



Could SARS-Cov-2 Establish Persistent Infection in a Certain Population of Infected Individuals

Ikuta K*

Division of Microbiology, Osaka Institute of Public Health, Osaka, Japan

***Corresponding author:** Kazuyoshi Ikuta, Division of Microbiology, Osaka Institute of Public Health, Osaka, Japan, Email: ikuta@iph.osaka.jp

Opinion

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Opinion

Novel coronavirus (SARS-CoV-2) is the causative agent for a new type of pneumonia (COVID-19) that firstly appeared in Wuhan, China, in December, 2019. The virus spread globally throughout the world within just three months next to its eruption, according to the Center for System Science and Engineering (CSSE), Johns Hopkins University, with nearly 2 million infected as of April 14, 2020, and nearly 120,000 deaths.

The SARS-CoV-2 is recognized to be widely similar to, meanwhile different from the SARS-CoV that prevailed in 2002-2003. The main similarity between SARS-CoV-2 and SARS-CoV, is the 79% genome sequence identity, that is lower compared to those of several bat-derived SARS-like CoVs [1]. Interestingly, SARS-CoV-2 has a receptor-binding domain in the spike (S) protein similar to that of SARS-CoV that uses the angiotensin-converting enzyme 2 (ACE2) as a receptor in human [2]. The main difference is attributed to the lethality, where SARS-CoV presented a higher rate of lethality (~10%), while that for SARS-CoV-2 infection is currently 2-3% as reported by the WHO.

A recent study suggested a possible diminishing virulence of SARS-CoV-2 during the continuous transmission in human [3]. In fact, many young generations displayed a mild or asymptomatic course even at acute phase of infection, and about 80% or more of infected individuals followed such clinical course. In addition, the incubation period from infection to onset of clinical signs is 2-10 days for SARS-CoV, whereas SARS-CoV-2 is rather longer, 2-14 days.

SARS-CoV did not show viral transmission during the incubation period, while SARS-CoV-2 does, as shown via transmission from pre-symptomatic and even asymptomatic carriers [4]. Consequently, SARS-CoV is highly virulent and

therefore it killed many infected individuals during the acute phase of infection, whereas those who survived the acute phase had a complete immune clearance after the immune responses. In cases of SARS-CoV-2 infection, most of the infected individuals among healthy young populations showed only mild symptoms, and some individuals of those were found to have low or no specific antibody titers to this virus, even though sufficient days have passed since the onset of infection [5,6].

In addition, there were some who have passed the acute phase and turned positive again after they were confirmed to be negative by PCR. Thus, it is postulated that the initially infecting virus could have been persistently expressed in those infected individuals, and the viral threshold once decreased to below the PCR detection limit, however, increased again enabling detection by PCR. It is possible that this phenomenon, at least in part, is related to no or low level of immune responses in those individuals.

Thus, it can be assumed that SARS-CoV-2 is characterized by low pathogenicity compared to SARS-CoV. However, viral evolution from its tropism to the lungs with the high ACE2 expression to that to the throat with the low ACE2 expression could be greatly facilitating viral transmission world-wide.

Knowing the above backgrounds on COVID-19, I remembered one suggestive evidence that we obtained on SARS-CoV long time ago, when I used to supervise research on this virus at the Research Institute for Microbial Diseases, Osaka University. We examined Vero E6 cells infected with SARS-CoV. Following the death of most of the Vero cells because of the infection, we continued to maintain the cells that survived with fresh medium. Cell cloning from the surviving cell population by limiting dilution, led us to

establish a total of 87 cell clones [7]. Analysis of those cell clones revealed that one clone (#21) was found to be a long-term high producer of infectious viral particles during 5 months observation after primary infection. Then, when the viral genome of this cell clone was analyzed, two amino acid substitutions were found in the viral S protein that led to reduced amounts of S protein expressed on the versions [8].

These results suggest that, at least SARS-CoV persistently infects cells following acute infection, and this may be derived from mutations in the viral S protein. Consequently, it may be inferred that some of the SARS-CoV-2 infected individuals may have expressed mutations in the S protein, which may facilitate persistent infection. It is possible that the virus released from such an infected individual becomes more attenuated, mildly injured or asymptomatic, and as a result, transmission of infection may become easier and efficient.

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