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## Autophagy and treatment of patients with COVID-19; which drugs target the autophagy pathway?

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#### *Implication for health policy/practice/research/medical education:*

Autophagy is a way to create new cellular structures, clear cells invaded by microbes, and block accumulating proteins that can cause disease. Moreover, it can destroy all cellular organs and pathogens, including fungi, parasites, bacteria, and viruses, either randomly or selectively. Many research groups are examining a strategy to combat COVID-19. In particular, research is underway to identify drugs that can target autophagy in COVID-19 virus infection. Several known drugs are currently under clinical evaluation for the autophagy process, given that regulating autophagy is a way to combat COVID-19. This study introduces drugs that target the autophagy pathway.

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Autophagy is an evolutionary process for removing damaged organelles or malfunctioning intracellular proteins by the autophagosome's bilayer membrane, which eventually combines with the lysosome (1). The process is the only pathway that can destroy all cellular organs and pathogens, including fungi, parasites, bacteria, and viruses, either randomly or selectively (2). Various known agents are currently under clinical consideration for the autophagy process, including aminoquinoline (CQ) and hydroxychloroquine (HCQ) derivatives (3). According to the study by Bonam et al

on chloroquine (CQ)/ HCQ, compounds targeting the autophagy pathway may be suitable for treating patients with COVID-19 (3). These compounds are endosome/lysosome regulators that target intracellular organs in autophagy processes (4).

The initial hypothesis was that the Covid-19 virus could disrupt the replication complexes of dual membrane vesicles (5). Evidence suggests that Covid-19 can inhibit autophagy (6). SARS-CoV-2 enters host cells by angiotensin-converting enzyme 2 (ACE2) receptors. Following fusion with the cell and lysosomal membrane

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and subsequent uncovering of the viral nucleocapsid in the cytoplasm, the virus's replication process begins. Then, exocytosis mediates the release of replicated virus.

Chloroquine inhibits autophagy by increasing the pH of the endosome/lysosome. Chloroquine hinders lysosomes' enzymatic activity by constructing a basal pH in lysosomes and prevents the integration of viral-lysosomal membranes (3,6). Corticosteroids inhibit autophagy by inhibiting LC3, and some antiviruses, such as lopinavir/ritonavir and ruxolitinib, as well as Interferon alfa-2b can lead to cellular apoptosis by increasing the accumulation of autophagosomes and autolysosomes (7).

Based on a study by Gills et al., nelfinavir causes cell death through different pathways, including caspase-dependent apoptosis, non-apoptotic death, and inducing endoplasmic reticulum stress and autophagy. It also inhibits growth factor receptor activation and disrupts Akt growth-dependent signaling. It inhibits tumor growth and regulates endoplasmic reticulum stress markers, autophagy, and apoptosis. Currently, some scientists are testing nelfinavir in phase I clinical trials of cancer treatment (8). Another study indicated that Lys05 is a new type of lysosomal autophagy inhibitor, which can be used in anti-cancer products (9). Wang et al represented that nitazoxanide inhibited cell growth by up-regulating ING1 (inhibitor of growth family member 1) expression and stopped the cell cycle. Nitazoxanide suppressed autophagy by blocking late-stage lysosome acidification, reducing ING1 cleavage. They also revealed that as an autophagy inhibitor, nitazoxanide stopped the cell cycle by upregulating ING1 expression due to increased transcription and reduced post-translational degradation by late-stage autophagy inhibition (10).

The PI3K/AKT/mTOR pathway is often overactive in endometrial cancer (EC). We evaluate the effect of ABTL0812, a new first-class molecule that offers a unique mechanism of action to inhibit this pathway (11). ABTL0812 modulates TRIB3 expression and thus inhibits the PI3K/AKT/mTOR axis and induces autophagy cell death. Therapeutic effects of ABTL0812 have been shown in vivo. ABTL0812 increases TRIB3 mRNA levels. TRIB3 mRNA levels can use ABTL0812 treatment monitoring (12). MSL is an autophagy enhancer that activates calcineurin and induces dephosphorylation/nuclear transfer of transcription factor EB (TFEB), the major regulator of lysosomal biogenesis and autophagy gene expression (13).

#### Authors' contribution

Primary draft by EAD, SD, SS, DH and AHD. First edit by ZM and NK. Second edit by LS. Finalization by MAS and AHD. All authors read and signed the final paper.

#### Conflicts of interest

The authors declare that there is no conflict of interest.

#### Ethical considerations

The authors have entirely observed ethical issues (including plagiarism, informed consent, misconduct, data fabrication, falsification, double publication, submission, and redundancy).

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