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COMMENTARY AND VIEWS

Autophagy/virophagy: a "disposal strategy" to combat COVID-19

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ABSTRACT

Given the devastating consequences of the current COVID-19 pandemic and its impact on all of us, the question arises as to whether manipulating the cellular degradation (recycling, waste disposal) mechanism known as macroautophagy/autophagy (in particular, the selective degradation of virus particles, termed virophagy) might be a beneficial approach to fight the novel coronavirus, SARS-CoV-2. Knowing that "autophagy can reprocess everything", it seems almost inevitable that, sooner rather than later, a further hypothesis-driven work will detail the role of virophagy as a fundamental "disposal strategy" against COVID-19, yielding most needed therapeutic interventions.

Abbreviations: ATG, autophagy-related; CoV/CoVs coronavirus/coronaviruses; COVID-19, coronavirus disease 2019; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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The outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) across the planet has emerged rapidly and unexpectedly as a global public health emergency by causing coronavirus disease 2019 (COVID-19), unprecedented chaos and panic, and a myriad of events affecting healthcare and socioeconomic well-being [1]. While instantaneous prevention, drastic social distancing and isolation measures implemented by worldwide governments and health organizations in control of the rapid spread of SARS-CoV-2 virus are absolutely essential, scientists around the world have quickly engaged in the challenging race against time by studying the basic cellular and molecular mechanisms/processes that can be used to fend off pathogenic coronaviruses (CoVs) (namely, SARS-CoV and its relatives, Middle East respiratory syndrome coronavirus [MERS-CoV] and the novel SARS-CoV-2) in humans as well as searching for effective therapeutic strategies against this deadly virus. Autophagy is one of these basic/fundamental and evolutionarily conserved cellular processes that "touches" every corner of the cell in terms of metabolism, regulation, membrane dynamics and, most prominently, intracellular degradation (also known as cellular recycling or waste disposal) [1–6].

Autophagy, in all its various forms, is responsible for (non) selective degradation of a divergent cellular cargo of unwanted, superfluous, harmful and defective cellular components (e.g., long-lived proteins, lipids, protein aggregates) enabling cells to quickly and efficiently generate recycled basic building materials/constituents (e.g., amino acids, fatty acids) and secure a sufficient energy supply in the face of a wide range of nutritional deficiencies, physiological conditions and pathophysiological cues, in order to increase fitness at a cellular level and consequently at the organismal level. Additionally, as a multi-step and well-orchestrated (i.e., regulated by over 40 autophagy-related [ATG] proteins and numerous auxiliary/accessory proteins) process for maintaining homeostasis in the complex landscape of the eukaryotic cell, autophagy is the only pathway that is capable of degrading entire cellular organelles (e.g., mitochondria, peroxisomes, endoplasmic reticulum, the nucleus) and invading pathogens, including fungi, parasites, bacteria and viruses either randomly or in a targeted/selected fashion. Selective autophagy captures its cargo via the recruitment of selective autophagy receptors, including those involved in the autophagic degradation of viruses and viral-derived antigens via a specialized form of selective autophagy known as xenophagy (also termed virophagy, when referring to viruses) [7–11].

In the case of human viral infections, the induction of virophagy can be either proviral or antiviral. On the one hand, with regard to proviral virophagy, invading viruses have evolved strategies to escape, hijack, subvert, manipulate or even inhibit virophagic machinery, giving them replicative benefits. At present, various scientific (sometimes controversial) reports have converged on two important questions: whether CoVs induce virophagy, and whether the virophagy machinery and/or ATG proteins are involved in the infection and replication of CoVs. There is scientific evidence (with some discrepancies probably due to different viruses used, different cells tested and even the different techniques used in the study of virophagy/autophagy) indicating that virophagy plays an important role in viral replication and pathogenesis with CoVs, poliovirus, hepatitis C virus and dengue virus, which are all known to stimulate and require virophagy for accelerated replication. Therefore, inducing

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autophagy could have adverse consequences for the overall disposal of these viruses, and there would be clear limits to the potential of autophagy/virophagy induction to fight viral infections. However, several subsequent studies have challenged the notion that virophagy is implicated in CoV infection. Thus, these observations suggest that the virophagy machinery is not directly implicated in the viral replication process, and it appears that there is a certain type of interplay between the virophagy machinery and CoVs, with the exact nature of such interactions to be further elucidated [1–6,10,12–15].

On the other hand, antiviral virophagy can: (1) selectively target viruses for degradation, (2) promote virus recognition and inflammatory cytokine responses, (3) regulate inflammation, (4) control cell survival, (5) promote antigen presentation and/or (6) be regulated in a paracrine-mediated fashion, a departure from the classic cell autonomous route. Intriguingly, a body of evidence indicates that CoVs may actually inhibit autophagy, which in turn suggests an antiviral role for autophagy. Accordingly, a number of studies have shown that increasing autophagic capacity may be beneficial against CoVs infection. Additionally, some specific accessory proteins, which by definition are not essential for CoVs replication but are involved in the modulation of host cells and immune evasion, may represent targets for reducing the autophagy-inhibitory effects of CoVs. While data regarding such attempts remain preliminary at this stage, we can speculate that autophagy/virophagy might be a possible druggable target for therapeutic interventions [1–6,10,12–15].

In the past two decades, the implication of virophagy in CoVs infection has attracted substantial attention, probably due to the following: (1) the SARS outbreak in 2002–2003, (2) the MERS-CoV outbreak in 2012, (3) the SARS-CoV-2 outbreak in 2019 and (4) the emerging field of autophagy research during the same period. The existing and newly-generated scientific evidence and publications allow for speculation that autophagy/virophagy induction might counteract CoV infection at different levels, although more specific data are certainly required. Irrespective of whether autophagy/virophagy modulation will eventually be part of the "disposal strategies" in the fight against COVID-19, it is essential to further establish and secure global healthcare as well as to promote and extend robust research including the potential role of autophagy/virophagy as it pertains to infectious diseases, including CoVs [1–15]. The biomedical research enterprise, scientists and researchers, including auto-phagy researchers, are more than willing to respond to the challenge of COVID-19; however, it has become apparent that much needed coordination among important constituencies is lacking. Therefore, it will certainly require a close academia-industry/biopharmaceuticals-government partnership in order to establish goals, set timetables, and form focused groups to deal with specific COVID-19 issues and make rapid progress in a collaborative framework for prioritizing therapeutic candidates and vaccines with predicted successful outcomes in order to minimize and even eliminate future CoVs/COVID-19-related hospitalizations and deaths.

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