Membrane cholesterol and SARS-CoV-2 infection: a possible connection

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This opinion describes a probable relationship between membrane cholesterol and viral infection with special attention to SARS-CoV-2 infection. Monitoring the cholesterol level of infected population might open up the possibility of the former being a marker for risk of infection.

Since the beginning of 2020, SARS Coronavirus-2 (SARS-CoV-2) is wreaking havoc across the world, irrespective of local weather or people’s nationality or financial status. More than six lakh people have been identified as infected till date, and 24 thousand people have already lost their lives to it. Scientists all over the world are working extremely hard, day and night, to find a proper treatment for the affected patients, and hundreds of publications related to Coronavirus-2 are being published rapidly. This shows the zeal and commitment of the scientific community to protect humanity.

Receptor-binding domain of the spike protein of SARS-CoV-2 is established to bind to angiotensin converting enzyme 2 (ACE 2) with similar affinity as the spike protein of SARS-CoV1. This binding facilitates the fusion between viral envelope and host cell, thereby ensuring transfer of the genetic material to the host cell. Hence, fusion between viral envelope and the host cell is clearly the first step of infection.

Cryo-electron microscope results have shown the spike protein to be trimeric in pre-fusion stage, similar to that in earlier corona viruses, hence prompting our expectation of it to form a six-helix bundle in the post-fusion conformation, as in SARS-CoV3. We had previously reported the fusion peptide of coronavirus to undergo oligomerization in the presence of high levels of membrane cholesterol. Many others have also reported the requirement of membrane cholesterol for maximal efficiency of the fusion between host cell and the virus, which in turn, could be correlated with the trimeric conformation of S2 protein.

Careful investigation of the age-wise infection rate of SARS-CoV-2, till date, clearly indicates that elderly people are extremely prone to the infection. Approximately 17% of the US population is 65 years or older and 31% of total cases in the US is in that group. The worldwide death rate for the population above 60 years of age is approximately 27% while that for the population below 60 years is less than 2%. Further, if we focus on the population having pre-existing health conditions, death rate is about 17% for those having cardiovascular diseases and hypertension. Generally, the medicines prescribed for cardiovascular diseases and hypertension activate ACE 2 (ref. 6), higher expression of which has been attributed to higher morbidity and mortality of the above-mentioned population. However, the high cholesterol level of the population with cardiovascular issues and hypertension might be responsible for the higher fusogenicity of the viral envelope to the host cell, since the S2 protein exists in fusion-efficient oligomeric form (trimer) in the membrane in presence of higher proportion of cholesterol. The situation is similar for the older generation (above 60 years of age), who have more propensity for higher blood cholesterol than the younger population, in general. Serum lipid levels, especially cholesterol level, have been shown to be important for several virus infections, including flavivirus7. Therefore, cholesterol level might be a promising marker for categorizing people susceptible to SARS-CoV-2 infection. Monitoring blood cholesterol level of the infected population might provide better insight into the relationship between cholesterol and morbidity.

5. Centers for Disease Control and Prevention, USA Report.

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