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Review

Interplay between autophagy and coronavirus: autophagy mechanism

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Summary

Regardless of the fascinating progress of humanity, biotechnology and medicine, the outbreak of the global pandemic of the SARS-CoV-2 virus has shown us that we are just as vulnerable as in previous eras when communicable diseases decimated the world's population. But the discoveries made so far at the molecular level allow us to connect knowledge interdisciplinary and find solutions and therapeutic strategies where there seems to be no link. It was the previous coronavirus infections that served as a homologous model for finding the connection between the SARS-CoV-2 virus and autophagy. Autophagy, a conserved universal process of all eukaryotic cells responsible for cell survival under stressful circumstances, has been shown to play a significant role in viral invasions. It contributes to both direct and indirect antiviral responses such the elimination of viruses, the presentation of their antigens, and the reduction of inflammatory responses. The autophagy machinery of host cells can, however, be suppressed, evaded, or used by viruses to their benefit. Therefore, autophagy has an ambiguous role in coronavirus-related infections, especially in COVID-19.

Keywords: COVID-19, pandemic, autophagy, SARS-CoV-2 virus

Introduction

Autophagy makes a contribution to to a huge number of diseases, and bacterial and viral infections. Since autophagy is a process used to break down damaged organelles, pathogens, and cells, it aids in cell survival under conditions of deprivation, metabolic stress, and hypoxemia. If improperly activated, autophagy can promote type I cell death (apoptosis) or function as an alternative pathway of cell death, known as autophagic cell death (type II). Autophagy can support in the cancer cell death or operate as a protective mechanism against apoptotic or necrotic death carried on by a wide range of factors [1].

The interaction between autophagy and coronavirus (CoV) infections has received a lot of attention, and numerous hypotheses have been put out to provide light on the underlying molecular mechanisms. According to research, autophagy may play a role in antiviral reactions such the elimination of viruses, the presentation of their antigens, and the inflammatory responses reduction [2]. A type of selective autophagy known as xenophagy involves the capture of viruses, antigens produced from viruses, and viral components by autophagy receptors [3]. Viruses, on the other hand, can block, escape, or use the host cells' autophagy and autophagy-related genes (ATG) proteins to replicate or to manipulate the autophagy to interfere with the cells' antiviral defenses [4, 5]. Therefore, the autophagy is ambiguous in CoV-associated infections, particularly COVID-19 [6].

When autophagy is mentioned, macroautophagy, the best studied process is usually meant, although there are two other autophagy forms, microautophagy and chaperone-mediated autophagy. Chaperone-mediated autophagy is found in higher eukaryotes. Chaperones bind to a specific protein causing its unfolding and enabling it to get through the lysosomal membrane. In microautophagy, the cytoplasmic cargo reaches the lysosome by invagination. Macroautophagy (known as autophagy) is followed by autophagosome formation, a double membrane vesicle (DMV) that encompasses the cytoplasmic cargo, then merging with a lysosome for degradation of cargo.

The process of autophagy includes several phases: initiation, nucleation, membrane closure and maturation, fusion with lysosomes, and degradation of cargo. Each step is regulated by a specific Atg protein [7].

Several classes of Atg proteins are responsible for the formation of autophagosomes: Atg1 kinase and its regulators, phosphatidylinositol 3-kinase complex (PI3K), Atg9, Atg2-Atg18 complex as well as two ubiquitin conjugation systems [7].

Formation of autophagosome begins at the location where phagophores are assembled (PAS) identified in yeast. PAS is a preautophagosomal structure built of Atg protein [8]. Equivalent structure, omegasome is present on the mammalian endoplasmic reticulum (ER) [9].

After initiation, double membrane grows, and in that phase it is called phagophora or isolation membrane. As the membrane grows, it takes on a spherical shape, encompasses the cargo for transport and seal ends to form autophagosome.

Once formed, it can fuse with another autophagosome or with an early or late endosome, forming organelles, amphisomes, before fusion into lysosomes which product is termed autolysosome. In the second case, it can directly merge with lysosome in autolysosome [10].

Nonselective and selective autophagy

Autophagy can be either selective or non-selective. Non-selective autophagy, which degrades non-specific cytoplasmic content, occurs as a response to a lack of nutrients and energy, with the goal of cell survival. Selective autophagy is involved in cell maintenance and homeostasis. Specific content can be mitochondria, peroxisomes, proteins or microorganisms [11].

Using ubiquitination, cells identify content for selective degradation. The ubiquitin-binding protein sequestosome 1 (SQSTM1/p62) targets viruses and bacteria that are degraded by xenophagy (also known as virophagy) [12]. SQSTM1 functions as an adaptor protein that reacts with phosphatidylethanolamine modified microtubule-associated proteins 1A/1B light chain 3B (LC3-II), resulting in aggrephagy, a type of specific macroautophagy of protein aggregates [13]. Other receptors involved in tagging proteins or pathogens to autophagosomes include NBR1 and optineurin (OPTN) [14].

Autophagy phases

Induction/initiation

Initiation of autophagosome formation begins with the formation of the ULK-mAtg13-FIP200-Atg101 complex. During nutrient-rich conditions, the ULK-mAtg13-FIP200-Atg101 complex is primarily present in the cytosol. Complex becomes inactivate by mammalian target of rapamycin (mTORC1). During nutrient-rich conditions, the direct interaction of raptor (mTORC1 subunit) and ULK1 leads to the phosphorylation of ULK1 and mAtg13. During starvation, mTORC1 does not interact with the ULK complex, which results in dephosphorylation, and thus activation of the ULK complex [15].

Nucleation

To form an autophagosome, phosphatidylinositol 3-phosphate (PI3P) is necessary. Class III phosphatidylinositol 3 kinase (PI3K; hVps34) generates PI3P. Mammals have two hVps34 complexes that play a role in endosomal transport or fusion of autophagosomes and lysosomes through interaction with UVRAG (UV irradiation resistance-associated gene) and Rubicon (or KIAA0226, Run domain protein as Beclin 1interacting and cysteine rich containing).

Regulation of the PI3K complex occurs through the interaction of beclin 1 (BECN1), which is necessary for autophagy, and other proteins. The antiapoptotic protein Bcl-2 binds beclin 1 preventing its interaction with PIK3C3 inhibiting autophagy [16]. Rubicon inhibits PIK3C3 activity in the UVRAG-PI3K complex [12]. AMBRA1, which binds directly to Beclin 1, and Bif 1, which through UVRAG interacts with Beclin 1 and participates in forming the shape (rounding) of the membrane are two positive regulators of the PI3K complex [17].

Another category of PI3P effectors are WD-repeat proteins that interact with phosphoinositides (WIPI)1-4. WIPI2 is essential for the maturation of omegasomes in autophagosome [18].

Elongation

There are two ubiquitin conjugation systems (UBL), Atg12 and LC3, in the last stages of autophagosome formation, which contribute to the growth and closure of the membrane [19].

Atg12 conjugates with Atg5 protein. On the isolation of the membrane's outer surface, Atg16L attaches to the Atg12-Atg5 complex and breaks from the membrane that was just before or exactly after autophagosome formation [19].

Another UBL system is ubiquitin-like protein LC3, produced as precursor and processed by the cysteine protease Atg4. The Atg4-processed form of LC3 is marked as LC3-I, and it covalently bound to the amino group of phosphatidylethanolamine (PE), and then is marked as LC3-II. LC3-II is membrane-bound, located on the isolation membrane and on the autophagosome, and has a role in membrane binding (joining opposite ends of a growing membrane) [20].

Autophagosome maturation and fusion with endosome/lysosome

The last step of macroautophagy is the maturation of the phagophore, which closes in the finalized autophagosome and fuses with an endosome or lysosome, resulting in the formation of an autolysosome. Microtubules allow autophagosomes to move to lysosomes [21].

Regulation of autophagy

Regulation of autophagy is controlled by the mTOR (mammalian target of rapamycin) pathway, which negatively regulates this process. Autophagy is controlled by a number of signaling pathways downstream of mTOR, namely

control of autophagy downstream of mTOR by the ULK1-Atg13-FIP200 complex, control of autophagy by amino acid deficiency via Rag/mTOR1, control of autophagy by growth factors via PI3KC1a/Akt/TSC /mTORC1 and the control of autophagy through stress and deprivation of energy via AMPK/TSC/mTORC1 [22].

In addition to classical mTOR autophagy, there have also been described mTOR-independent autophagy control pathways, such as the inositol signaling pathway, Ca2+/calpamin pathway, cAMP/Epac/Ins(1,4,5)P3 pathway, JNK1/Beclin-1/PI3KC3 pathway. Also, there are autophagy control pathways by other mTOR-independent small molecules which mechanism has not yet been described [22].

In CoV infection, mTOR activation of autophagy occurs, although due to the alarming disruption of cellular stability, other autophagy pathways are also linked to viral infection [23].

Autophagy antiviral mechanisms of SARS-CoV-2 virus infection

In viral infections, AMP-activated protein kinase (AMPK) activates PI3K/protein kinase B while suppressing the mammalian target of rapamycin complex 1 (mTORC1) (Akt1), which as result have autophagy induction and virion encapsulation. After that, the formation of autophagosomes is activated, which then fuse with lysosomes to eliminate its viral content [24]. But, SARS-CoV-2 might have specific mechanisms of avoiding the autophagy-mediated cellular clearance [25]. Therefore, drug-targeting of escape mechanisms can attenuate viral replication. By interfering with various metabolic pathways, such as the regulation of glycolysis by inhibiting AMPK and mTORC1 [26], SARS-CoV-2 may decrease the level of autophagic flow. This may prevent the viral replication of substances like spermidine, which are pro-autophagic. Studies indicated that ACE2 is SARS-CoV-2 the entry receptor, as well as SARS-CoV-1 [27, 28]. Indeed, ACE2 can prevent lung cell autophagy and reduce cell death [28].

Autophagy proviral mechanisms in SARS-CoV-2 virus infection

Based on the finding that the ATG12 and LC3 proteins were linked to the formation of DMVs during the course of the infection of Vero cells infected with mouse hepatitis virus (MHV), it was suggested that viral replication may involve autophagy [29]. In cells infected with SARS-CoVs, studies have shown that replicase proteins co-localize to complexes in cytoplasma that contain markers for autophagosome membranes, such as LC3 [30]. It has been discovered that NSP6, the viral replicase protein of Avian CoV, can induce the production of autophagosomes with Atg5 and LC3II [31], block further autophagosome expansion, and inhibit the transfer of the virus to the lysosome [32]. The papain-like protease PLP2 (PLP2-TM) of CoVs was identified to interact with LC3 and Beclin-1, increasing autophagosome flux and inhibiting autophagosomes from fusing to lysosomes [33].

Drugs affecting the autophagic pathway in SARS-CoV-2 virus infection

There are a number of autophagy modulators which are described as a part of communicable and non-comunicable disease therapy. Therapeutic effects of these drugs on the patient during SARS-CoV, MERS-CoV and SARS-CoV2 infection have been also under investigation.

Chloroquine and its derivates, which are used as antimalaric and anti-inflammatory drugs, manifest some pleiotropic characteristics. Chloroquine has potential of lysosome

acidic hydrolases inhibition. Beside these effects, it can lead to autophagosome accumulation with consequential cell death and viral components elimination [34]. From the other hand, in vivo investigation, conducted in mices, showed that chloroquine reduces lung injury during COVID 19 infection, which indicates effects independent from viral replication [35].

Rapamycin and its analogs, as mTORC1 inhibitors, affect many different physiological aspects, such as immune response in mammals [36]. This drug shows similar effect on coronavirus cellular replication as mTORC1 and related kinases. During SARS-CoV and SARS-CoV2 infection autophagic flux seems to be increased because of mTORC1 inhibition, contrary to MERS-CoV infection, when mTORC1 phosphorylation and kinase activity is increased [36].

AMPK activators, also known as autophagy initiators, during SARS-CoV2 infection can be connected with increased level of viral replication. Suprisingly, Bramante and associates demonstrated that metformin (an AMPK activator) treated patients show lower mortality rates but autophagy involment in this case is still not evaluated [37, 38].

Sorafenib is a multikinase inhibitor, which also can initiate autophagy process, by inhibiting mTOR signaling and AMPK phosphorylation promoting [39]. Because of capability of inhibition MERS-CoV and SARS-CoV2 *in vitro* replication, it is considered as promising pharmaceutical for future clinical evaluation [40].

Statins are recently recognized as autophagy inducers. Although the mode of autophagy initiation is not completely studied yet, it is considered that they can inhibit mTORC1 activity [41]. They are traditionally aplied as a part of coronary heart disease therapy, but recent pandemic demonstrated that patients under long term treatment shows a lower risk for severe form of SARS-CoV2 infection. It is believed that this protective effect of statins comes from theirs anti-inflamatory features [41, 42].

Ivermectin represents an antiparasitic pharamceutical, which also posses in vitro antiviral activity. It also can induce autophagy by regulation of mTOR/AMPK pathway [43]. Among other effects, this drug can influence some physiologic activities, as well as some viral enzymes, such as RNA-dependent RNA polymerase and 3-chymotrypsin like protease [44].

Modulators that target lysosomal biogenesis promise some positive effects regarding MERS-CoV and SARS-CoV2 replication [38, 45]. As known, merging between autophagosome and lysosome can put pro-inflammatory pathway under the control and decrease potential damage. Curcumin, digoxin, niclosamide, quercetin, resveratrol and valinomycin are some of modulators which are belonging to this group and that can be used as a potential part of coronavirus therapy [46, 47, 48, 49].

There are some cellular stressors described, which can initiate autophagy after exposure to ROS stress. Pharmaceuticals such as plumbagin and tunicamycin theoretically can be applied in the coronavirus treatment, but theiz clinical evaluation is difficult because they posses important toxity [50].

Conclusion

The review highlights how autophagy has been directly associated to SARS-CoV-2 infection. Control of autophagy is a crucial regulatory step, as we are aware, in various different communicable and non-communicable diseases. Unfortunately there have not been much data reported on autophagy regulation in COVID-19. Therefore, it is essential to understand mechanisms of autophagy, and to provide newer opportunities for treatment in COVID-19 therapy with autophagy modulators in COVID-19 patients.

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Međuigra autofagije i koronavirusa: mehanizam autofagije

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Bosna i Hercegovina

Bez obzira na fascinantan napredak čovječanstva, biotehnologije i medicine, izbijanje globalne pandemije SARS-CoV-2 virusa nam je pokazalo da smo jednako ranjivi kao i u prethodnim epohama kada su zarazne bolesti desetkovale svjetsku populaciju. Ali, dosadašnja otkrića na molekularnom nivou nam omogućavaju interdisciplinarna povezivanja znanja i pronalazak rješenja i terapeutskih strategija gdje naizgled nema spone. Upravo su dosadašnje infekcije koronavirusa poslužile kao homologi model za pronalazak veze između SARS-CoV-2 virusa i autofagije. Autofagija, konzerviran univerzalni proces svih ćelija eukariota zaslužan za preživljavanje ćelije u stresnim okolnostima, je pokazala da ima značajnu ulogu u invazijama virusa. Uključena je u direktne i indirektne antivirusne odgovore kao što su uklanjanje virusa, prezentacija njihovih antigena, smanjenje inflamatornih odgovora. Međutim, virusi mogu da potisnu, pobjegnu ili iskoriste mašineriju autofagije ćelija domaćina da bi se replicirali ili modifikovali autofagiju u svoju korist. Stoga, autofagija ima dvosmislenu ulogu kod infekcija povezanih sa koronavirusom, posebno kod COVID-19.

Ključne riječi: COVID-19, pandemija, autofagija, SARS-CoV-2 virus