Aksaray Üniversitesi Tıp Bilimleri Dergisi
ASUJMS, 2(3): 30-33

Derleme

The Importance of Autophagy Mechanism as a Novel Therapeutic Target in SARS-CoV-2

SARS-CoV-2'de Yeni Terapötik Hedef Olarak Otofaji Mekanizmasının Önemi

Sevide SENCAN*

Department of Pathology, Turgut Özal Medical Center, İnönü University, Malatya, Turkey

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic and major public health issue called the disease as coronavirus disease-2019 (COVID-19). It spreads rapidly from an infected person via respiratory droplets by breathing, sneezing, coughing. The symptoms of COVID-19 are dry cough, fever, fatigue, shortness of breath, pneumonia. The epidemiological and pathological features of SARS-CoV-2 are still unclear and require further investigation. In previous studies, coronaviruses have been shown to use the endocytic pathway and autophagy mechanism to enter and replicate into the host cells. Chloroquine (CQ) is used in COVID-19 treatment, also known autophagy inhibitor. Therefore, Autophagy has been identified as one of the new therapeutic target against SARS-CoV-2. In this mini-review, we will briefly summarize the role of the autophagy mechanism in SARS-CoV-2 infection and therapeutic potential of this pathway to treatment of COVID-19.

Keywords: SARS-CoV-2, COVID-19, Coronavirus, Autophagy

ÖZET

Şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2), koronavirüs hastalığı-2019 (COVID-19) olarak da adlandırılan küresel bir salgına ve önemli bir halk sağlığı sorununa neden olmuştur. Enfekte bir kişiden solunum, hapşırma, öksürme ile damlacıklar yoluyla hızla yayılır. COVID-19 semptomları kuru öksürük, ateş, yorgunluk, nefes darlığı, zatürredir. SARS-CoV-2'nin epidemiyolojik ve patolojik özellikleri hala belirsizdir ve daha fazla araştırma gerektirmektedir. Daha önceki çalışmalar, koronavirüslerin konak hücrelere girmek ve replikasyon için endositik yolu ve otofaji mekanizmasını kullandığı gösterilmiştir. Otofaji inhibitörü olarak da bilinen klorokin (CQ), COVID-19 tedavisinde kullanılmaktadır. Bu yüzden, otofaji SARS-CoV-2' ye karşı yeni terapötik hedeflerden biri olarak tanımlanmıştır. Bu mini derlemede, SARS-CoV-2 enfeksiyonunda otofaji mekanizmasının rolü ve COVID-19 tedavisine yönelik terapötik potansiyelini kısaca özetleyeceğiz.

Anahtar Kelimeler: SARS-CoV-2, COVID-19, Koronavirus, Otofaji

*Sevide SENCAN
Department of Pathology, Turgut Ozal Medical Center, Inonu University, Malatya, Turkey
e-mail: sencan.sevide@gmail.com
ORCID ID:// 0000-0002-4312-1043

Geliş tarihi: 22.02.2021
Kabul tarihi: 21.06.2021

INTRODUCTION

Coronaviruses (CoVs) are a broad family of viruses that cause common respiratory diseases such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). CoVs are divided into three groups: Alpha-, Beta- and Gamma-coronavirus. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to beta-coronavirus and has a positive-polarity, single-strand RNA virus and is composed of four major structural proteins: the spike (S), membrane (M), envelope (E) and the nucleocapsid (N) protein [1, 2]. The viral life cycle is described the five steps: attachment, penetration, replication, assembly and release.

The key step in viral infection is the process of viral entry into the host cells. SARS-CoV-2 binds angiotensin-converting enzyme II (ACE2) as its receptor to enter into the host cells [3]. Although ACE2 expression was firstly found in heart, kidney, testis, its expression is shown to be higher in lung epithelium and small intestine [4]. It has been shown that CoVs including MHV, SARS-CoV and MERS-CoV entry into different host cells by using endosomal pathways [5]. Clathrin-dependent endocytosis and cathepsin-mediated S protein cleavage are two important steps for viral entry and infection. Viral polyproteins and nonstructural proteins are synthesized after viral replication is initiated by translation of the replicase protein [6, 7]. SARS-CoV-induced double-membrane vesicles (DMVs) by nonstructural protein (Nsp) 3-4-6 are formed from ER, and viral replication occurs within these DMVs [7-9]. All human coronavirus virions take place through budding into the ER golgi intermediate compartment (ERGIC) lumen, then they are released via exocytosis from the host cells [10, 11].

Autophagy is an intracellular degradation process that remove damaged organelles, unused proteins and also pathogen microorganisms to maintain cell homeostasis [12]. It takes role differentiation, embryonic development, aging, immune system. Imbalance autophagy may lead to cancer, neurodegenerative diseases and infections [13-15]. Autophagy related genes (ATG) ensure the regulation and completion of the autophagy process. Cellular stress such as starvation, hypoxia, DNA damage is important autophagy inducers. mTOR (Mammalian Target of Rapamycin), serin-threonine protein kinase, is involved in cell survival, proliferation, motility [16]. Autophagy triggers when dissociation of ULK1 kinase complex, which includes Atg13, Fib200, from inactive mTOR. Beclin-1/PI3KIII complex consisting of Beclin-1(ATG6), Vps34 (PI3KC3), p150 (Vps15, PI3KR4), Uvrag, Atg14L, Ambra1, Bif-1 are involved in the autophagosome formation [17, 18]. Two ubiquitin-like conjugation systems which include Atg12- Atg5, Atg16 and LC3-II are required for autophagosome membrane elongation [19]. Then, Autophagosome fuses lysosome to degrade cell components.

The autophagy is one of the crucial ways to degrade invading viruses from host cell, is known as xenophagy (also called to virophagy for viruses). The invasive viruses have developed different mechanism to escape autophagic mechanism and hijack the autophagosomes, and also their replication and spread have provided [20, 21]. Measles virus-MeV, Chikungunya virus-CHIKV, human immunodeficiency virus type 1/HIV-1, Macacine alphaherpesvirus 1/MCHV, Picornaviruses and Coronaviruses hijack and manipulate autophagy mechanism [22]. The first studies of autophagy and coronavirus was carried out by using mouse hepatitis virus (MHV), also known as mouse coronavirus (MCoV). Prentice et al. demonstrated that the formation of double-membrane vesicles (DMV) in mouse hepatitis virus (MHV) are similar to the autophagosome and viral RNA replication complexes on DMV were associated with the autophagy proteins [23]. In addition, the replication of MHV decreased in ATG5 knockout embryonic stem cell. These results suggested that autophagy requires DMV formation and MHV replication [23]. Nsp6 which is encoded by the replicase gene activate autophagy [24]. Another study showed that SARS-CoV and MERS-CoV inhibit autolysosomes formation blocking lysosome fusion while they trigger autophagosome formation [25, 26]. Moreover, p62/SQSTM1 has a role in autophagic clearance and the level of its was shown to be increased in infected cells [27]. Coronavirus proteins such as Nsp3, PLP-TM, of HCoV-NL63 block the fusion of autophagosomes with lysosomes by binding to BECN1, is one of the key protein of autophagy, and accumulate autophagosomes in HeLa, HEK293T, and MCF-7 cells [17]. Thus, viral replication is protected without passing through lysosome. Given that, induced autophagy process might be beneficial against SARS-CoV infection.

However, some conflicting data in the literature has shown that SARS-CoV replication is independent of autophagy process. The colocalization between LC3 as a marker of autophagy and SARS-CoV in Vero cells was not found [9]. Furthermore, The replication of SARS-CoV has not been inhibited by the knockdown of ATG5 or ATG7 in infected MHV cells [24, 28, 29]. The weight of evidence suggests that SARS-CoV is indirectly regulated by autophagy. Taken together, whether and how autophagy plays a role in CoV infection is still controversial. It may be a consequence of the use of various viruses, different cells, and several techniques in the study of autophagy.

Various anti-viral drugs such as CQ and HCQ have been proposed to COVID-19 treatment, these drugs remain controversial though. CQ and HCQ autophagy inhibitors, prevent formation of autolysosomes [30]. Moreover, The antiviral-effects of CQ and HCQ have been shown by disturbing early step in the viral life cycle [31]. Liu et al have offered that these drugs may be a target the entry of the virus through the endocytic pathway [32]. In addition, it has been suggested that these drugs can lead to apoptosis because of the accumulation of autophagosomes [33]. Autophagy directly or indirectly causes the destruction of SARS-CoV via several distinct mechanisms. Autophagy function can change depending on virus entry, kind of virus, cell types.

CONCLUSION

There is not yet an effective treatment choice against COVID-19. SARS-CoV-2 is a highly contagious virus and spread rapidly so there is an urgent need to improve effective and safer antiviral drugs. Some autophagy-related drugs are candidates for treatment COVID-19, while the role of autophagy is unclear. Given that the role of autophagy in the viral life cycle and the effect of autophagy inhibitors, it could be a viable treatment strategy for COVID 19.

Confilict of interest: The authors declare that they have no conflict of interest.

Financial Disclosure: There are no financial supports.

REFERENCE

1.Weiss SR and Navas-Martin S (2005) Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiol Mol Biol Rev 69:635-64. doi: 10.1128/mmbr.69.4.635-664.2005

2.de Haan CA and Rottier PJ (2005) Molecular interactions in the assembly of coronaviruses. Adv Virus Res 64:165-230. doi: 10.1016/S0065-3527(05)64006-7

3.Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y and Zuo W (2020) Single-Cell RNA Expression Profiling of ACE2, the Receptor of SARS-CoV-2. Am J Respir Crit Care Med 202:756-759. doi: 10.1164/rccm.202001-0179LE

4.Danilczyk U and Penninger JM (2006) Angiotensin-converting enzyme II in the heart and the kidney. Circ Res 98:463-71. doi: 10.1161/01.RES.0000205761.22353.5f

5.Wang H, Yang P, Liu K, Guo F, Zhang Y, Zhang G and Jiang C (2008) SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. Cell Res 18:290-301. doi: 10.1038/cr.2008.15

6.Wolff G, Limpens R, Zevenhoven-Dobbe JC, Laugks U, Zheng S, de Jong AWM, Koning RI, Agard DA, Grunewald K, Koster AJ, Snijder EJ and Barcena M (2020) A molecular pore spans the double membrane of the coronavirus replication organelle. Science 369:1395-1398. doi: 10.1126/science.abd3629

7.Hagemeijer MC, Monastyrska I, Griffith J, van der Sluijs P, Voortman J, van Bergen en Henegouwen PM, Vonk AM, Rottier PJ, Reggiori F and de Haan CA (2014) Membrane rearrangements mediated by coronavirus nonstructural proteins 3 and 4. Virology 458-459:125-35. doi: 10.1016/j.virol.2014.04.027

8.Gosert R, Kanjanahaluethai A, Egger D, Bienz K and Baker SC (2002) RNA replication of mouse hepatitis virus takes place at double-membrane vesicles. J Virol 76:3697-708. doi: 10.1128/jvi.76.8.3697-3708.2002

9.Snijder EJ, van der Meer Y, Zevenhoven-Dobbe J, Onderwater JJ, van der Meulen J, Koerten HK and Mommaas AM (2006) Ultrastructure and origin of membrane vesicles associated with the severe acute respiratory syndrome coronavirus replication complex. J Virol 80:5927-40. doi: 10.1128/JVI.02501-05

10.Stertz S, Reichelt M, Spiegel M, Kuri T, Martinez-Sobrido L, Garcia-Sastre A, Weber F and Kochs G (2007) The intracellular sites of early replication and budding of SARS-coronavirus. Virology 361:304-15. doi: 10.1016/j.virol.2006.11.027

11.Hassanpour M, Rezaie J, Nouri M and Panahi Y (2020) The role of extracellular vesicles in COVID-19 virus infection. Infect Genet Evol 85:104422. doi: 10.1016/j.meegid.2020.104422

12.Moreau K, Ravikumar B, Renna M, Puri C and Rubinsztein DC (2011) Autophagosome precursor maturation requires homotypic fusion. Cell 146:303-17. doi: 10.1016/j.cell.2011.06.023

13.Cao Y and Klionsky DJ (2007) Physiological functions of Atg6/Beclin 1: a unique autophagy-related protein. Cell Res 17:839-49. doi: 10.1038/cr.2007.78

14.Jin S and White E (2007) Role of autophagy in cancer: management of metabolic stress. Autophagy 3:28-31. doi: 10.4161/auto.3269

15.Moreau K, Luo S and Rubinsztein DC (2010) Cytoprotective roles for autophagy. Curr Opin Cell Biol 22:206-11. doi: 10.1016/j.ceb.2009.12.002

16.Munson MJ, Allen GF, Toth R, Campbell DG, Lucocq JM and Ganley IG (2015) mTOR activates the VPS34-UVRAG complex to regulate autolysosomal tubulation and cell survival. EMBO J 34:2272-90. doi: 10.15252/embj.201590992

17.Chen Y and Klionsky DJ (2011) The regulation of autophagy - unanswered questions. J Cell Sci 124:161-70. doi: 10.1242/jcs.064576

18.Obara K and Ohsumi Y (2011) PtdIns 3-Kinase Orchestrates Autophagosome Formation in Yeast. J Lipids 2011:498768. doi: 10.1155/2011/498768

19.Mizushima N, Noda T, Yoshimori T, Tanaka Y, Ishii T, George MD, Klionsky DJ, Ohsumi M and Ohsumi Y (1998) A protein conjugation system essential for autophagy. Nature 395:395-8. doi: 10.1038/26506

20.Fung TS and Liu DX (2019) The ER stress sensor IRE1 and MAP kinase ERK modulate autophagy induction in cells infected with coronavirus infectious bronchitis virus. Virology 533:34-44. doi: 10.1016/j.virol.2019.05.002

21.Abdoli A, Alirezaei M, Mehrbod P and Forouzanfar F (2018) Autophagy: The multi-purpose bridge in viral infections and host cells. Rev Med Virol 28:e1973. doi: 10.1002/rmv.1973

22.Mao J, Lin E, He L, Yu J, Tan P and Zhou Y (2019) Autophagy and Viral Infection. Adv Exp Med Biol 1209:55-78. doi: 10.1007/978-981-15-0606-2_5

23.Prentice E, McAuliffe J, Lu X, Subbarao K and Denison MR (2004) Identification and characterization of severe acute respiratory syndrome coronavirus replicase proteins. J Virol 78:9977-86. doi: 10.1128/JVI.78.18.9977-9986.2004

24.Cottam EM, Maier HJ, Manifava M, Vaux LC, Chandra-Schoenfelder P, Gerner W, Britton P, Ktistakis NT and Wileman T (2011) Coronavirus nsp6 proteins generate autophagosomes from the endoplasmic reticulum via an omegasome intermediate. Autophagy 7:1335-47. doi: 10.4161/auto.7.11.16642

25.Chen X, Wang K, Xing Y, Tu J, Yang X, Zhao Q, Li K and Chen Z (2014) Coronavirus membrane-associated papain-like proteases induce autophagy through interacting with Beclin1 to negatively regulate antiviral innate immunity. Protein Cell 5:912-27. doi: 10.1007/s13238-014-0104-6

26.Gassen NC, Niemeyer D, Muth D, Corman VM, Martinelli S, Gassen A, Hafner K, Papies J, Mösbauer K, Zellner A, Zannas AS, Herrmann A, Holsboer F, Brack-Werner R, Boshart M, Müller-Myhsok B, Drosten C, Müller MA and Rein T (2019) SKP2 attenuates autophagy through Beclin1-ubiquitination and its inhibition reduces MERS-Coronavirus infection. Nat Commun 10:5770. doi: 10.1038/s41467-019-13659-4

27.Gassen NC, Papies J, Bajaj T, Dethloff F, Emanuel J, Weckmann K, Heinz DE, Heinemann N, Lennarz M, Richter A, Niemeyer D, Corman VM, Giavalisco P, Drosten C and Müller MA (2020) Analysis of SARS-CoV-2-controlled autophagy reveals spermidine, MK-2206, and niclosamide as putative antiviral therapeutics. bioRxiv:2020.04.15.997254. doi: 10.1101/2020.04.15.997254

28.Zhao Z, Thackray LB, Miller BC, Lynn TM, Becker MM, Ward E, Mizushima NN, Denison MR and Virgin HWt (2007) Coronavirus replication does not require the autophagy gene ATG5. Autophagy 3:581-5. doi: 10.4161/auto.4782

29.Schneider M, Ackermann K, Stuart M, Wex C, Protzer U, Schatzl HM and Gilch S (2012) Severe acute respiratory syndrome coronavirus replication is severely impaired by MG132 due to proteasome-independent inhibition of M-calpain. J Virol 86:10112-22. doi: 10.1128/JVI.01001-12

30.Mauthe M, Orhon I, Rocchi C, Zhou X, Luhr M, Hijlkema KJ, Coppes RP, Engedal N, Mari M and Reggiori F (2018) Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. Autophagy 14:1435-1455. doi: 10.1080/15548627.2018.1474314

31.Savarino A, Di Trani L, Donatelli I, Cauda R and Cassone A (2006) New insights into the antiviral effects of chloroquine. Lancet Infect Dis 6:67-9. doi: 10.1016/s1473-3099(06)70361-9

32.Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, Li Y, Hu Z, Zhong W and Wang M (2020) Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 6:16. doi: 10.1038/s41421-020-0156-0

33.Shojaei S, Koleini N, Samiei E, Aghaei M, Cole LK, Alizadeh J, Islam MI, Vosoughi AR, Albokashy M, Butterfield Y, Marzban H, Xu F, Thliveris J, Kardami E, Hatch GM, Eftekharpour E, Akbari M, Hombach-Klonisch S, Klonisch T and Ghavami S (2020) Simvastatin increases temozolomide-induced cell death by targeting the fusion of autophagosomes and lysosomes. FEBS J 287:1005-1034. doi: 10.1111/febs.15069