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Possible assistance of host microbiome in SARS-CoV-2 fitness

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Abstract

> The COVID-19 outburst that has immobilized a large part of the world originated in late 2019. It was associated with a bat-carried SARS-like virus, SARS-CoV-2. Many features of the disease nevertheless leave physicians and hospitals puzzled with respect to known viral infections. One issue is the discontinuous detection of viral RNA among patients, as well as its differential detection in faeces with respect to respiratory tract samples. Discontinuous detection will raise problems when cities and countries return to full activity, and already has in South Korea, where it was proposed that about one patient out of seven could become re-infected. A possible explanation for this proposed 're-infection' would be interactions of the virus with its host's microbiome.

A possible rationale for the discontinuous detection of the virus[1] and its extended presence in faeces samples can be found exploring existing sequencing data[2]. In some RNA-seq analyses, bacteria from geni Prevotella and Veillonella are indeed present[3], often in much more abundant amounts than SARS-CoV-2 RNA. Chakraborty recently suggested this could provide some explanations regarding the 're-infection' phenomena and discontinuous RNA detections[4].

Here we propose that an interaction between bacteria and the virus is indeed involved in the observed virulence, but not through the phage mechanism alluded to by Chakraborty, which seems unlikely owing to the known genetics of SARS-CoV-2. The hypothesis that those, or other gut commensal bacteria, could increase the infectivity of the SARS-CoV-2 virus, is indeed supported by existing knowledge on a possible facilitation of viral infection by bacteria. In mouse, it was shown that animals with antibiotics-depleted gut flora were less susceptible to poliovirus disease, with poliovirus binding bacteria through their lipo-polysaccharide molecules[5]. Co-infection of coronavirus PEDV with Chlamyidiaceae was also observed in cell cultures, with larger inclusions in co-infected cells[6]. In humans, co-infection by Epstein-Barr virus in Mycoplasma pneumoniae patients was recently shown to increase symptoms duration, with increased levels of CRP and IL-2[7].

This view would also fit with other observations performed on COVID-19 patients and already described as symptoms for a gut bacterial infection, such as severe gut symptoms for multiple patients[8], a burst in immune response, including an increase in Interleukins and cytokine[9], as well as an observed decreased bioavailability of iron[10]. The present hypothesis further enables one to understand the higher reliability or longer presence of SARS-CoV-2 RNA in faeces as opposed to oral or nasal swabs, with favorable interaction with gut bacteria[2]. The high rate of false negatives of patients dismissed from hospitals, with syndroms later re-emerging, could also be related to such an interaction[1]. In addition, an involvement of Prevotellae would match the higher prevalence of COVID-19 among overweight persons, this genus being over-represented in their gut microbiome[11]. Finally, this hypothesis would match the observation of symptoms both in the lungs and guts of patients. Prevotellae are indeed associated with increased inflammation in chronic obstructive pulmonary disease, asthma and cystic fibrosis, along with Veillonellae[12], as well as in the guts of mice with provoked colitis[13].

A rationale for a dysregulation of gut flora due to SARS-CoV-2 can be found in the literature by exploring the physiological roles of its main target, ACE2. In the intestinal epithelium, ACE2 assists in the uptake of amino-acids by an Slc6-family transporter[14], and in the biosynthesis of antimicrobial peptides[15]. Inhibition of ACE2 by SARS-CoV-2 would thus lead to an alteration of gut flora and diarrhea, a frequent COVID-19 symptom[16], and to anemia, a predominant pathology among some COVID-19 cohorts[17].

Overall, the combination of an inhibition of the widespread ACE2 protein with constructive interactions with gut and/or lung bacteria would cover many of the observed COVID-19-related symptoms. While this hypothesis must await more extensive patients data to be or not validated, therapies with antibiotics, or with compounds that would help restore natural flora, such as probiotics or nicotinamide[15][18], should in the meantime be given more consideration.

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