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Mini Review

A Mini-Review on an Association between Nutrition and Mucosal Immunity in the Midst of the COVID-19 Pandemic

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Abstract

In the midst of the COVID-19 pandemic, which the World Health Organization officially declared a pandemic on March 11, 2020, we write a mini-review on an association between nutrition and mucosal immunity. The human immunity consists of non-specific innate immunity recognizing pathogen-associated molecular patterns and subsequent adaptive immunity specific for the target antigens. The immune system of the intestine as mucosal immunity must have functions to defend against constant threat of invading pathogens while suppressing immune responses to harmless dietary antigens and commensal bacteria. Nutrition seems to have a major role in non-heritable influences on the innate and adaptive immunity. It has been demonstrated in humans that some nutrients including β-glucan have the potential to boost the mucosal immunity to viral infections. Conversely, it is conceivable that continuing supplementation of (large-dose) β-glucans or lipopolysaccharides can suppress the innate immunity by stimulating regulatory T cells. For now, the impact of nutrition on human immunity should neither be overestimated nor be underestimated.

Keywords: Nutrition; Innate Immunity; Adaptive Immunity; Mucosal Immunity; COVID-19

Introduction

The World Health Organization officially declared COVID-19 (caused by severe acute respiratory syndrome coronavirus 2) a pandemic on March 11, 2020. It started in Wuhan, a city in the Hubei Province of China at the end of 2019 and has spread worldwide [1,2]. In the midst of the COVID-19 pandemic, public health measures including handwashing, respiratory etiquette and social distancing are promoted to prevent the spread of the virus [3]. It is important to have a good (balanced) immune system, especially innate immunity, for being in resistance to novel pathogens such as a new coronavirus [4-6]. To maintain or not to compromise good immunity, it is necessary to care about stress-related changes in the human immunity [7]. It is useful to know a role of nutrition in mucosal immunity that is recently attracting interest. In this mini-review, we briefly describe the human immunity and refer to some relevant studies on an association between nutrition and mucosal immunity with regard to respiratory viral infections.

Innate and adaptive immunity

As described in an overview of the immune system [4], the human immunity consists of non-specific innate immunity that is encoded in its mature form by the germ-line genes and specific adaptive immunity that is encoded by somatically rearranged genes. As the first line of host defense against invading pathogens, the innate immunity, broadly defined, includes constitutively active barriers such as the mucociliary layer that overlays the epithelium in the respiratory tract. Antimicrobial peptides are released from epithelium by microbial products, cytokines and growth factors [8]. Others are activated by interactions of host cells including antigen-presenting dendritic cells, macrophages, granulocytes, natural killer cells and innate lymphoid cells with invading pathogens [9,10]. In there, membrane-bound and cytoplasmic receptors (Toll-like receptors, C-type lectin receptors, retinoic acid-inducible gene-I-like receptors, etc.) recognize pathogen-associated molecular patterns that do not exist in host cells, leading to the production of inflammatory cytokines and type 1 interferons.

The adaptive system is composed of specialized immune cells that respond following the response of innate immunity in host defense. It manifests exquisite specificity for its target antigens and produces long-lived cells that persist in an apparently dormant state (immune memory) for rapid responses at the second encounter [4]. The adaptive responses are based on the antigen-specific receptors expressed on the surface of T- and B-lymphocytes. The majority of T lymphocytes are defined by selective surface expression of cluster determinant 4 (CD4) or T helper (Th1 and Th2) cells primarily to regulate the cellular and humoral immune responses and that of CD8 or cytotoxic T cells primarily to kill cells infected with intracellular microbes. The antigen-specific receptors recognize peptide antigens presented in a complex with class I or class II major histocompatibility cell (MHC) proteins [11]. The innate and adaptive immune responses are interlinked, for example, through antigen-presenting dendritic cells and Th17 cells, the outline of which is illustrated in Figure 1.

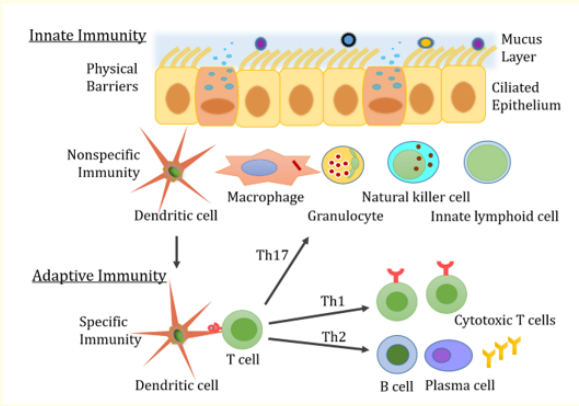

Figure 1: An outline of the innate and adaptive immune system. See text for details [4,10].

Mucosal immunity and intestinal microbiota

The immune system of the intestine must have functions to defend against constant threat of invading pathogens while suppressing immune responses to harmless dietary antigens and commensal bacteria (Figure 2). In addition to dendritic cells and macrophages against bacteria or antigens transcytosed by epithelial microfold (M) cells [12,13], there are unique lymphocyte populations in the intestinal mucosa, such as Immunoglobulin A (IgA)-secreting plasma cells, γδT cells, innate lymphoid cells and Th17 cells. Innate lymphoid cells lacking antigen-specific receptors in mucosal immunity are comprising the innate counterpart of T cells seen in the adaptive immunity and secrete cytokines in response to pathogenic tissue damage for the subsequent adaptive immunity. By contrast, the suppression of immune responses to harmless antigens is mainly induced by forkhead box P3-expressing $CD4^+$ regulatory T (T_{reg}) cells [10,14]. It is of interest that alterations of intestinal microbiota can cause immune dysregulation, leading to autoimmune disorders and food allergy [13,15,16]. It is suggested that the intestinal microbiota plays a key role in immune initiation and adaptation in the gastrointestinal tract (serving as a primary sensor of invading pathogens) and also at other distal mucosal sites such as the lung [17].

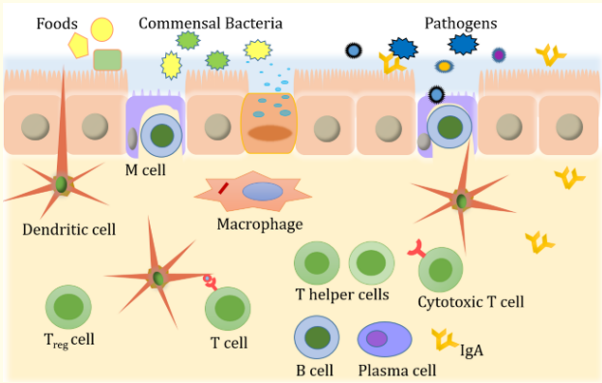

Figure 2: An illustration of mucosal immunity of the intestine. See text for details [10,12,14].

With regard to intestinal microbiota, a comprehensive review [18] describes that the commensal microbiota and invading viruses can be affected by each other through diverse mechanisms, thereby having stimulatory or suppressive roles in viral infections. It is expected that the intestinal microbiota can contribute to direct and indirect suppression of viral infection, for example, by directly binding to viruses, producing antiviral peptides and boosting antiviral immunity. On the contrary, it should be noted that the commensal microbiota can help viruses to invade the host in some occasions, by enhancing viral stability, stimulating attachment to permissive cells and contributing to viral replication. Moreover, the commensal microbiota can be involved in suppressing local antiviral immune responses possibly through commensal microbiota-in-

duced T_{reg} cells and T_{reg} cell-related cytokines. It is also known that respiratory RNA viruses such as a new coronavirus have evolved to have some strategies to evade the innate immunity [19].

Nutrition in the prevention of upper respiratory tract infections

The immune system has evolved to protect the host from invading pathogenic microbes that are also evolving [4,19]. Such a relationship like coevolution is presumed to influence the lifespan of animals [5,20]. Interestingly, the human immune system is highly variable between individuals as a consequence of heritable and non-heritable influences, while the immune system is relatively stable over time in a given individual. The variation is mostly explained by commensal and pathogenic microbes and other non-heritable influences [21]. Among them, nutrition seems to have a major role in non-heritable influences on the innate and adaptive immunity [22-24]. It is known that energy and nutrient deficiencies are responsible for multiple immune problems, which can be addressed with good dietary practices for balanced uptake of nutrients [11].

Nutrients	Studies	Results	References
Vitamin C	Systematic review	Failure of vitamin C supplementation (0.2g or more daily) to reduce the incidence of colds in the normal population Potential usefulness of the vitamin C supplementation for people exposed to brief periods of severe physical exercise or cold environments Inconsistent effects of regular vitamin C supplementation (1 to 2 g/day) on the duration or severity of colds in therapeutic trials	[25]
Vitamin D	Systematic review	Protective effects of vitamin D supplementation (oral vitamin D_3 or D_2 daily or weekly) on acute respiratory tract infections (URTI and lower respiratory tract infections) (Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.)	[26]
Quercetin (Flavonoid)	Double-blinded trial 500 or 1000 mg/day Double-blinded trial 1000 mg/day Double-blinded trial 500 or 1000 mg/day	Reduction in total sick days and symptom severity associated with URTI in a subgroup of subjects at age 40 or older Markedly lower incidence of URTI in well-trained subjects after intensified training, but no effects on exercise-induced immune dysfunction, inflammation and oxidative stress No effect on measures of innate immune function or inflammation in community-dwelling adult females	[27]
Catechins (Polyphenols)	Randomized trial 57 mg once daily 57 mg 3 times daily	Reduction in the UTRI incidence in the high-catechin group, but no effect in the low-catechin group among health workers	[28]
Zinc with vitamin A	Randomized trial Zinc, 10 mg/day Retinol, 60 mg/day	Reduction in the percentage of days with URTI in a population of preschool Indonesian children with marginal nutritional status (Vitamin A supplementation was associated with a decreased number but an increased duration of URTI episodes.)	[29]
β-Glucan (Yeast-derived)	Double-blinded trial 100 mg/day	Enhancement of physical endurance in children with respiratory problems, helping their mucosal immunity through stabilization of the secretory IgA levels	[30]

Table 1: Clinical effects of nutritional supplementation on upper respiratory tract infections (URTI) or mucosal immunity.

In Table 1, several representative nutrients that have been demonstrated to have the potential to defend against respiratory viral infections in humans are listed. Randomized, placebo-controlled and double-blinded trials have demonstrated the potential effects of the supplementation of vitamin C, vitamin D and quercetin (a flavonoid found in fruits and vegetables) on upper respiratory tract infections (URTI) or common colds [25-27]. Similar to the effect of quercetin, catechins (polyphenols) contained mainly in green tea have exhibited antiviral activity against URTI [28]. Vitamin A plays an important role in the regulation of innate and adaptive immunity by acting through retinoic acids and their nuclear receptors. In a deficient state of vitamin A, its supplementation seems to considerably boost the immunity against viral infections, as is probably the case in zinc supplementation [11,29]. β-Glucans causing non-specific immunomodulation are natural polysaccharides found in yeast, mushrooms, seaweed and grains. Short-term oral supplementation of β-glucan has been reported to enhance physical endurance in children with respiratory problems, helping their mucosal immunity through stabilization of the secretory IgA levels [30,31].

Similar to the effect of β-glucans on the mucosal immunity through receptors recognizing pathogen-associated molecular patterns, lipopolysaccharides (LPS) may impede respiratory viral infections. LPS-mediated Toll-like receptor 4 activation of innate immune cells is suggested to be necessary for appropriate immune crosstalk and the immunity to future encounters with viruses [32]. A little exposure to a novel RNA virus under the activation of innate immunity could be somewhat similar to the strategy of mRNA vaccines that can also stimulate the innate immunity [33,34]. Under the condition of much enhanced innate immunity, a large exposure to it could cause a cytokine storm syndrome [35]. Conversely, it is conceivable that continuing supplementation of (large-dose) β-glucans or LPS can suppress the innate immunity by stimulating T_{reg} cells, as mentioned above in the case of the commensal microbiota. When considering the enhancement of non-specific innate immunity, it would be worthy paying attention to ongoing Bacillus Calmette-Guerin (BCG) trials for COVID-19 treatment [36].

Conclusion

It is needed to practice several precaution measures for COVID-19, while keeping good systemic immunity by stress management and good nutrition. It has been demonstrated that some nutrients including β-glucan and LPS have the potential to boost innate immunity or mucosal immunity to novel pathogens. In the circumstances at higher risk for viral infections, it may be advised to avoid exposure to the viruses as much as possible, even under the good immune condition. For now, the impact of nutrition on human immunity should neither be overestimated nor be underestimated in the midst of the COVID-19 pandemic.

Conflict of Interest Statement

The authors have indicated no potential conflict of interest.

Bibliography

1. Zhu N., *et al*. "A novel coronavirus from patients with pneumonia in China, 2019". *The New England Journal of Medicine* 382.8 (2020): 727-733.

2. Grasselli G., *et al*. "Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy". *Journal of the American Medical Association* (2020).

3. Bedford J., *et al*. "COVID-19: towards controlling of a pandemic". *The Lancet* 395.10229 (2020): 1015-1018.

4. Chaplin D.D. "Overview of the immune response". *Journal of Allergy and Clinical Immunology* 125.2 (2010): S3-S23.

5. McDade T.W., *et al*. "Trade-offs between acquired and innate immune defenses in humans". *Evolution, Medicine, and Public Health* (2016). 1-16.

6. Thevarajan I., *et al*. "Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19". *Nature Medicine* (2020).

7. Segerstrom S.C., *et al*. "Stress, energy, and immunity: an ecological view". *Current Directions in Psychological Scienc*e 16.6 (2007): 326-330.

8. Hiemstra PS. "The role of epithelial beta-defensins and cathelicidins in host defense of the lung". *Experimental Lung Research* 33.10 (2007): 537-542.

9. Mogensen T.H., *et al*. "Pathogen recognition and inflammatory signaling in innate immune defenses". *Clinical Microbiology Reviews* 22.2 (2009): 240-273.

10. Panda S.K., *et al*. "Innate lymphoid cells in mucosal immunity". *Frontiers in Immunology* 10 (2019): 861.

11. Saeed F., *et al*. "Studying the impact of nutritional immunology underlying the modulation of immune responses by nutritional compounds - a review". *Food and Agricultural Immunology* 27.2 (2016): 205-229.

12. Dillon A., *et al*. "M cells: intelligent engineering of mucosal immune surveillance". *Frontiers in Immunology* 10 (2019): 1499.

13. Kobayashi N., *et al*. "The roles of Peyer's patches and microfold cells in the gut immune system: relevance to autoimmune diseases". *Frontiers in Immunology* 10 (2019): 2345.

14. Tanoue T., *et al*. "Development and maintenance of intestinal regulatory T cells". *Nature Reviews Immunology* 16.5 (2016): 295-309.

15. Wu H.-J., *et al*. "The role of gut microbiota in immune homeostasis and autoimmunity". *Gut Microbes* 3.1 (2012): 4-14.

16. Lee K.H., *et al*. "The gut microbiota, environmental factors, and links to the development of food allergy". *Clinical and Molecular Allergy* 18 (2020): 5.

17. Samuelson D.R., *et al*. "Regulation of lung immunity and host defense by the intestinal microbiota". *Frontiers in Microbiology* 6 (2015): 1085.

18. Li N., *et al*. "The commensal microbiota and viral infection: a comprehensive review". *Frontiers in Immunology* 10 (2019): 1551.

19. Kikkert M. "Innate immune evasion by human respiratory RNA viruses". *Journal of Innate Immunity* 12 (2020): 4-20.

20. Xia J., *et al*. "Convergence of longevity and immunity: lessons from animal models". *Biogerontology* 20.3 (2019): 271-278.

21. Brodin P., *et al*. "Human immune system variation". *Nature Reviews Immunology* 17.1 (2017): 21-29.

22. Schaible U.E., *et al*. "Malnutrition and infection: complex mechanism and global impacts". *PLoS Medicine* 4.5 (2007): e115.

23. Cereda E., *et al*. "The association of geriatric nutritional risk index and total lymphocyte count with short-term nutrition-related complications in institutionalized elderly". *Journal of the American College of Nutrition* 27.3 (2008): 406-413.

24. Mora J.R., *et al*. "Vitamin effects on the immune system: vitamins A and D take centre stage". *Nature Review Immunology* 8.9 (2008): 685-698.

25. Hemila H., *et al*. "Vitamin C for preventing and treating the common cold". *Cochrane Database of Systematic Reviews* (2013): CD000980.

26. Martineau AR., *et al*. "Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data". *British Medical Journal* 356 (2017): i6583.

27. Li Y., *et al*. "Quercetin, inflammation and immunity". *Nutrients* 8.3 (2016): 167.

28. Furushima D., *et al*. "Prevention of acute upper respiratory infections by consumption of catechins in healthcare workers: a randomized, placebo-controlled trial". *Nutrients* 12.1 (2020): 4.

29. Kartasurya M.I., *et al*. "Zinc combined with vitamin A reduces upper respiratory tract infection morbidity in preschool children in Indonesia". *British Journal of Nutrition* 108.12 (2012): 2251-2260.

30. Richter J., *et al*. "β-glucan affects mucosal immunity in children with chronic respiratory problems under physical stress: clinical trials". *Annals of Translational Medicine* 3.4 (2015): 52.

31. Vetvicka V., *et al*. "Placebo-driven clinical trials of yeast-derived β-(1,3) glucan in children with chronic respiratory problems". *Annals of Translational Medicine* 1.3 (2013): 26.

32. Man W.H., *et al*. "The microbiota of the respiratory tract: gatekeeper to respiratory health". *Nature Reviews Microbiology* 15.5 (2017): 259-270.

33. Schlake T., *et al*. "Developing mRNA-vaccine technologies". *RNA Biology* 9.11 (2012): 1319-1330.

34. Zhang C., *et al*. "Advances in mRNA vaccines for infectious diseases". *Frontiers in Immunology* 10 (2019): 594.

35. D'Elia R.V., *et al*. "Targeting the "cytokine storm" for the therapeutic benefit". *Clinical and Vaccine Immunology* 20.3 (2013): 319-327.

36. Redelman-Sidi G. "Could BCG be used to protect against COVID-19?" *Nature Reviews Urology* (2020).