RNA and protein levels of four different genotypes of enterovirus 71, which is closely associated with the inhibition of enterovirus 71-induced autophagy by activating

AKT and inhibiting the activation of the MEK-ERK signaling pathway [222]. This evidence suggests that berberine and its derivatives, such as compound 2d, may also inhibit SARS-CoV-2 by inhibiting autophagy. Collectively, autophagy inhibitors can effectively inhibit SARS-CoV-2 infection and increase the antiviral immune response in the early stages of SARS-CoV-2 infection.

5. Targeting the inhibition of NLRP3 inflammasome-mediated lung inflammation via autophagy induction in COVID-19

Typical symptoms of COVID-19 are fever, dry cough and fatigue, and in more severe cases, breathing difficulties may occur [223]. Although most people experience mild to moderate symptoms after being infected with SARS-CoV-2, approximately 12–15% of patients will experience severe complications such as pneumonia and ARDS [224,225], and these symptoms will eventually lead to systemic respiratory failure and death. In the incubation period and early and mild stages, the immune

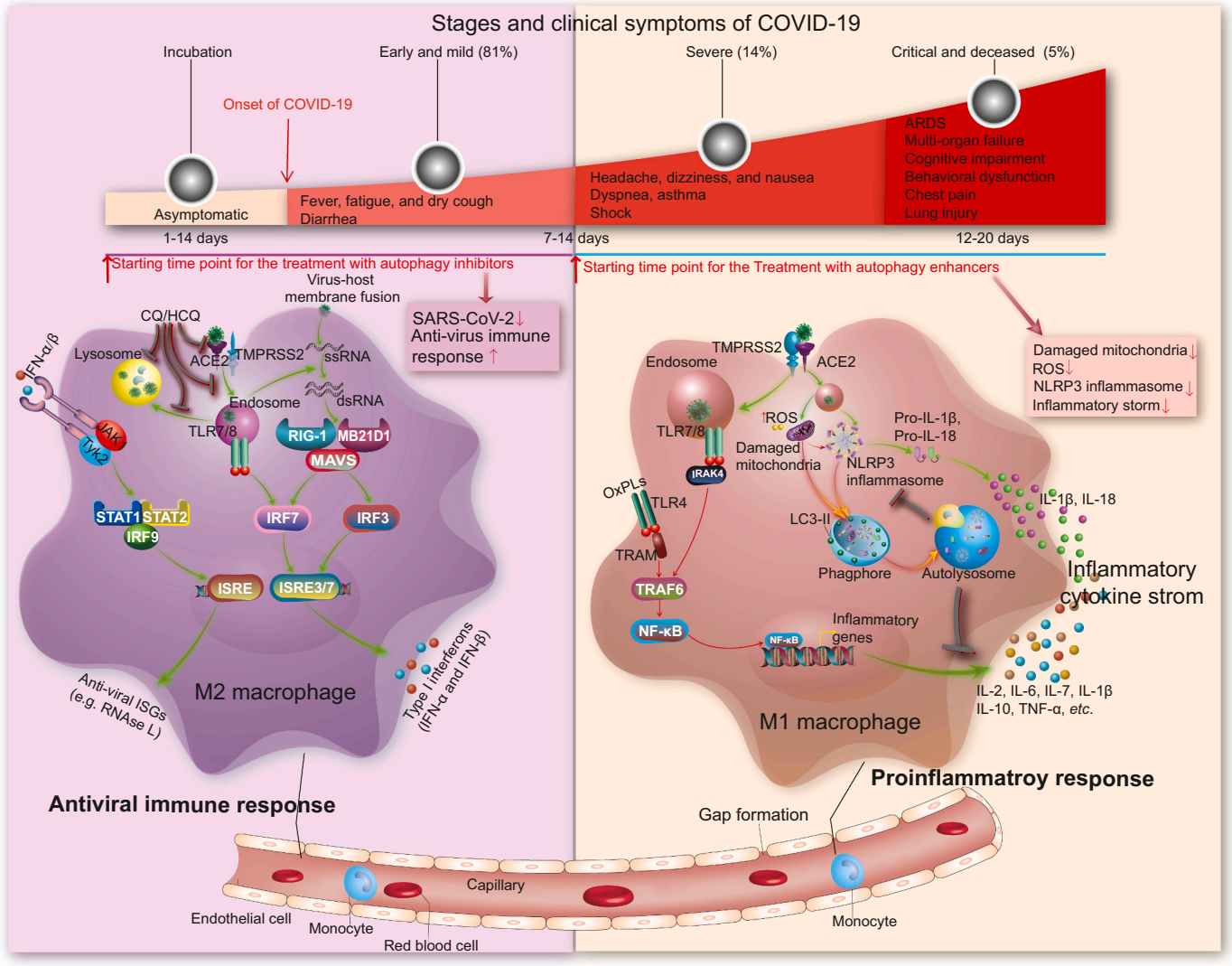

Fig. 6. Targeting the regulation of inflammatory immune responses using autophagy modulators at different stages of COVID-19. COVID-19 is divided into 3 stages, including the incubation, early and mild stage (81%), severe stage (14%), and critical and deceased stage (5%). The typical symptoms of COVID-19 are fever, dry cough, and fatigue, and in more severe cases, breathing difficulties can occur. During the early phases of COVID-19, induction of the type I IFN response is essential in limiting viral replication and modulating the innate and adaptive immune responses. Upon entry into host cells via TMPRSS2 and ACE2 during the incubation, early, and mild stages, SARS-CoV-2 is sensed by the endosomal single-stranded (ss)RNA sensors TLR7/8 and the cytosolic double-stranded (ds)RNA sensor RIG-I/MDA-5. Then, these sensors recruit adaptor proteins, including MyD88 and MAVS, which leads to the activation of the transcription factors IRF3/7 and the subsequent production of type I interferons (IFN-α/β). IFN-α/β bind to their receptor to activate the JAK-STAT signaling pathway, which leads to the formation of the STAT1–2-IRF9 complex and the subsequent induction of antiviral ISGs, such as RNase L. In addition, treatment with autophagy inhibitors, such as CQ/HCQ, can inhibit the binding of SARS-CoV-2 with ACE2 by interfering with terminal N-glycosylation, as well as the endocytosis of SARS-CoV-2 and viral genome release, which ultimately reduces SARS-CoV-2 infection and increases the antiviral immune response of COVID-19. When COVID-19 enters the severe or critical and deceased stage, OXPLs accumulate in infected lungs and activate macrophages through the TLR4-TRAF6-NF-κB pathway. In addition, the virus in the endosome activates the TLR7-IRAK4 pathway, which promotes the activation of the TRAF6-NF-κB pathway and releases many inflammatory cytokines, including IL-2, IL-6, IL-7, IL-1β, IL-10, and TNF-α. Meanwhile, the NLRP3 inflammasome is activated by the virus and ROS generated from damaged mitochondria, as well as other DAMPs, leading to the release of a large number of cytokines, including IL-1β and IL-18, which ultimately induce cell pyroptosis. Under the condition of a proinflammatory response in M1 macrophages, treatment with autophagy enhancers inhibits the activation of the NLRP3 inflammasome, reduces the production of cytokines and maintains the homeostasis and survival of macrophages.

function can be activated to exert its antiviral ability [226]. After SARS-CoV-2 enters host cells via TMPRSS2 and ACE2, it is sensed by endosomal single-stranded (ss) RNA sensors TLR7/8 and cytoplasmic double-stranded sensing (ds) RNA sensors DDX58/RIG-I and IFIH1/MDA-5. These sensors then recruit adaptor proteins, leading to the transcription of type I interferons (IFN-α/β) [227]. IFN-α/β binds to its receptors to activate the JAK-STAT and activator of transcription) signaling pathways, leading to the formation of the STAT1-STAT2-IRF9 complex and the subsequent induction of antiviral interferon-stimulated genes [228] (Fig. 6).

There is conclusive evidence that the NLRP3 inflammasome is overactivated during the severe stage of COVID-19, accompanied by the extensive release of IL-18 and IL-1β, together with other proinflammatory cytokines, which leads to uncontrolled inflammation and cytokine storm syndrome [76]. In COVID-19, the NLPR3 inflammasome is activated via multiple pathways. On the one hand, viral proteins directly activate the NLRP3 protein via their interaction with NLRP3 [229,230]. Meanwhile, the binding of SARS-CoV-2 N protein with the NLRP3 protein also induces the activation of the NLRP3 inflammasome and IL-1β release in macrophages and dendritic cells [231]. However, the NLRP3 inflammasome can also be indirectly activated in COVID-19 [128,232,233]. After the SARS-CoV-2 viral genome is translated, its viral porins ORF3a and E trigger K^+ efflux or Ca^{2+} influx to promote the activation of the NLRP3 protein [229,234]. When COVID-19 enters severe or critical and death stages, oxidized phospholipids (OXPLs) accumulate in infected lungs and activate macrophages through the TLR4-TRAF6-NFKB pathway [144,227]. In addition, the oxidation of lung surface-active phospholipids produces several OXPLs, which promote the activation of the NLRP3 inflammasome via the cleavage of CASP-4 and/or CASP-5 [128,232]. At the same time, the NLRP3 inflammasome is activated by the generated ROS from damaged mitochondria together with other DAMPs owing to SARS-CoV-2 infection, leading to the release of numerous cytokines, including IL-1β and IL-18, ultimately inducing cell pyroptosis [235]. In virus-infected lung cells, damaged mitochondria and high levels of ROS activate the NLRP3 inflammasome, or the released ATP binds to the P2X7 receptor, leading to K^+ efflux and NLRP3 activation [128]. Therefore, the NLRP3 inflammasome has been demonstrated to be overactivated and plays a key role in the pathology and progression of COVID-19 (Fig. 6).

In recent years, increasing evidence has emphasized the importance of autophagy in limiting NLRP3 inflammasome-mediated excessive inflammation in various human diseases, such as neurodegenerative diseases, diabetes, and cardiovascular diseases [236–238]. In the past decade, many studies have proven that autophagy negatively regulates the activation of NLRP3 inflammasomes through various mechanisms. First, the activation of the NLRP3 inflammasome can be directly inhibited as the NLRP3 inflammasome and its components are degraded via the autophagy-lysosomal pathway [239–241]. In THP-1 cells treated with LPS/ATP, the immunostaining results showed that endogenous NLRP3 overlapped with LC3, suggesting that the NLRP3 inflammasomes were engulfed by autophagosomes and degraded via autophagy induction [239]. In addition, the Mediterranean fever gene (MEFV/MEFV) innate immunity regulator pyrin (TRIM20) recognizes and binds inflammasome components and brings ULK1 to the NLRP3-TRIM20 receptor-target recognition complex, which then mediates the assembly of autophagosomes to isolate and degrade the inflammasome components [240,241]. Recently, it has been reported that the phosphorylation of NLRP3, which is mediated by the deletion of protein tyrosine phosphatase nonreceptor 22 (PTPN22), inhibits the activation of NLRP3 inflammasomes, and the inhibition of the NLRP3 inflammasome by PTPN22 deletion can be eliminated when autophagy is inhibited [242–244]. The phosphorylation of NLRP3 also mediates the inactivation of the NLRP3 inflammasome by promoting the entry of NLRP3 protein into autophagosomes. Furthermore, pro-IL-1β is also cleared via the autophagy pathway [245,246]. It has been reported that pro-IL1β is specifically sequestered into autophagosomes in macrophages treated with TLR ligands, and rapamycin treatment promotes the degradation of pro-IL-1β and prevents the secretion of mature cytokines. 3-MA abolishes the effect of rapamycin on the inhibition of the NLRP3 inflammasome and increases the secretion of IL-1β [245]. However, another study reported that autophagy induced by starvation or the mTOR inhibitor pp242 promotes the secretion of IL-1β and IL-18 in primary murine bone marrow-derived macrophages [246]. Therefore, the role of autophagy in the regulation of IL-1β release is complicated and may be related to specific conditions, such as cell type, inflammasome activator, and autophagy inducer/inhibitor. On the other hand, the activation of NLRP3 inflammasomes can also be inhibited indirectly via the autophagic clearance of damaged mitochondria and ROS [95,247]. The increased ROS from damaged mitochondria leads to the activation of NLRP3-dependent CASP-1 and IL-1β secretion in macrophages [95]. Rapamycin, a potent autophagy inducer, inhibits the activation of NLRP3 inflammasomes and the production of IL-1β and IL-18 by eliminating mitochondrial ROS in macrophages [247], while 3-MA promotes the accumulation of mitochondrial ROS and the subsequent overactivation of the NLRP3 inflammasome [95].

The clinical application of autophagy activators in COVID-19 is also becoming increasingly extensive. For example, metformin, an AMPK activator, activates autophagy through the AMPK-mTOR signaling pathway to stop the cell translation process [248]. At the same time, in a small retrospective study of T2DM patients hospitalized due to COVID-19, it was observed that the patients who administrated metformin had a significant decrease in IL-6 expression [249]. In addition, metformin inhibits mitochondrial ROS signal transduction, thereby opening the Ca^{2+} channel to release the activated Ca^{2+} to reduce the release of IL-6 caused by SARS-CoV-2 infection [250]. Therefore, this evidence suggests that metformin inhibits COVID-19 inflammation via autophagy induction. Furthermore, under the dual stimulation of H_2O_2 and mitochondrial DNA-ATP in RAW264.7 macrophages, metformin significantly decreases the generation of ROS levels and the subsequent high expression of NLRP3 and activation of CASP-1. In contrast, treatment with CQ and 3-MA or knockdown of Atg5 eliminates the inhibitory effects of metformin on the NLRP3 inflammasome [238]. Collectively, metformin may decrease ROS levels by activating autophagy through the AMPK-mTOR signaling pathway, thereby indirectly inhibiting the NLRP3 inflammasome to exert its anti-inflammatory effect at the late stage of COVID-19. In addition, studies have found that the administration of rapamycin at the early stage of the cytokine storm can prevent COVID-19 from progressing to a severe form by downregulating the senescence-associated secretory phenotype, mTOR-NLRP3-IL-1β axis, and IL-6 pathway, as well as decreasing the number of senescent T cells [251], suggesting that rapamycin as a potent autophagy activator may inhibit the NLRP3 inflammasome via autophagy induction. Vitamin D, a fat-soluble vitamin that is naturally present in a few foods, has been shown to activate autophagy by downregulating the mTOR pathway [252]. According to the NIH Trialnet database, several observational and interventional studies have demonstrated the efficacy of vitamin D on COVID-19 [253]. A recent clinical study in Iran shows that there are no COVID-19 deaths reported in the hospital if the serum concentration of 25-hydroxy vitamin D, the main storage form of vitamin D in the body, is higher than 41 ng/mL in COVID-19 patients (<80 years old) [254]. In addition, vitamin D has been demonstrated to inhibit NLRP3 inflammasomes through autophagy induction to treat a variety of inflammatory diseases [255,256]. Taken together, these findings suggest that vitamin D may reduce the cytokine storm in COVID-19 by targeting the autophagy-NLRP3-IL-1β axis. Recent studies have found that resveratrol, an autophagy activator, has therapeutic potential for multiple respiratory virus infections, including SARS-CoV-2 [257]. Interestingly, low levels of ACE2 are observed in COVID-19 patients with poor prognosis and cytokine storm, while resveratrol could increase the expression of ACE2 on the cell surface [258–260]. Meanwhile, resveratrol activates the ACE2-Ang1–7-MasR axis, which has been demonstrated to reduce excessive inflammation in COVID-19 patients

[260,261]. Therefore, resveratrol increases the expression of ACE2 and reduces excessive inflammation via autophagy induction. At the same time, resveratrol inhibits the replication of SARS-CoV-2 in Vero cells via SIRT1 and reduces the excessive inflammatory response [262,263]. Therefore, resveratrol may also inhibit the activation of NLRP3 and IL-1β release by promoting autophagy via the upregulation of SIRT1 in COVID-19. Trehalose, a mTOR-independent inducer of autophagy, has been approved as a food ingredient in many countries. In addition, trehalose activates transcription factor EB and promotes lysosomal biosynthesis [264]. Trehalose also promotes the fusion of amphisomes and lysosomes after the trafficking of viral double-membrane vesicles [264]. Therefore, trehalose can enhance the degradation of the SARS-CoV-2 virus with the action of lysosomes. In addition, trehalose not only prevents the entry of SARS-CoV-2 but also reduces cell apoptosis and the release of inflammatory cytokines by inducing autophagy [265], thereby alleviating the inflammatory response at the later stage of COVID-19. Therefore, trehalose has been considered a promising drug for the treatment of COVID-19 via autophagy induction [266,267]. In short, these pieces of evidence indicate that the inhibition of NLRP3 inflammasome-mediated lung inflammation by activating autophagy is a feasible therapeutic strategy for COVID-19. Before considering randomized clinical trials of these autophagy activators for the treatment of COVID-19, the correlation between their anti-inflammatory effects and the activation of autophagy still needs more rigorous study, which provides evidence for the development of autophagy activators as anti-COVID-19 drugs (Table 2).

6. Conclusion

SARS-CoV-2-induced damage to multiple organs and systems represented by lung inflammation has brought huge losses to global public health. As a representative inflammasome in COVID-19, the NLRP3 inflammasome has been proven to activate immunity against the virus in the early stage but exacerbate the excessive inflammatory response in the advanced stage of COVID-19, especially in severe cases [284]. Its long-term late activation may cause the excessive release of cytokines, lung endothelial damage accompanied by immune cell infiltration, and systemic hypercoagulability [285,286]. As a conservative self-degradation system, autophagy plays a significant role in inhibiting inflammation and resisting viruses. Initially, SARS-CoV-2 can induce autophagosomes to escape the host's antiviral response and provide conditions for its replication [201]. Thus, inhibitors of autophagy could restrain viral replication [13]. Since autophagy and inflammation have a mutually inhibiting relationship, after the activation of autophagy, the NLRP3 inflammasome can be inhibited in different ways, including the direct degradation of the NLRP3 inflammasome and its components and the indirect clearance of mitochondrial ROS to reduce or eliminate excessive inflammation at the late stage of COVID-19 [247]. Therefore, the maintenance of the homeostasis of the immune response in COVID-19 via the regulation of autophagy activity and NLRP3 inflammasome activation can improve the antiviral response, limit inflammation, and avoid complications.

At present, NLRP3 inflammasome inhibitors including MCC950 and anakinra, together with autophagy modulators including HCQ, CQ, rapamycin, and metformin have successively entered the clinical treatment of COVID-19 [14,106,146,248,274]. However, more studies still need to be conducted to confirm their clinical therapeutic effects and explore the potential toxicity and side effects. The immune inflammatory response and autophagy are two more complex regulatory mechanisms that affect each other. Most studies currently focus on the adverse effects of excessive activation of NLRP3 inflammasomes but neglect the protective effect of inflammasome signaling in the early SARS-CoV-2 infection of COVID-19. Similarly, inhibiting autophagy to reduce virus escape upon infection is a research hotspot, while activating autophagy to reduce SARS-CoV-2-induced NLRP3 inflammasome-mediated inflammatory cytokine signal transduction has also been extensively studied. Nevertheless, more future studies are also needed to better understand the relationship between autophagy and the NLRP3 inflammasome in COVID-19. Meanwhile, more clinical trials are expected to be carried out to determine the efficacy of modulators of autophagy, inhibitors of the NLRP3 inflammasome, or combinational therapies of autophagy modulators with inhibitors of the NLRP3 inflammasome, antiviral drugs, or anti-inflammatory drugs in the fight against COVID-19. We believe that combinational therapy targeting the

Table 2
Autophagy modulators and their mechanisms of action for the treatment of COVID-19.

Compounds	Modulation of Autophagy	Mechanisms of action	The possible effects on COVID-19	Reference(s)
Hydroxychloroquine and Chloroquine	Inhibitors	Inhibition of the AL fusion.	Inhibition of virus replication	[211,268]
VPS34-IN1 and VVPS34-IN1 and their analogs	Inhibitors	Inhibition of VPS34.	Inhibition of virus replication	[217–219,269]
Eugenol	Inhibitor	Inhibition of oxidative stress and activation of ERK1/2, p38MAPK and IKK/NF-κB; Inhibition of the dissociation of BECN1-BCL2 heterodimer.	Inhibition of the interaction between SARS-CoV-2 Spike S1 and ACE2	[220,221]
Corticosteroids	Inhibitor	Inhibition of autophagy by blocking LC3 recruitment	Downregulation of ACE2 receptor expression and inhibition of viral entry by inhibiting type I interferon	[270,271]
Berberine derivatives	Inhibitors	Inhibition of the MEK-ERK signaling pathway.	Inhibition of virus replication	[222,272]
Evodiamine	Inhibitors	Inhibition of the formation of the Atg5-Atg12-Atg16 heterotrimer and expression of Atg5, Atg7 and Atg12.	May inhibit virus replication	[273]
Rapamycin and derivative compounds	Activator	Inhibition of mTOR.	Controlment of viral particle synthesis	[274]
Metformin	Activator	Activation of AMPK and inhibition of mTOR.	Disruption of the interaction between the host and viral proteins	[275]
Vitamin D3	Activator	Not reported	Inhibition of SARS-CoV-2 replication machinery enzymes	[276,277]
Interferon Alpha-2b	Activator	Induction of autophagy and the formation of AL	Inhibition of virus replication	[278,279]
Ritonavir/Lopinavir	Activator	Induction of the formation of autophagosome	Blockade of viral RNA synthesis by targeting RNA-dependent RNA polymerases	[280,281]
Resveratrol	Activator	Activation of the cAMP-PRKA-AMPK-SI RT1 signaling pathway.	Inhibition of virus replication	[257,282]
Trehalose	Activator	Independent of mTOR.	Enhancement of the degradation of the SARS-CoV-2 virus with the action of lysosomes and inhibition of viral entry	[283]

modulation of autophagy and the NLRP3 inflammasome is an effective strategy for the treatment of COVID-19 in the future.

Declaration of Competing Interest

The authors declare no competing interests.

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