Research Ideas and Outcomes 6: e54802
doi: 10.3897/rio.6.e54802

Research Idea

Bioengineered probiotics to control SARS-CoV-2 infection

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Reviewed v1

Received: 27 May 2020 | Published: 29 May 2020

Citation: Senapati S, Dash J, Sethi M, Chakraborty S (2020) Bioengineered probiotics to control SARS-CoV-2 infection. Research Ideas and Outcomes 6: e54802. https://doi.org/10.3897/rio.6.e54802

Abstract

The outbreak of 2019 novel corona virus disease (COVID-19) is now a global public health crisis and declared as a pandemic. Several recent studies suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein binds to human angiotensin-converting enzyme 2 (ACE2). The information obtained from these structural and biochemical studies provides a strong rationale to target SARS-CoV-2 spike protein and ACE2 interaction for developing therapeutics against this viral infection. Here, we propose to discuss the scope of bioengineered probiotics expressing human ACE2 as a novel therapeutic to control the viral outbreak.

Keywords

SARS-CoV-2, ACE2, probiotics

Overview and background

In a recent study, Wang et al. (2020) have provided experimental evidence that shows binding of human angiotensin-converting enzyme 2 (ACE2) to spike protein (SP) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Earlier studies have also reported ACE2 as an entry receptor for SARS-CoV-2 (Walls et al. 2020). These studies

have provided strong rationale to target SP and ACE2 interaction for developing therapeutics against SARS-CoV-2 infection. Recently, Monteil et al. (2020) has demonstrated that human recombinant soluble ACE2 (hrsACE2) significantly blocks early stage of SARS-CoV-2 infections. We believe that bioengineered probiotics expressing cell surface bound or secretory human ACE2 might be useful as pharmacological tool to control SARS-CoV-2 infection.

ACE2 is mainly expressed by epithelial cells of intestine, lung, kidney, and blood vessels. Although, lung is the major organ where SARS-CoV-2 associated pathology is more common and severe, some patients also manifest gastrointestinal symptoms like diarrhea (Liang et al. 2020). Evidence also suggests that SARS-CoV-2 has been detected in stool samples of some patients. Thus, human intestinal tract has been speculated to be an alternate infection route for this virus. In view of these findings, possible gut-mediated viral infection or transmission must be taken into consideration to discover new therapeutic approaches in tackling this disease.

Probiotics generally regarded as safe (GRAS), are known to control multiple gut associated illness with almost no side effects. World health organization (WHO) has defined probiotics as “live microorganisms which when administered in adequate amounts confer a health benefit on the host”. In recent years, bioengineering of probiotic organisms has opened a wide range of opportunities to use these organisms as delivery vehicles, which finds application in immunomodulation, drug and vaccine delivery. Knowledge of different microbes or their toxins binding to host receptors for their pathogenesis have encouraged researchers to engineer probiotics expressing host receptor or toxin receptor mimics (Sola-Oladokun et al. 2017). These enginereed probiotics have been demonstrated to suppress pathogenesis of harmful enteric microbes by sponging the microbes or their toxins. In this bioengineering approach, sequestration of microbes reduce the availability of these organisms to bind to the receptors expressed on the surface of enterocytes, thus reducing the availability of microbes to bind to their target cells.

Objectives

To design probiotics for controling SARS-CoV-2 infection or transmission

Implementation

Based on the concept of probiotics as receptor mimics, engineered probiotics expressing ACE2 could be potential bio-remedies to neutralize SARS-CoV-2. Verma et al. (2019) have successfully generated *Lactobacillus paracasei* (LP) expressing secretory human ACE2 (in fusion with the non-toxin subunit B of cholera toxin) to serve as a live vector for oral delivery of human ACE2. The usefulness of this probiotic has been checked in the mouse model of diabetic retinopathy. This study has provided the proof of concept for the feasibility of using probiotics for expression of human ACE2. In corona virus infection, we propose that bioengineered probiotics expressing ACE2 (cell wall bound or secreted) can

control viral spread by sequestering the virus or blocking the spike protein interaction with host cell-associated receptors. Importantly, the secreted form of ACE2 (sACE2) produced by these probiotics might exert systemic effects to control viral entry at multiple organs including lungs (Fig. 1). In addition to this direct effect on virus entry, the probiotics might also confer innate immunity and have beneficial effects that control the dysbiosis in the SARS-CoV-2 infected patients.

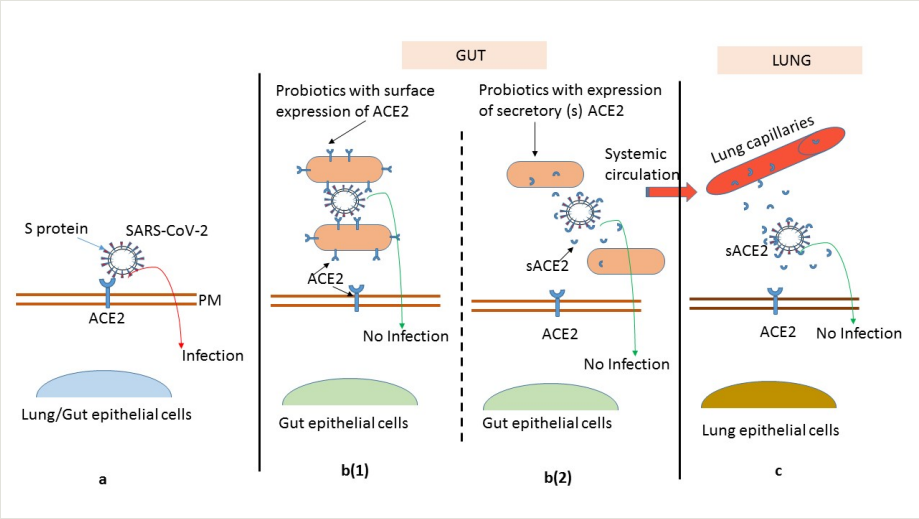

Figure 1. doi

Bioengineered probiotics to control SARS-CoV-2 infection. (a) Pathogenesis of SARS-CoV-2 depends on interaction between S protein of virus and angiotensin-converting enzyme 2 (ACE2) expressed on the surface of host cells. (b (1)) Engineered probiotics with expression of cell bound ACE2, sequesters the virus by making it bind to the ACE2 receptor on its surface thus inhibiting the viral entry into gut epithelial cells. (b (2)) The secreted form of ACE2 (sACE2) produced by probiotics confiscates the virus by binding to S proteins and masking their binding sites for gut epithelial ACE2. (c) The sACE2 could also have systemic effects due to its absorption into circulation and inhibiting the virus binding at distant organs like lungs.

Acknowledgements

SS and JD thank the Department of Biotechnology, Govt. of India for supporting ongoing grant on probiotics (BT/ILS/Flagship/2019). SS also thanks director, ILS Bhubaneswar for supporting the reserach on probiotics and coronavirus. We thank Dr. Neera Singh, ProCyto Labs Pvt. Ltd., India for editing the manuscript.

Author contributions

SS conceived the idea; SS, JD, MS and SC drafted the article.

Conflicts of interest

No potential conflict of interest declared.

References

- Liang W, Feng Z, Rao S, Xiao C, Xue X, Lin Z, Zhang Q, Qi W (2020) Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. Gut 2020-320832. https://doi.org/10.1136/gutjnl-2020-320832
- Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer R, Stahl M, Leopoldi A, Garreta E, Pozo CHd, Prosper F, Romero JP, Wirnsberger G, Zhang H, Slutsky A, Conder R, Montserrat N, Mirazimi A, Penninger J (2020) Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell 181: 905-91. https://doi.org/10.1016/j.cell.2020.04.004
- Sola-Oladokun B, Culligan E, Sleator R (2017) Engineered probiotics: Applications and biological containment. Annual Review of Food Science and Technology 8 (1): 353-370. https://doi.org/10.1146/annurev-food-030216-030256
- Verma A, Xu K, Du T, Zhu P, Liang Z, Liao S, Zhang J, Raizada M, Grant M, Li Q (2019) Expression of human ACE2 in *Lactobacillus* and beneficial effects in diabetic retinopathy in mice. Molecular Therapy - Methods & Clinical Development 14: 161-170. https://doi.org/10.1016/j.omtm.2019.06.007
- Walls A, Park Y, Tortorici MA, Wall A, McGuire A, Veesler D (2020) Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell https://doi.org/10.1016/j.cell.2020.02.058
- Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, Lu G, Qiao C, Hu Y, Yuen K, Wang Q, Zhou H, Yan J, Qi J (2020) Structural and functional basis of SARS-CoV-2 entry by using 2 human ACE2. Cell https://doi.org/10.1016/j.cell.2020.03.045