

## COMMENTARY

# May we target double-membrane vesicles and oxysterol-binding protein to combat SARS-CoV-2 infection?

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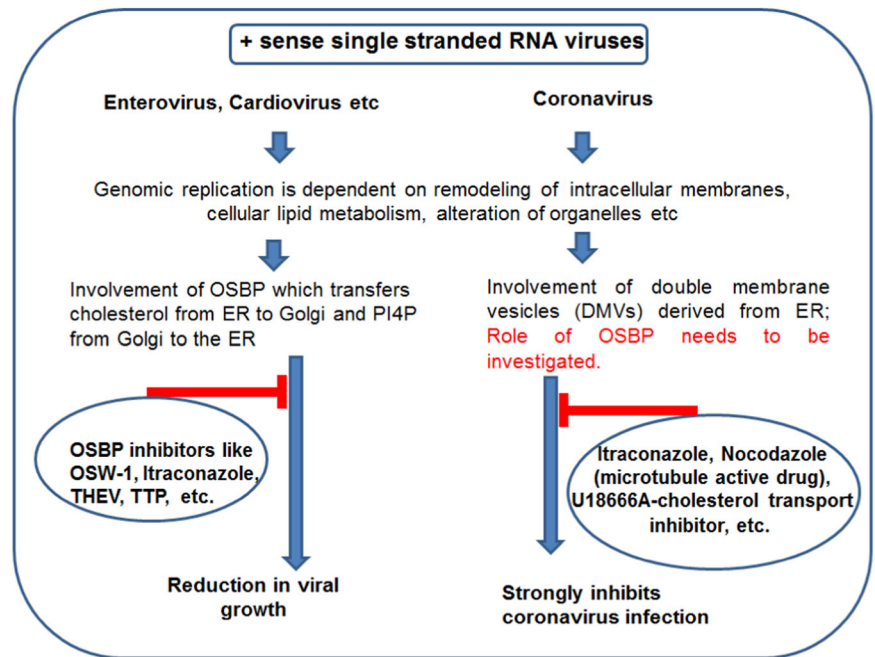
Since the first human infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in the Hubei (Wuhan) province of China, the world has been facing a relentless degree of socioeconomic and medical crisis. The disease of SARS-CoV-2 infection which is now called the coronavirus disease 2019 (COVID-19) pandemic has spread to several countries across the globe (Nicastrì et al., 2020). The symptoms of SARS-CoV-2 are similar to flu and usually include fever, cough, shortness of breath, and muscle ache (Huang et al., 2020). Although several drugs have been identified to be effective in SARS-CoV-2 infection in vitro and some anecdotal evidence presented for a handful of repurposed drugs, an effective treatment for COVID-19 has not yet been introduced (Yang et al., 2020). From those tried so far, concomitant use of antiviral and anti-inflammatory drugs as supportive therapy has been suggested to be effective in reducing the severity of SARS-CoV-2 (Stebbing et al., 2020). The various approaches for suppressing SARS-CoV-2 infection and/or COVID-19 therapy include inhibiting the RNA-dependent RNA polymerase, inhibiting the viral protease, blocking virus-cell membrane fusion, enhancing the innate immune system, attenuating the inflammatory response, symptomatic control, vaccine, and pathogen-specific artificial antigen-presenting cells (Tu et al., 2020). Considering the lengthy process of novel drug discovery programs, and the unprecedented level of the human and economic cost of the disease, repurposing the Food and Drug Administration-approved medications appear to be the best available option at this very moment. In this regard, reviewing the

lesson learned from the pathogenicity and therapeutic options for other related viruses is critical (Figure 1).

Coronavirus replication involves the formation of double-membrane vesicles (DMVs) derived from the endoplasmic reticulum (ER) in which the replication-transcription complexes (RTCs) composed of nonstructural proteins (nsp3, nsp4, and nsp6) are anchored (Angelini, Akhlaghpour, Neuman, & Buchmeier, 2013). Inhibition of DMV formation at an early step of the viral life cycle can prevent viral infection by impairing viral RNA synthesis. One such compound identified is K22, which suppresses both animal and human coronavirus replication by interacting with nsp6, the membrane-spanning integral component of RTC, present in DMV (Lundin et al., 2014). Nsp6 mutants display K22 resistance suggesting the inhibitory role of K22 in viral RNA synthesis. K22 has been found to have a virucidal effect against diverse lineages of *Nidoviruses* and members of *Flaviviridae*, suggesting its involvement in a critical and conserved step during viral replication (Rappe et al., 2018). More studies should be conducted on inhibitors of DMVs as they can be used as broad-spectrum antivirals.

Another target can be oxysterol-binding protein (OSBP), a lipid-binding protein found in all eukaryotes with a high affinity for 25-hydroxycholesterol and other oxysterols (Pietrangolo & Ridgway, 2018). Among the various known cellular functions of OSBP is a transfer of cholesterol in contact with membranes sites from ER to Golgi, while countertransporting phosphoinositide 4-phosphate

**FIGURE 1** Inhibitors of double-membrane vesicles and oxysterol-binding protein (OSBP) for coronavirus disease 2019. ER, endoplasmic reticulum



back to the ER (Mesmin et al., 2017). Some studies show that OSBP has an essential role in the proliferation of RNA viruses (Albulescu et al., 2015). For example, its critical role in enterovirus replication has been well-established and while the protein-ligand (OSW-1) inhibits viral replication in a nanomolar concentration range, over-expression of OSBP appears to rescue viral pathogenicity (Nchoutmboube, Ford-Siltz, & Belov, 2015). Interestingly, the enteroviruses (family Picornaviridae) are positive-strand RNA viruses just like the coronaviruses and their genomic replication is dependent on the remodeling of intracellular membranes (Dorobantu et al., 2015), as well as alteration of organelles/lipids function (Belov & van Kuppeveld, 2012). More importantly, picornavirus infection has been shown to be inhibited by targeting OSBP and some of the identified leads include OSW-1 (Roberts et al., 2018), itraconazole (Bauer et al., 2018), T-00127-HEV-2, and TTP-8307 (Arita, 2014). On the basis of their prophylactic activity against *Enterovirus* replication in vitro, the structure-activity relationship of various OSBP targeting compounds (OSW-1, itraconazole, T-00127-HEV-2, and TTP-8307) has also been established (Roberts et al., 2019). To date, however, neither the role of OSBP in coronavirus infection nor the efficacy of therapeutic agents targeting OSBP in COVID-19 has been studied. In view of the broad range of available OSBP targeting compounds and their established antiviral potential, studies on coronaviruses therapy via OSBP modulation are highly encouraged.

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#### REFERENCES

Albulescu, L., Strating, J. R., Thibaut, H. J., van derLinden, L., Shair, M. D., Neyts, J., & van Kuppeveld, F. J. (2015). Broad-range inhibition of

- enterovirus replication by OSW-1, a natural compound targeting OSBP. *Antiviral Research*, 117, 110–114.
- Angelini, M. M., Akhlaghpour, M., Neuman, B. W., & Buchmeier, M. J. (2013). Severe acute respiratory syndrome coronavirus nonstructural proteins 3, 4, and 6 induce double-membrane vesicles. *mBio*, 4, e00524-13.
- Arita, M. (2014). Phosphatidylinositol-4 kinase III beta and oxysterol-binding protein accumulate unesterified cholesterol on poliovirus-induced membrane structure. *Microbiology and Immunology*, 58, 239–256.
- Bauer, L., Ferla, S., Head, S. A., Bhat, S., Pasunooti, K. K., Shi, W. Q., ... Strating, J. R. (2018). Structure-activity relationship study of itraconazole, a broad-range inhibitor of picornavirus replication that targets oxysterol-binding protein (OSBP). *Antiviral Research*, 156, 55–63.
- Belov, G. A., & vanKuppeveld, F. J. (2012). (+)RNA viruses rewire cellular pathways to build replication organelles. *Current Opinion in Virology*, 2, 740–747.
- Dorobantu, C. M., Albulescu, L., Harak, C., Feng, Q., vanKampen, M., Strating, J. R., ... van Kuppeveld, F. J. (2015). Modulation of the host lipid landscape to promote RNA virus replication: the picornavirus encephalomyocarditis virus converges on the pathway used by hepatitis C virus. *PLoS Pathogens*, 11, e1005185.
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... Cheng, Z. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395, 497–506.
- Lundin, A., Dijkman, R., Bergström, T., Kann, N., Adamiak, B., Hannoun, C., ... Forlenza, M. (2014). Targeting membrane-bound viral RNA synthesis reveals potent inhibition of diverse coronaviruses including the Middle East respiratory syndrome virus. *PLoS Pathogens*, 10, e1004166.
- Mesmin, B., Bigay, J., Polidori, J., Jamecna, D., Lacas-Gervais, S., & Antony, B. (2017). Sterol transfer, PI4P consumption, and control of membrane lipid order by endogenous OSBP. *The EMBO Journal*, 36, 3156–3174.
- Nchoutmboube, J., Ford-Siltz, L. A., & Belov, G. A. (2015). Enterovirus replication: Go with the (counter) flow. *Trends in Microbiology*, 23, 183–184.

- Nicastri, E., Petrosillo, N., Bartoli, T. A., Lepore, L., Mondì, A., Palmieri, F., ... Antinori, A. (2020). National institute for the infectious diseases "L. Spallanzani," IRCCS. Recommendations for COVID-19 clinical management. *Infectious Disease Reports*, *12*, 8543.
- Pietrangelo, A., & Ridgway, N. D. (2018). Bridging the molecular and biological functions of the oxysterol-binding protein family. *Cellular and Molecular Life Sciences*, *75*, 3079–3098.
- Rappe, J. C. F., deWilde, A., Di, H., Müller, C., Stalder, H., V'kovski, P., ... Antinori, A. (2018). Antiviral activity of K22 against members of the order Nidovirales. *Virus Research*, *246*, 28–34.
- Roberts, B. L., Severance, Z. C., Bensen, R. C., Le, A. T., Kothapalli, N. R., Nuñez, J. I., ... Reddig, W. J. (2018). Transient compound treatment induces a multigenerational reduction of oxysterol-binding protein (OSBP) levels and prophylactic antiviral activity. *ACS Chemical Biology*, *14*, 276–287.
- Roberts, B. L., Severance, Z. C., Bensen, R. C., Le-McClain, A. T., Malinky, C. A., Evan, M., & Nunez, J. I. (2019). Differing activities of oxysterol-binding protein (OSBP) targeting anti-viral compounds. *Antiviral Research*, *170*, 104548.
- Stebbing, J., Phelan, A., Griffin, I., Tucker, C., Oechsle, O., Smith, D., & Richardson, P. (2020). COVID-19: Combining antiviral and anti-inflammatory treatments. *The Lancet Infectious Diseases*, *20*, 400–402.
- Tu, Y. F., Chien, C. S., Yarmishyn, A. A., Lin, Y. Y., Luo, Y. H., Lin, Y. T., ... Wang, M. L. (2020). A review of SARS-CoV-2 and the ongoing clinical trials. *International Journal of Molecular Sciences*, *21*, 2657.
- Yang, X., Yu, Y., Xu, J., Shu, H., Liu, H., Wu, Y., ... Wang, Y. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *The Lancet Respiratory Medicine*, *8*, 475–481. [https://doi.org/10.1016/S2213-2600\(20\)30079-5](https://doi.org/10.1016/S2213-2600(20)30079-5)

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