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COMMENTARY AND VIEWS

The role of autophagy in the pathogenesis of SARS-CoV-2 infection in different cell types

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly grown to be a major health crisis in many countries around the world. One of the most important aspects of studying COVID-19 is to investigate the properties of cellular defense against SARS-CoV-2 and the mechanism of viral elimination. Recently, the role of the selective and nonselective autophagy processes in the pathogenesis of SARS-CoV infections has been widely considered [1–5].

Autophagy or self-eating is a conserved catabolic pathway that exists in all eukaryotic organisms. This process is responsible for the degradation of various cytoplasmic components including long-lived or misfolded proteins, dysfunctional organelles, and intracellular infectious pathogens [6]. Several articles published in the past year strengthen the possibility of the involvement of autophagy dysfunction in the pathogenesis of COVID-19. Given the broad cell/tissue tropism of the virus and its destructive effect on human organs, it is crucial to investigate the role of autophagy in SARS-CoV-2 pathogenesis focusing on its impact on different cell types.

We should acknowledge that while the autophagy process plays a crucial role in maintaining cellular homeostasis and survival during viral infection, this process can be utilized against the host cells by the invading viruses. For example, specific viruses including SARS-CoV-2 evolved several strategies to escape, manipulate, or even block autophagic machinery in infected host cells [7–11]. Thus, it seems that this pathway can play two distinct roles, being "proviral" or "antiviral", depending on the infecting pathogen (Figure 1). In this commentary, we discuss some of the latest findings in this regard.

The role of autophagy process in the immune response against SARS-CoV-2 infection

The immune system employs a variety of methods to detect and eliminate viral infections. In the past two decades, many studies found that autophagy has an undeniable role in the proliferation, differentiation, maturation, and function of healthy immune cells. Not only are autophagy-related genes (*Becn1, Map1lc3/Lc3, Sqstm1, Atg3, Atg5*, and *Atg7)* expressed at many stages of B and T lymphocyte development in physiological condition, but this pathway is induced in many pathological conditions such as T or B cell antigen receptor stimulation, cytokine stimulation, and serum starvation [12,13]. Moreover, in the case of viral infections, autophagy widely contributes to the MHC I and MHC II antigen presentation to the $CD8^+$ and $CD4^+$ T cells, respectively [14]. This process orchestrates the delivery of intracellular viruses via autophagosomes to lysosomes. After lysosomal degradation, the viral particles will be displayed by the MHCs on the cell surface of infected cells and antigen-presenting cells (APCs) [15].

According to published reports, antigen presentation is damaged due to SARS-CoV-2 infection. Tomic et al. found that the activation of $CD4^+$ and $CD8^+$ T cells is considerably diminished especially in severe cases of COVID-19 [16]. They suggest that the reasons contributing to the poor response to the SARS-CoV-2 antigens may be the decreased number of APCs together with their reduced T cell activation abilities. Their results also show that the expression of *IRF8* (interferon regulatory factor 8) is reduced in COVID-19 patients [16]. *IRF8* is a transcription factor that is involved in regulation of autophagy in stress conditions. This factor also has an important role in regulation of dendritic cell function, antigen presentation, and elimination of intracellular pathogens [17,18]. Tomic et al. additionally evaluated the peripheral blood mononuclear cells of COVID-19 patients and found that the expression of certain autophagy-related genes (*ULK1, ATG5, UVRAG, AMBRA1, PIK3C3*, and *LC3*) are significantly decreased compared to healthy individuals [16].

In a recently published study, Zhang et al. discovered the direct interaction of a SARS-CoV-2 viral protein encoded by *ORF8* (open reading frame 8) with MHC I molecules that leads to MHC I downregulation and impairment of viral antigen presentation in SARS-CoV-2 infected cells and infected *HsACE2*-expressing mice [19]. Interestingly, they detected the

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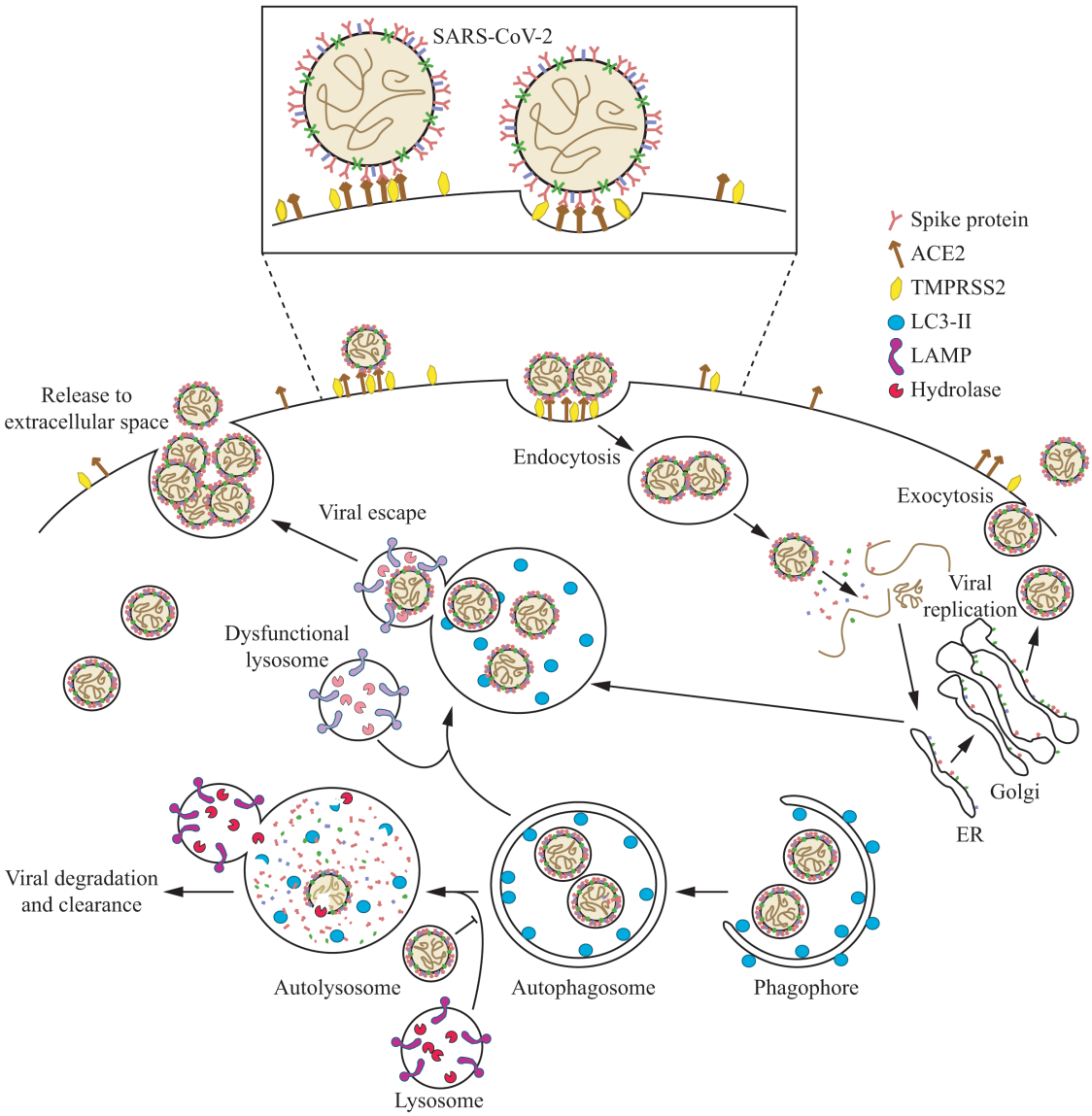

Figure 1. The distinct "proviral" or "antiviral" roles of autophagy in SARS-CoV-2-infected cells. The infection process begins with the binding of coronavirus spike glycoprotein through the recognition of the host cell target receptor, by its receptor-binding domain. TMPRSS2 primes the spike protein and facilitates viral entry. The viruses enter the host cell via endocytosis and release their RNA into the cytosol; this is followed by replicative translation with the membrane proteins being made in the endoplasmic reticulum. The newly formed viral particles may be released from the cell via exocytosis, or they may then intersect with autophagy. In general, autophagy plays an "antiviral" role, sequestering viral structural proteins or even completely assembled viral particles within autophagosomes; these will bind with lysosomes leading to degradation of the cargo by lysosomal hydrolytic enzymes. However, recent studies suggest that SARS-COV-2 disrupts and hijacks the autophagy-lysosomal pathway and subverts it. For example, the viral ORF3a protein may block autophagosome-lysosome fusion. In addition, viral proteins may be delivered to a de-acidified lysosome from which they can be released from the cell. This "proviral" role of the disrupted autophagy process leads to extensive production and release of the virus to the extracellular space causing the infection to spread to non-infected cells. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ACE2: angiotensin converting enzyme 2; TMPRSS2: transmembrane serine protease 2; LC3-II: lipidated MAP1LC3; LAMP; lysosomal associated membrane protein.

ORF8 colocalization with BECN1, LC3-labeled autophagosomes, and LAMP1$^+$ lysosomes. To confirm the involvement of autophagy, they inhibited this pathway by pharmacological inhibitors or knockdown of autophagy genes including *ATG5* and *ATG7* and found the significant restoration of MHC I expression. Their results suggest this virus employs the *ORF8* protein to hijack the autophagy pathway and causes MHC I downregulation, which subsequently protects the infected cells against their recognition and eradication by T cells [19]. Furthermore, data from a study by Ghosh et al. revealed that newly assembled SARS-CoV-2 viruses employ the lysosomal trafficking pathway as a route for release from the infected cells; this subversion of the lysosome can disrupt lysosomal acidification and degradation abilities and leads to perturbation of antigen cross-presentation [20]. These findings suggest that the reduced immune response in COVID-19 patients may be due to autophagy dysfunction.

The role of autophagy in SARS-CoV-2-infected respiratory cells

Given that the main route of SARS-CoV-2 entry to the human body is through the nasal cavity, this virus can extensively affect

the respiratory tract; along these lines, SARS-CoV-2 mostly infects type I and II pneumocytes as well as alveolar macrophages [21]. Electron microscopy investigations revealed that some of the abundant type I and II pneumocytes that are sloughed into the alveolar space, contain a large number of double-membrane vesicles; the SARS-CoV-2 viral particles are sporadically detected in some of these vesicles [22]. Although the authors proposed that these vesicles correspond to autophagosomes, further studies including the use of specific markers such as anti-LC3 will be needed to confirm their identification.

Numerous alveolar macrophages (AMs) including AM1 and AM2, reside within the alveoli of COVID-19 patients [23]. AM1s are responsible for attracting immune cells to the lung tissue, but the AM2s trigger the release of anti-inflammatory cytokines and eliminate the viral infection [24,25]. A recently published article revealed that while the AM2s efficiently clear the virus and eliminate its spread, AM1s tend to easily be hijacked by SARS-CoV-2 and prepare a favorable environment for their replication and further spread. Interestingly, the lysosomal acidity of AM1s is higher (5.5–6) compare to AM2s, which is suitable for the survival of this virus [26]. In addition, a previous article suggested that impaired autophagy promotes macrophage polarization toward AM1 (proinflammatory) and causes over-activation of the immune response [27]. Indeed, more investigations are necessary to elucidate a more detailed mechanism of AM polarization and function during SARS-CoV-2 infection, but it appears that autophagy plays an important role in this process.

The role of autophagy in SARS-CoV-2-infected cardiac cells

Although respiratory symptoms are the main clinical manifestations of COVID-19, serious cardiovascular complications caused by this disease raise significant concerns. It has been clear for years that a basal level of autophagy is necessary for the physiological function of myocardial cells; however, stress conditions such as hypoxia, nutritional starvation, and infections induce this process to maintain cellular homeostasis and accelerate the clearance of infectious pathogens and dysfunctional organelles [28].

Cardiomyocytes are susceptible to SARS-CoV-2 infection due to the expression of ACE2 (angiotensin-converting enzyme 2). The interesting fact is that angiotensin II type 1 and type 2 (AT1 and AT2) are involved in autophagy regulation in response to physiological and pathological stimulants by agonizing and antagonizing this process, respectively [29,30]. Given that ACE2 is a key factor for SARS-CoV-2 entry, further investigation regarding this receptor and its effects on autophagy machinery in cardiac cells may provide beneficial data.

According to Bulfamante et al., SARS-CoV-2 proteins and RNA genome are localized in cardiomyocytes of COVID-19 patients [31]. In addition, an *in vitro* experiment conducted by Marchiano *et al.*, suggests the viral particles are found surrounded by cytoplasmic double-membrane structures as well as lysosome-like vesicles that the authors proposed are a platform for viral replication and assembly. These authors suggest that the mature viruses hijack the vesicles (to facilitate their replication and assembly) and ultimately release them from the myocardial cells by exocytosis [32].

The role of autophagy in SARS-CoV-2-infected glial and neural cells

Last, we discuss the role of neural and glial autophagy in SARS-CoV-2 infection. Currently, there are no data reporting the exact mechanism of infection in these cell types. However, the presence of the viral particles in brain tissue and the susceptibility of neural cells to the infection is confirmed. According to Paniz-Mondolfi et al., the SARS-CoV-2 components that are detected inside the postmortem frontal lobe are located in intracytoplasmic vesicles that are possibly related to the autophagic-lysosomal pathway [33].

In addition, systemic inflammation caused by COVID-19 may indirectly affect the autophagy process in the brain. In 2018, a study revealed that pro-inflammatory cytokine TNF drives the glial polarization toward the M1 phenotype by activating AKT-MTOR signaling and the subsequent blockade of the autophagy pathway that ultimately results in significant neuroinflammation [34]. Thus, it is likely that the COVID-19-induced cytokine storm plays a destructive role in glial autophagy so detailed investigations are needed to clarify its possible mechanism.

Furthermore, a recent study revealed that SARS-CoV-2 targets the cortical neurons and induces MAPT/tau pathologies such as hyperphosphorylation, aggregation and subsequent neurodegeneration in the infected neural cells [35]. This is a valuable finding because the autophagic pathway is essential for the degradation of pathological MAPT/tau as well as intracellular infectious pathogens. Autophagic dysfunction caused by or resulting from MAPT/tau hyperphosphorylation received a great deal of attention in recent years [36,37]. Further investigations are necessary to evaluate the COVID-19-associated MAPT/tau pathology and autophagy dysfunction in the brain.

Understanding more details of the pathomechanisms of COVID-19 can be considered as key to open new horizons of safe and effective pharmacological treatments. We think that the autophagy process could be a target as it plays a pivotal role in the pathogenesis of SARS-CoV-2 injuries in various tissues and organs. Therefore, more detailed investigations on postmortem tissues of COVID-19 patients as well as *in vitro* models are needed to elucidate the exact role of autophagy in different SARS-CoV-2-infected cell types.

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