CONCLUSION

METS-MIRAI analysis updated showed that C1QA, C1QB and MAVS/VISA are targeted by SARS-CoV-2 viral miRNAs. Therefore, we found that the C1Q deficiency and MAVS/VISA suppression would be the strategy of SRAS-CoV-2 to evade the host quantum miRNA immunity. We also found that MAVS/VISA deficient haplotype and the complement deficient haplotype in the host could be the deadly risk factor of COVID-19. On the contrary, normal host MAVS/VISA activation by HAUS8 aggregation would be a factor of increasing asymptomatic carriers under the C1Q deficiency by viral infection. Very high frequency (approximate 100 times) of haplotype C79F in Caucasian-American and African-American might cause the death rate difference among ethnic populations. Aged deadly risk in COVID-19 would be dependent on mitochondria senescence.

Although the stem loop 1 and 2 were located into the orf10 in the SARS-CoV-2 genome **(Figure 3)**, C1QA, C1QB and MAVS/VISA deficiencies were augmented by Cov-miR-2 and Cov-miR-4 in the stem loops of the orf10 **(Figures 1 and 4)**. Comparing with SARS coronavirus, the orf10 is a unique insert downstream of N orf **(Figure 3)**. Since loss of smell sense and taste would be the specific symptom of COVID-19, we investigated the neuro-pharmacologic targets. By Target Scan analysis at a ubiquitous network, we found that the 3'UTR of acetylcholine esterase (ACHE) was targeted by hsa-miR-663b, and the seed of miR-663b was partially homologous to that of Cov-miR-2. Therefore, the ACHE 3'UTR were tested to match the 8 seed of Cov-miR-2 **(Figure 4)**. Consequently, we found that the ACHE would be targeted by Cov-miR-2 **(Figure 5)**. Firstly, nerve transmission would be blocked by ACHE suppression; therefore, loss of smell sense and taste would be observed in infected individuals. Secondary, since acetylcholine was increased by suppression of ACHE, inflammation in the lung would be enhanced through the nicotinic acetylcholine receptor on the lung macrophages [42], suppression of heart rate would be induced and finally autonomic imbalance would be happened. In the deadly risk of COVID-19, smoking would cause the increase of the nicotinic acetylcholine receptor rather than the angiotensin-converting enzyme 2 (ACE-2) increasing [43], and then, the nicotinic acetylcholine receptor would enhance inflammation of the lung. If so, anti-choline agents, such as long acting muscarinic antagonist (LAMA) and long acting beta2-agonist (LAMA) would be available for treatment of COVID-19 with corticosteroid ones, which are used for chronic obstructive pulmonary disease (COPD) implicated in the nicotinic acetylcholine receptor gene haplotype [44]. After all, the deadly risk of COVID-19 RNA genome may be specifically explained as the effects of the inserted orf10 ribozyme-like structure **(Figure 5)** because hiv-miR-N367 in the HIV-1 nef/3'LTR region is implicated in HIV-1 clinical symptoms [1].

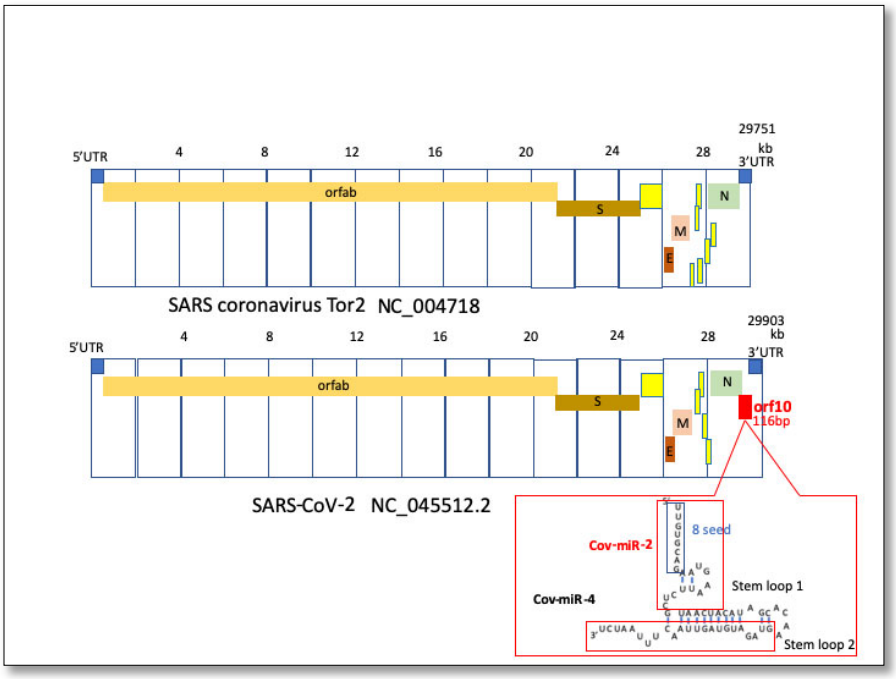

Figure 3. The genome structure of SARS coronaviruses. The RNA genomes of SARS coronavirus Tor2 (the upper panel) and SRAS-CoV-2 (the lower panel) were illustrated as open reading frame (orf). The stem loop 1 and 2 were contained in the orf10 of SARS-CoV-2 genome (red bar). Putative Cov-miR-2 and -4 were derived from stem loop 1 and 2, respectively.

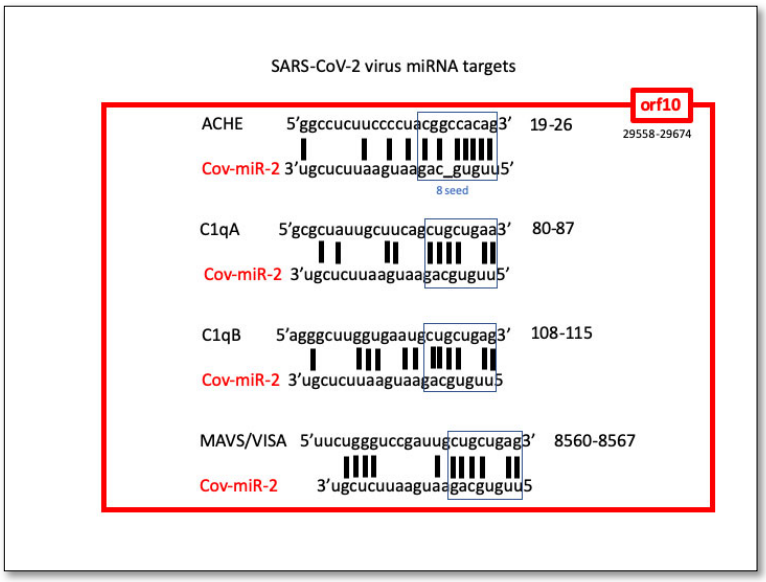

Figure 4. Cov-miR-2 target proteins. The 3'UTRs of ACHE, C1qA, C1qB and MAVS/VISA target site were depicted.

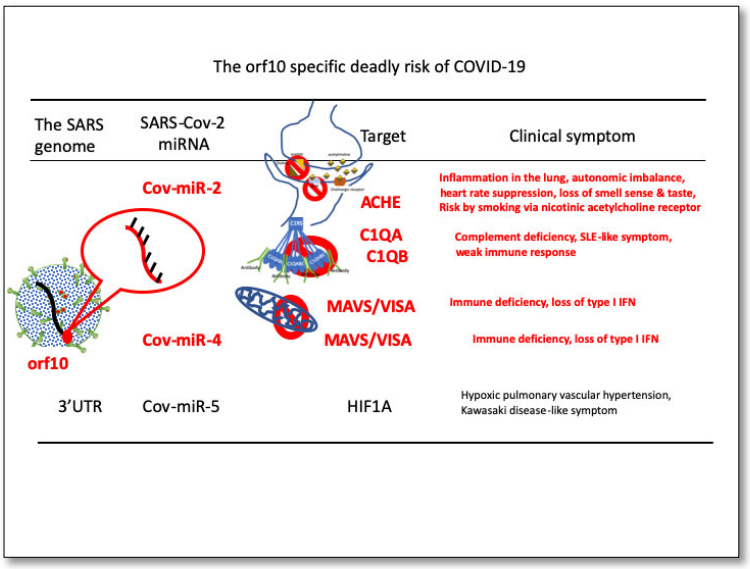

Figure 5. Orf10 specific deadly risk of COVID-19.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

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