Actively or passively deacidified lysosomes push β-coronavirus egress

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In a very recent issue of Cell, Ghosh et al. describe how β-coronaviruses utilize deacidified lysosomes to egress from the infected cells and impair antigen presentation process1. This deacidified lysosome-mediated trafficking can be blocked by the Rab7 GTPase competitive inhibitor CID1067700 and alleviates β-coronavirus spread1.

SARS-CoV-2, one member of β-coronaviruses, breaks out all over the world in late 20192. Although remdesivir, hydroxychloroquine, and other targeted drugs were tested in SARS-CoV-2 treatment, until now, there is no fully effective cure and vaccine3-5. What gives us a glimmer of hope is: not all people exposed to SARS-CoV-2 were infected and not all infected patients developed severe respiratory diseases6,7. This shows that the way the virus enters, replicates, and exits vary from person to person. A series of studies on SARS-CoV-2 have been reported, and the details of β-coronavirus entry and replication in the host cells have been understood, however, how newly assembled viruses egress from the host cells is still unclear. Now, Ghosh et al. made new and important contributions to help understand this unconventional egress process by describing that β-coronaviruses traffic to lysosomes and egress by Arl8b-dependent lysosomal exocytosis1. This non-lytic release happens with the lysosome deacidification, limited lysosomal degradation enzyme activation, and impaired antigen presentation1. This deacidified lysosome-dependent exocytosis may be the reason why it is difficult for the host to generate an efficient antivirus immune response and antibody production.

The interface between β-coronaviruses and host cells largely determines the infection and spread of the viruses. The egress pathway of β-coronaviruses has been assumed as a biosynthetic secretory vesicle-dependent plasma membrane trafficking manner9. The newly synthesized genomic RNA of β-coronaviruses is coated by virus N proteins and subsequently budding into ER–Golgi for the next process of egress trafficking. Nevertheless, Ghosh et al. verified the above hypothesis and found that is not the case. Brefeldin A (BFA), a small molecule for shutting down all anterograde biosynthetic secretory traffic from the ER/ERGIC out to the plasma membrane, has no effect on the egress of β-coronaviruses1. In addition, β-coronaviruses are enriched in the late endosomes and lysosomes during egress, and Rab7 inhibitor significantly inhibits β-coronavirus egress through interrupting biogenesis and maintenance of lysosomes. Therefore, β-coronavirus egress is dependent on a lysosomal manner, but not the previously assumed biosynthetic secretory pathway.

When a large number of β-coronaviruses are generated in the cells, the new viruses actively invade the lysosomes, or the lysosomes swallow the new viruses. Ghosh et al. found that plasma membrane LAMP1 levels have ~2.5-fold increase in the infected cells, indicating obvious fusion of lysosomes with the plasma membrane3. In addition, about two-fold increased cathepsin D and three-fold increased pro-cathepsin D secreted to the extra-cellular media of the infected cells, and the further research confirmed that lysosomes are deacidified and lysosomal enzymes are inactive in β-coronavirus-infected cells1. Given that acidified lysosomes are important for protease processing and antigen presentation of antigen-presenting cells (APCs), the β-coronavirus infection must be bound to affect the host’s immune response. This coincides with the clinical phenomenon that susceptible COVID-19 patients cannot utilize the immune system to
Fig. 1 Actively or passively deacidified lysosomes push β-coronavirus egress. Lysosomal deacidification may be caused by β-coronavirus infection, or the infected cells actively deacidify lysosomes to release newly generated β-coronaviruses for relieving their own viral burden.
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