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Highlights in the fight against COVID-19: does autophagy play a role in SARS-CoV-2 infection?

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ABSTRACT

In the preceding months, the novel SARS-CoV-2 pandemic has devastated global communities. The need for safe and effective prophylactic and therapeutic treatments to combat COVID-19 – the human disease resulting from SARS-CoV-2 infection – is clear. Here, we present recent developments in the effort to combat COVID-19 and consider whether SARS-CoV-2 may potentially interact with the host autophagy pathway.

Abbreviations: ACE2, angiotensin converting enzyme II; βCoV, betacoronavirus; COVID-19, Coronavirus Disease 2019; CQ, chloroquine; DMV, double-membrane vesicle; GI, gastrointestinal; HCQ, hydroxychloroquine; IL, interleukin; MAP1LC3/LC3, microtubule associated protein 1 light chain 3; MEFs, mouse embryonic fibroblasts; MERS-CoV, Middle East respiratory syndrome coronavirus; MHV, murine hepatitis virus; PE, phosphatidylethanolamine; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2; TNF, tumor necrosis factor; WHO, World Health Organization

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SARS-CoV-2 global pandemic

In December 2019, an outbreak of severe pneumonia in Wuhan, Hubei province, China, was later identified to be caused by a novel betacoronavirus (βCoV) – initially named 2019-nCoV, and, later, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. SARS-CoV-2 is a member of the *Coronaviridae* family (*Nidovirales* order); coronaviruses are enveloped, single-stranded positive-sense RNA viruses [2,3]. SARS-CoV-2 is related to severe acute respiratory syndrome coronavirus (SARS-CoV; 2002–2003 endemic) and Middle East respiratory syndrome coronavirus (MERS-CoV; first identified in 2012); SARS-CoV and MERS-CoV are also βCoVs although of different lineages [4]. No vaccines or specific-drug treatments have been approved for either SARS-CoV or MERS-CoV [4]. Zoonotic origin has been attributed as the source of these outbreaks [5,6] and is further reviewed elsewhere [4]. SARS-CoV-2 is likely derived from a bat reservoir [5], although other sources have been proposed, including pangolins as an intermediate host [7,8], and multiple recombination events between bats and pangolins [9,10]. However, more recent data suggest that there is insufficient evidence to conclude that pangolins played a direct role in the emergence of SARS-CoV-2 [11]. At this time, the precise details of the zoonotic spillover event contributing to the current global crisis have yet to be determined. The potential mechanisms contributing to the evolution of SARS-CoV-2 are further reviewed elsewhere [11].

The World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) a global pandemic on 11 March 2020. As of 12 October 2020, over 37 million confirmed cases and 1 million deaths world-wide have been reported to the WHO [12]. The United States leads the world with the highest number of cases thus far (over 7.5 million confirmed cases as of 12 October 2020) [12]. The resulting human illness due to infection with the novel coronavirus SARS-CoV-2 is most frequently characterized by fever, fatigue, cough, acute pneumonia, and, less frequently, diarrhea [2]. Additionally, individuals infected with SARS-CoV-2 have also reported anosmia, or loss of smell [13]. Neurological symptoms, including headache, nausea, and vomiting, have been noted; the virus has also been identified in the brainstems of infected individuals [14]. The development of a cytokine storm has been associated with patients suffering from severe COVID-19 [15]. Elevated cytokine levels (IL6, IL10, and TNF/TNF-α), lymphopenia (in $CD4^+$ and $CD8^+$ T cells), and decreased IFNG/IFN-γ expression in $CD4^+$ T cells have been reported [15]. This cytokine storm contributes to the development of acute respiratory distress syndrome/ARDS and may lead to increased organ damage and mortality [16].

Earlier in the pandemic, transmission was primarily attributed to respiratory droplets and fomites [17,18]. The risk of airborne transmission by aerosols has become more widely recognized [19,20], and the role of fomites as a transmission risk has been minimized [21]. Asymptomatic or mild infections have now been identified to be a source of underrecognized transmission [22,23], further exacerbating the spread.

SARS-CoV-2 entry mechanism

To gain entry into host cells, SARS-CoV-2 uses the SARS-CoV receptor ACE2 (angiotensin I converting enzyme 2)

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[5,24,25] and the transmembrane serine protease 2 (TMPRSS2) for spike (S) protein priming by host cell proteases [24]. Structural studies suggest that the receptor binding domain of SARS-CoV-2 interacts with ACE2, and that two trimeric S proteins bind to an ACE2 dimer [26]. The S protein of SARS-CoV-2 binds ACE2 with higher affinity than the S protein of SARS-CoV [27]. The SARS-CoV-2 S protein also mediates fusion of the virion with the host cell plasma membrane (reviewed in [27]). Recent work by Bruchez *et al.* also demonstrates that CD74, which is the major histocompatibility/MHC class II invariant chain for antigen presentation, inhibits SARS-CoV-2 entry in Vero cells [28].

Sungnak and colleagues applied single-cell RNA sequencing/scRNA-seq to identify the localization of SARS-CoV-2 entry factors – *ACE2* and *TMPRSS2* – to sites associated with transmission and infection, including nasal, respiratory, corneal, and gastrointestinal epithelial cells, supporting an underlying basis for SARS-CoV-2 transmissibility [29]. Lamers *et al.* also reported that ACE2 is highly expressed on differentiated human gut enterocytes [30]. Likewise, both SARS-CoV and SARS-CoV-2 productively infect human small intestinal organoids/hSIOs in culture [30]. These studies [29,30] provide a physiological basis for the gastrointestinal symptoms reported in some SARS-CoV-2 patients [2].

Coronaviruses and autophagy

Historically, the relationship between the host autophagy pathway and viruses has been somewhat provocative. Nevertheless, more recently, the dual roles of autophagy in the context of unique virus infections and cell types has become more widely recognized. Host autophagy may function in an antiviral capacity (also referred to as xenophagy or virophagy) to suppress virus infection. However, some viruses, may usurp and exploit the autophagy machinery to support replication (for further review on virus-host autophagy interactions, see [31,32]).

Earlier work examining a potential link between coronavirus-host autophagy interactions primarily focused on SARS-CoV or murine hepatitis virus (MHV) [33,34]. Briefly, from previous studies, coronaviruses form double-membrane vesicles (DMVs) during infection which may function as scaffolds for RNA replication [35–38], suggesting potential interactions between these viruses and the host autophagy pathway. These DMV scaffolds may function as a platform to improve the efficiency of viral RNA synthesis [3]. Similar to mammalian autophagosomes, DMVs are likely derived from the endoplasmic reticulum/ER and other cellular membranes [35,39,40]. Additional evidence from work by Prentice *et al.* in 2004 identified the colocalization of SARS-CoV replicase protein NSP8 with the autophagy marker MAP1LC3/LC3 [41], suggesting that SARS-CoV may interact with the autophagy machinery. LC3 is a mammalian ortholog of the highly conserved Atg8-family proteins and associates with both the emerging phagophore and complete autophagosome [42]. In contrast, another study showed that SARS-CoV replication was not significantly affected in autophagy-deficient *atg5* null MEF cells exogenously expressing human ACE2 [33], even though ATG5 is required for canonical autophagy activity [43].

Additional studies investigating the relationship between coronaviruses and host autophagy have focused on the βCoV MHV [34,44]. Prentice and colleagues found that MHV replication complexes colocalize with autophagy proteins LC3 and ATG12 [34], further suggesting a role for autophagy in supporting MHV infection. ATG12 functions in the heterotrimeric ATG12–ATG5-ATG16L1 complex to facilitate LC3 conjugation to phosphatidylethanolamine (reviewed in [45]). MHV-dependent DMV formation and MHV replication are inhibited in embryonic stem cells lacking *Atg5*; the expression of exogenous ATG5 is sufficient to restore MHV replication [34]. However, another study by Zhao *et al.* determined that ATG5 is not required for MHV infection in bone marrow-derived macrophages or low-passage mouse embryonic fibroblasts (MEFs) [44].

A later study by Reggiori *et al.* demonstrated an autophagy-independent role for nonlipidated LC3-I in MHV infection [39]. In the same study, the authors concluded that MHV replication does not require a functional autophagy pathway based on studies in *atg7* null MEFs [39]. These results suggest that with MHV, infection may occur independent of the canonical autophagy machinery, and/or the role of autophagy in MHV infection could be dependent on the cell type under study (for a more extensive review on the relationship between coronaviruses and autophagy, see [46] and the review by Miller *et al.* in this issue [47]). At the time this editorial went to press, there are currently no published studies on SARS-CoV-2 and autophagy. Thus, there remains a need for validated experiments on SARS-CoV-2 in the relevant cell types to provide conclusive evidence (or lack thereof) for the role of autophagy in its infectious life cycle.

Potential treatments for COVID-19

Chloroquine and hydroxychloroquine

There has been an ongoing search to find a safe and effective therapy to prevent or cure SARS-CoV-2 infection. The application of chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) as a treatment for COVID-19 has been met with controversy. CQ and HCQ are routinely used in the clinic for the treatment of malaria and various autoimmune diseases (reviewed in [48]). CQ and HCQ inhibit autophagy by preventing the fusion of the autophagosome with the lysosome and deacidifying the lysosome (reviewed in [49,50]). HCQ exhibits antiviral activity toward SARS-CoV-2 in cell culture studies [51]. However, the Federal Drug Administration has cautioned against the use of CQ or HCQ for COVID-19 treatment outside of clinical trials or hospital settings due to cardiac concerns and other serious side-effects [52]. In addition, a study examining postexposure prophylaxis with HCQ did not find any significant difference in new infection in those treated with HCQ compared to placebo within 4 days after exposure [53]. Furthermore, a clinical study published in the *New England Journal of Medicine* did not find any benefit to the administration of HCQ in >4,700 patients [54]. In fact, the study demonstrated that

patients who received HCQ suffered from an elevated risk of receiving mechanical ventilation or death within 28 days [54]. COVID-19, autophagy, and autophagy-modifying drugs are further discussed in recent *Autophagy* commentaries by Bonam and colleagues [55], Brest *et al.* [56], and Tang *et al.* [57].

Remdesivir and other potential treatments

According to its manufacturer Gilead Sciences, remdesivir (GS-5734) is "an investigational nucleotide analog with broad-spectrum antiviral activity" [58]. This drug inhibits the viral RNA-dependent RNA polymerase and was previously demonstrated to have antiviral efficacy *in vitro* against SARS-CoV, MERS-CoV, and, recently, SARS-CoV-2 [51,59,60]. Remdesivir was used to treat the United States' first confirmed case of COVID-19 in the clinic with no obvious side-effects reported, but the report also called for ongoing trials to assess the safety and efficacy of the drug [61]. The Federal Drug Administration authorized remdesivir for emergency use as a COVID-19 treatment [62]. Preliminary results of the clinical trial administered by the National Institutes of Allergy and Infectious Disease/NIAID cited a quicker recovery time in patients receiving remdesivir compared to placebo [63]. A study published in *the Lancet* around the same time, found no statistically significant differences in the improvement of critically ill COVID-19 patients when treated with remdesivir; however, the authors did note that illness duration decreased in the remdesivir group compared to control [64], which corroborates the results stated by the NIAID clinical trial [63]. A recently published report in the *New England Journal of Medicine* demonstrates that patients who received intravenous remdesivir benefited from a shortened recovery time and decreased mortality [59]. When patients were given remdesivir earlier in the illness, a greater benefit was observed [59].

Dexamethasone is a glucocorticoid that may alleviate inflammation underlying lung injury and respiratory failure in COVID-19 patients [65]. Patients receiving respiratory support who were administered intravenous dexamethasone were found to have decreased mortality in a preliminary report [65]. Other potential therapies under consideration include tocilizumab, a humanized recombinant anti-human IL6 receptor monoclonal antibody, which could suppress severe inflammatory responses and alleviate the cytokine storm exhibited by patients with severe COVID-19 [66]. Additional potential drug candidates are in development targeting various aspects of the virus life cycle, including the main SARS-CoV-2 protease M^{pro} that mediates viral replication and transcription [67]. The ribonucleoside analog β-D-N^4-hydroxycytidine (NHC; EIDD-1931) has demonstrated *in vitro* efficacy against various coronaviruses including SARS-CoV-2, MERS-CoV, and SARS-CoV [68]. Furthermore, prophylactic and therapeutic administration of EIDD-2801, an orally bioactive NHC prodrug (β-D-N^4-hydroxycytidine-5′-isopropyl ester), in mice reduces MERS-CoV and SARS-CoV titers [68]. Similar to other antiviral therapies, such as Tamiflu®, the timing of the administration for drugs targeting SARS-CoV-2 during patient infection is likely critical, and, moving forward, will require optimization once a promising candidate is identified. In addition, a number of vaccines are currently under investigation [69].

Conclusions

At the time this article went to press, there is a lack of direct experimental evidence to conclude whether autophagy is involved (either in an antiviral or proviral manner, or in any biologically significant capacity) in SARS-CoV-2 infection either *in vitro* in cell culture or *in vivo* – in animal models or clinical findings. Direct inquiry into the factors involved in the physiologically relevant cell types is necessary to determine the full range of the host response to SARS-CoV-2. In addition, investigation into how unique gene variants (such as host factors important for viral infection) may influence COVID-19 pathophysiology – for example, asymptomatic infection and, on the other end of the spectrum, severe disease pathology – will be key to not only furthering our understanding of SARS-CoV-2, but also that of the host response to emerging viruses.

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