Viral Respiratory Coinfections Enhance the Spread of SARS-CoV-2

To the Editor:

Recently, a group of researchers at the University of Glasgow published an article in the *Journal of Infectious Diseases* on the primary preventive effect of rhinovirus 16 infection (HRV16) on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] The results of this article indicate that HRV16 simultaneous or primary infection with SARS-CoV-2 prevents COVID-19 disease.[1] This phenomenon has been attributed to the antiviral effect of interferons produced in cells with virus infection.[2]

Here is an important point that we want to share with you. Previous studies show that viral respiratory coinfections do not reveal simultaneously or immediately after primary infections of some respiratory viruses, such as influenza A virus.[3] Although some studies detected a high rate of coinfection between SARS-CoV-19 and influenza A virus (H1N1), adenoviruses tend to cause coinfections with other respiratory viruses.[4,5] Previous studies reveal the vast coinfections between other respiratory pathogens and SARS-CoV-2.[6,7]

Rhinoviruses as the main and most common cause of seasonal viral cold are a small virus with a small and rapidly reproducing genome.[8,9] The rhinovirus replication cycle completes from 8 to 12 hours after attaching to the host cell receptors.[8,9] Like the rhinovirus, the SARS-CoV-2 virus has a single-stranded RNA with positive sense that has larger size and longer genome.[10] Therefore, the replication and maturation of SARS-CoV-2 virus require more time than rhinovirus. Rhinovirus, with a short incubation period of several days, induces the rapid production of antiviral interferons, which have the preventive effects against late viral infections.[1] On the other hand, the conditions of rhinovirus replication are different from SARS-CoV-2.[8] Rhinovirus often colonizes on the upper respiratory tract and replicates at 33°C, whereas SARS-CoV-2 colonizes on the lower respiratory tract and replicates at 37°C.[8–10] Therefore, the upper respiratory tract infection, as the site of sampling for COVID-19 infection polymerase chain reaction test, will be priority of rhinovirus colonization site in coinfection cases.[8] Therefore, we think that coinfection between rhinoviruses and SARS-CoV-2 could occur simultaneously but in the separate anatomic sites on the upper and lower respiratory tract.

What about antiviral effect of interferons in viral coinfection? Sequel of respiratory viruses' coinfection includes synergism, indifference, or interference effects.[1] The interference among respiratory viruses' infections could reduce the incidence of SARS-CoV-2 infection cases by interferon defense mechanisms.[1–10] A recent related article demonstrates the effect of HRV16 interference with SARS-CoV-2 virus infection via interferon.[1] It is noteworthy that previous studies on cellular signaling in virus' infections have shown that antiviral interferons increase the expression of the ACE2 gene as a receptor of the SARS-CoV-2 virus.[11,12] Therefore, in the presence of primary viral infection, the chance of SARS-CoV-2 virus binding to host cells will increase. Furthermore, relevant studies show that binding and entry of SARS-CoV-2 virus into host cells do not lead to the proliferation and maturation of viral particles.[1] Antiviral interferons upregulate interferon-induced genes to express proteins, such as viperin, which prevent the virus replication and particle assembly.[13] As a conclusion, although early coinfection with respiratory viruses will increase the attachment and spread of SARS-CoV-2, interferon production prevents the virus infection cycle.

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