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

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© June 2021; Revised September 2021; Accepted September 2021

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, Sqaš1m1, 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
**ORF8** co-localization 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 stimuli 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.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the National Institute of General Medical Sciences [GM131919].

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References

[1] Bonam SR, Muller S, Bayry J, et al. Autophagy as an emerging target for COVID-19: lessons from an old friend, chloroquine. Autophagy. 2020;16(12):2260–2266.

[2] Mijailja D, Klionsky DJ. Autophagy/virophagy: a "disposal strategy" to combat COVID-19. Autophagy. 2020;16(12):2271-2272.

[3] Sargazi S, Sheevvaliou R, Rokni M, et al. The role of autophagy in controlling SARS-CoV-2 infection: an overview on virophagy-mediated molecular drug targets. Cell Biol Int. 2021;45(8):1599–1612.

[4] Ren S, Ding C, Sun Y. Morphology remodeling and selective autophagy of intracellular organelles during viral infections. Int J Mol Sci. 2020;21(10):3689.

[5] Miller K, McGrath ME, Hu Z, et al. Coronavirus interactions with the cellular autophagy machinery. Autophagy. 2020;16(12):2131–2139.

[6] Glick D, Barth S, MacleodKF. Autophagy: cellular and molecular mechanisms. J Pathol. 2010;221(1):3–12.

[7] Budida R, Stankov MV, Döhnner K, et al. Herpes simplex virus 1 interferes with autophagy of murine dendritic cells and impairs their ability to stimulate CD8+ T lymphocytes. Eur J Immunol. 2017;47(10):1819–1834.

[8] Campbell GR, Rawat P, Bruckman RS, et al. Human immunodeficiency virus type 1 Nef inhibits autophagy through transcription factor EB sequestration. PLoS Pathog. 2015;11(6):e1005018.

[9] Fecchi K, Anticoli S, Peruzzu D, et al. Coronavirus interplay with lipid rafts and autophagy unveils promising therapeutic targets. Front Microbiol. 2020;11:1821.

[10] Zhang Y, Sun H, Pei R, et al. The SARS-CoV-2 protein ORF3a inhibits fusion of autophagosomes with lysosomes. Cell Discov. 2021;7(1):1–12.

[11] Prentice E, Jerome WG, Yoshimori T, et al. Coronavirus replication complex formation utilizes components of cellular autophagy. J Biol Chem. 2004;279(11):10136–10141.

[12] Pua HH, Dzhagalov I, Chuck M, et al. A critical role for the autophagy gene Atg5 in T cell survival and proliferation. J Exp Med. 2007;204(1):25–31.

[13] Watanabe K, Tsubata T. Autophagy connects antigen receptor signaling to costimulatory signaling in B lymphocytes. Autophagy. 2009;5(1):108–110.

[14] Valečka J, Almeida CR, Su B, et al. Autophagy and MHC-restricted antigen presentation. Mol Immunol. 2018;99:163–170.

[15] Öynebräten I. Involvement of autophagy in MHC class I antigen presentation. Scand J Immunol. 2020;92(5):e12978.

[16] Tomić S, Dokić J, Stevanović D, et al. Reduced expression of autophagy markers and expansion of myeloid-derived suppressor cells correlate with poor T cell response in severe COVID-19 patients. Front Immunol. 2021;12:208.

[17] Sichien D, Scott CL, Martens L, et al. IRF8 transcription factor controls survival and function of terminally differentiated conventional and plasmacytoid dendritic cells, respectively. Immunity. 2016;45(3):626–640.

[18] Gupta M, Shin D-M, Ramakrishna L, et al. IRF8 directs stress-induced autophagy in macrophages and promotes clearance of Listeria monocytogenes. Nat Commun. 2015;6(1):1-14.

[19] Zhang Y, Chen Y, Li Y, et al. The ORF8 protein of SARS-CoV-2 mediates immune evasion through down-regulating MHC-I. Proc Nat Acad Sci. 2021;118:23.

[20] Ghosh S, DelliBovi-Ragheb TA, Kerviel A, et al. β-Coronaviruses use lysosomes for egress instead of the biosynthetic secretory pathway. Cell. 2020;183(6):1520–1535.e14.

[21] Chu H, Chan JF-W, Wang Y, et al. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19. Clin Infect Dis. 2020;71(6):1400–1409.

[22] Bradley BT, Maioli H, Johnston R, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. Lancet. 2020;396(10247):320–332.

[23] Liao M, Liu Y, Yuan J, et al. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat Med. 2020;26(6):842–844.

[24] Abassi Z, Knaney Y, Karram T, et al. The lung macrophage in SARS-CoV-2 infection: a friend or a foe? Front Immunol. 2020;11:1312.

[25] Hu G, Christman JW. Editorial: alveolar macrophages in lung inflammation and resolution. Front Immunol. 2019;10:2275.

[26] Lv J, Wang Z, Yu Q, et al. Distinct uptake, amplification, and release of SARS-CoV-2 by M1 and M2 alveolar macrophages. Cell Discov. 2021;7(1):1–12.

[27] Liu K, Zhao E, Ilyas G, et al. Impaired macrophage autophagy increases the immune response in obese mice by promoting proinflammatory macrophage polarization. Autophagy. 2015;11 (2):271–284.

[28] Gatica D, Chiong M, Lavandero S, et al. Molecular mechanisms of autophagy in the cardiovascular system. Circ Res. 2015;116 (3):456–467.

[29] Porrello ER, Delbridge LM. Cardiomyocyte autophagy is regulated by angiotensin II type 1 and 2 receptors. Autophagy. 2009;5 (8):1215–1216.

[30] Porrello ER, D’Amore A, Curl CL, et al. Angiotensin II type 2 receptor antagonizes angiotensin II type 1 receptor–mediated cardiomyocyte autophagy. Hypertension. 2009;53(6):1032–1040.

[31] Bullamante GP, Perrucci GL, Falleni M, et al. Evidence of SARS-CoV-2 transcriptional activity in cardiomyocytes of COVID-19 patients without clinical signs of cardiac involvement. Biomedicines. 2020;8(12):626.

[32] Marchiano S, Hsiang T-Y, Khanna A, et al. SARS-CoV-2 infects human pluripotent stem cell-derived cardiomyocytes, impairing electrical and mechanical function. Stem Cell Rep. 2021;16 (3):478–492.

[33] Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol. 2020;92(7):699–702.

[34] Jin M-M, Wang F, Qi D, et al. A critical role of autophagy in regulating microglia polarization in neurodegeneration. Front Aging Neurosci. 2018;10:378.

[35] Ramani A, Müller I, Ostermann PN, et al. SARS-CoV-2 targets neurons of 3D human brain organoids. The EMBO J. 2020;39(20): e106230.

[36] Kang S, Son SM, Baik SH, et al. Autophagy-mediated secretory pathway is responsible for both normal and pathological tau in neurons. J Alzheimers Dis. 2019;70(3):667–680.

[37] Samimi N, Asada A, Ando K. Tau abnormalities and autophagic defects in neurodegenerative disorders; a feed-forward cycle. Galen Med J. 2020; 9:1681.