https://doi.org/10.32394/pe.75.45

Elahe Aleebrahim-Dehkordi[1,2], Dariush Hooshyar[3,4], Shirin Saberianpour[5], Parnian Shobeiri[6,7,8], Ali Hasanpour-Dehkordi[9]*

LETTER TO THE EDITOR: AUTHOPHAGY: AS AN IMPORTANT HOST DEFENCE MECHANISM AGAINST VIRAL INFECTION SARS-COV-2

[1]Systematic Review and Meta-analysis Expert Group (SRMEG),
Universal Scientific Education and Research Network (USERN), Tehran, Iran.
[2]Medical Plants Research Center, Basic Health Sciences Institute,
Shahrekord University of Medical Sciences, Shahrekord, Iran.
[3]Student Research Committee, Faculty of Medicine,
Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[4]Infectious and Tropical Diseases Research Center, Hormozgan Health Institute,
Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[5]Vascular and Endovascular Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
[6]School of Medicine, Tehran University of Medical Sciences (TUMS), Tehran, Iran.
[7]Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA),
Universal Scientific Education and Research Network (USERN), Tehran, Iran.
[8]Non–Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute,
Tehran University of Medical Sciences, Tehran, Iran
[9]Social Determinants of Health Research Center, School of Allied Medical Sciences,
Shahrekord University of Medical Sciences, Shahrekord, Iran
[*]Corresponding author

Self-destructive processes like autophagy are vital for balancing energy sources at key points in development and response to nutritional stress. Although autophagy has been linked to cell death in the absence of apoptosis, it is widely considered a survival strategy. However, the mechanisms governing selective autophagy have not yet been completely figured out, therefore it is possible for the removal of certain organelles, ribosomes, and protein aggregates to occur in either a nonselective or selective manner during the autophagic process (1).

Autophagy also plays role in antiviral response, including response against coronaviruses. Coronaviruses are a group of coated, single-stranded RNA viruses. One of the most important determinants of viral infection is the entry of the virus into host cells. The coronavirus carries out this process through two pathways: the endocytic pathway and the non-endocytic pathway (2). As a result, the endocytic pathway, including endosomes and lysosomes, has become an important target for the developing of therapeutic strategies in the fight against CoVs (3). RNA replication of coronaviruses occurs in the cytoplasm of the host cell and is directly related to the endoplasmic reticulum (ER). Some studies on coronaviruses suggest that replication of the virus can interfere with the normal functioning of the ER, create ER stress, and ultimately, the UPR (unfolded protein response) in virus-infected cells. UPR is activated in response to the accumulation of unfolded protein or incorrectly opened proteins in the endoplasmic reticulum lumen. The stress created in the ER can be a major factor in the virus-host interaction. It can also affect patients' antiviral response (4).

UPR also activates autophagy. Autophagy is essential for maintaining tissue homeostasis and prevents the onset and progression of many diseases. Autophagy is a process that occurs in most cells and is responsible, i.e., for the removal of the damaged organelles through lysosomal degradation (5). Several viruses employ cellular autophagy to aid their reproduction, including coronaviruses (CoVs). The SARS-CoV open reading frame (ORF) induces intracellular stress and affects the innate immune system. Endoplasmic reticulum stress, lysosomal damage, and activation of Transcription Factor EB (TFEB) are all triggered by aggregation of ORF8b in cells. In epithelial cells, ORF8b induces cell death,

which may be partly reversed by lowering the capacity of the protein to assemble. Interestingly, accumulating ORF8b cytosolic aggregates may lead to mitochondrial malfunction and caspase-independent cell apoptosis in those cells deficient for NLRP3 (6). SARS-CoV-2 protein ORF-8b forms intracellular aggregates that trigger cellular stress, specifically NLRP3 (NLR Family Pyrin Domain Containing 3) inflammasome activation, and IL-1β release. The NLRP3 activates macrophages that are involved in the regulation of IL-1β and IL-18 (3, 4). Simultaneously viral proteins' replication induces ER stress, UPR and, consequently, autophagy process is also activated in virus-infected cells.

The autophagy can indirectly regulate the cytokine process in infected cells. Collectively, SARS-CoV-2 exploits cellular autophagy in enhance its own proliferation (2, 6). Angiotensin-converting enzyme 2 (ACE2), the main receptor for SARS-CoV-2, not only mediates the entry of SARS-CoV-2 into host cells but also is associated with autophagy. Studies have shown that autophagy was decreased due to ACE2 activity, as the overexpression of ACE2 was apparent in autophagy-deficient cells (5). Modulation of the immune response also plays a key role in fighting the disease. Neutrophils release neutrophil external traps (NETs) under the stimulation of autophagy.

NETs are a vast extracellular, web-like structure produced by neutrophils in the extracellular area which, because of their neutralizing and killing properties, are helpful in preventing the spread of diseases. Decondensed chromatin and proteins from the cytoplasm and granules make up these structures. From the nucleus and mitochondrial material, NET's DNA is derived. NET comes in two flavors. NETosis (NET-mediated cell deaths) is one of the most important steps in the innate immune response and can be produced by infectious agents and some stimuli, such as cytokines, cholesterol crystals, autoantibodies, and immune complexes. Suicidal NETosis is one example. Antimicrobial peptides generated from granules are then mixed with chromatin and DNA. Ultimately, Reactive Oxygen Species (ROS) are discharged into the extracellular area. Then, in a vital NETosis, which releases NETs without harming the cells, phagocytosis is still possible. NET can control inflammation by activating the immune system, as well as by modulating the function of monocyte-derived dendritic cells by stimulating the expression of Th2-type cytokines and reducing the synthesis of Th1 and Th17 cytokines. The

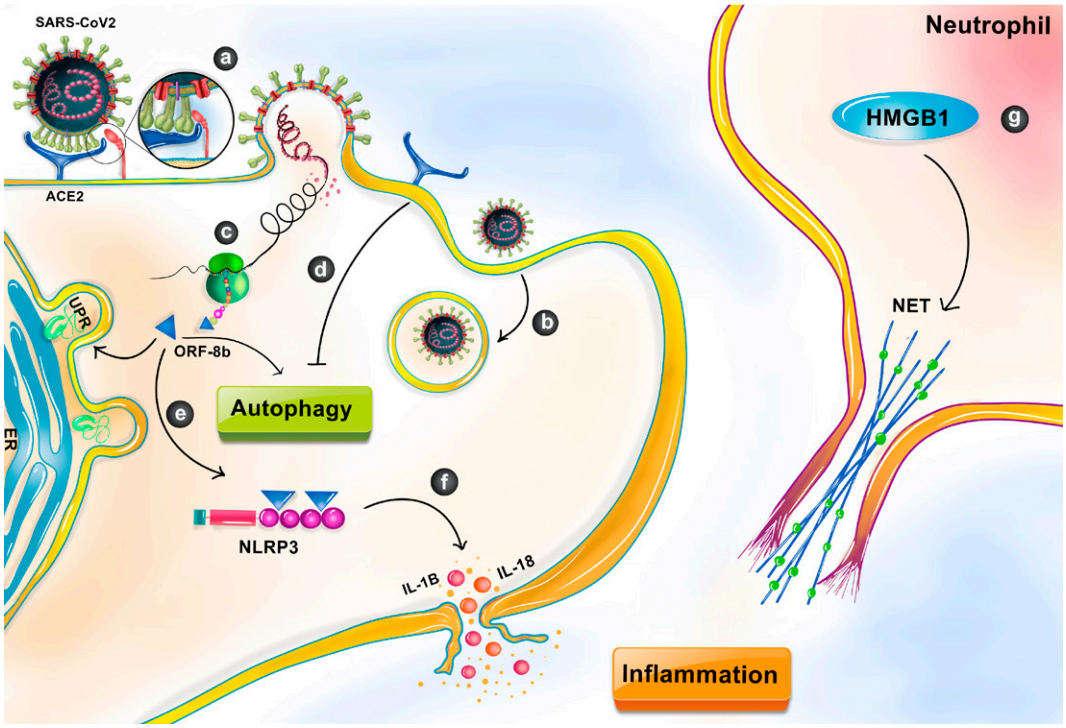

Fig 1. The role of endocytic and autophagy pathways in the pathogenesis of COVID-19 infection
SARS-CoV-2 enters the cell by two endocytic (b) and non-endocytic (a) pathways. After translation (c), ORF-8b can cause ER stress and, consequently, an unfolded protein response (UPR) in infected cells. ORF-8b also induces autophagy and NLRP3 inflammasomes (e), which is associated with pyro ptosis and the release of inflammatory cytokines such as IL-1β and IL-18 (f). Autophagy is also inversely related to Angiotensin-converting enzyme 2 (ACE2) receptor expression (d). Besides, activating of the NETosis in neutrophils by HMGB1 can exacerbate inflammation in COVID-19 patients (g) (13, 14).
Source: Own elaboration.

NET response triggered by lung epithelial destruction and the severity of the disease seem to be connected in terms of pathology, biochemistry, and clinical observations in SARS-CoV-2 infection. SARS-CoV-2 infection-related severe pneumonia has previously been linked to NETs, based on studies on serum NET elevations in COVID-19, the cytokine profile, and the clinical course (7, 8).

Different molecules can induce NETosis and autophagy. Some of the strongest activators have been damaged-associated molecular patterns (DAMPs), particularly high-mobility group 1 (HMGB1) boxes. This molecule is released by damaged lung cells and can trigger a strong innate immune response. On the other hand, increased HMGB1 protein and NETosis in COVID-19 infection can cause persistent inflammation. HMGB1 acts as a multifunctional protein through recombination, transcriptional regulation, and inflammation. This protein is actively secreted into the extracellular environment and acts as a cytokine, chemokine, and promotes inflammation growth factors. In addition, TLR-4 activation is required for NET formation, and viral proteins binding to TLR-4 initiate NETosis (7, 8). Finally, while NET formation can be harmful in pathogenesis of COVID-19 during prolonged periods of inflammation, we note that in general there is little evidence for its antiviral effect (8). Some effect has been only so far detected in the context of syncytial respiratory virus (RSV) and influenza virus (9). Therefore, it can be concluded that targeting molecules involved in NETosis and autophagy (e.g., NETs, DAMPs) can be considered as a therapeutic approach in COVID-19 and more research can be done in this field (3, 6-14). With all these descriptions, autophagy regulation is actually a way to deal with COVID-19. Given that COVID-19 infection has become a global problem, further research on UPR caused by the virus could be one of the goals in identifying new and effective treatments to improve patients' outcomes (4).

Ethical considerations: Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or fal-sification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest: The authors declare that there is no conflict of interest.

REFERENCES

1. Nakatogawa H, Suzuki K, Kamada Y, et al. Dynamics and diversity in autophagy mechanisms: lessons from yeast. Nat Rev Mol Cell Biol 2009;10(7):458-67. doi: 10.1038/nrm2708. Epub 2009 Jun 3.
2. Barrantes FJ. While we wait for a vaccine against SARS-CoV-2, why not think about available drugs? Front Physiol 2020;11:820. doi: 10.3389/fphys.2020.00820.
3. Yang N, Shen HM. Targeting the endocytic pathway and autophagy process as a novel therapeutic strategy in COVID-19. Int J Biol Sci 2020;16(10):1724-1731. doi: 10.7150/ijbs.45498.
4. Sureda A, Alizadeh J, Nabavi S. et al. Endoplasmic reticulum as a potential therapeutic target for covid-19 infection management? Eur J Pharmacol 2020;882(5):173288. doi: 10.1016/j.ejphar.2020.173288.
5. Gharib Z, Sanchooli N, Sanadgol N. Expression Changes of Genes Involved in Autophagy of the Endoplasmic Reticulum Network in Animal Models of Alzheimer's Disease. J Arak Uni Med Sci 2020;23(2):184-197.
6. Brest P, Benzaquen J, Klionsky DJ, et al. Open questions for harnessing autophagy-modulating drugs in the SARS-CoV-2 war: hope or hype? J Autophagy 2020;16(12):2267-2270. doi.org/10.1080/15548627.2020.1779531.
7. Samimi N, Farjam M, Klionsky DJ, et al. The role of autophagy in the pathogenesis of SARS-CoV-2 infection in different cell types. Autophagy 2021;1-4. doi: 10.1080/15548627.2021.1989150.
8. Thierry AR, Roch B. Neutrophil extracellular traps and by-products play a key role in COVID-19: pathogenesis, risk factors, and therapy J Clin Med 2020;9(9):p.2942.
9. Aleebrahim-Dehkordi E, Molavi B, Mokhtari M, et al. T helper type (Th1/Th2) responses to SARS-CoV-2 and influenza A (H1N1) virus: From cytokines produced to immune responses. Transpl Immunol 2022;70:101495. doi: 10.1016/j.trim.2021.101495.
10. Shi CS, Nabar NR, Huang NN, et al. SARS-Coronavirus Open Reading Frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell death Discov 2019;5;5(1):1-2.
11. Cicco S, Cicco G, Racanelli V, et al. Neutrophil Extracellular Traps (NETs) and Damage-Associated Molecular Patterns (DAMPs): Two Potential Targets for COVID-19 Treatment. Mediators Inflamm 2020;2020:7527953. doi: 10.1155/2020/7527953.
12. Mohammadi K, Tabatabaee A, Akbari M. Kinin-kallikrein system; a possible pathway responsible for COVID-19. Immunopathol Persa 2021;7(1):e11. doi:10.34172/ ipp.2021.11.
13. Prestes EB, Bruno JCP, Travassos LH, et al. The Unfolded Protein Response and Autophagy on the Crossroads of Coronaviruses Infections. Front Cell

Infect Microbiol 2021;11:668034. doi: 10.3389/fcimb.2021.668034.
14. Aleebrahim-Dehkordi E, Saberianpour S, Soleiman-Dehkordi E, et al. Autophagy and treatment of patients with COVID-19; which drugs target the autophagy pathway?. J Nephropathol 2022;1;11(1). doi: 10.34172/jnp.2021. xx.

Received: 02.10.2021
Accepted for publication: 21.01.2022

Address for correspondence:
Prof. Ali Hasanpour Dehkordi
Social Determinants of Health Research Center
School of Allied Medical Sciences
Shahrekord University of Medical Sciences,
Shahrekord, Iran
Tel: 989133830205
Email: ali20121968@yahoo.com
drhasanpour.skums@gmail.com