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Short Communication

"X Factor" of Japanese to Suppress Covid-19 Mortality

Shaw Watanabe[1]*, Kazumoto Inuma[2], Kota Kikuchi[3] and Tetsuro Yamamoto[4]

[1]President, Asia Pacific Clinical Nutrition Society, Lifescience Promoting Association, Japan

[2]RiceTech Co. Ltd., Japan

[3]Ministry of Agriculture, Forest and Fishery, Japan

[4]Research Center, EPS Holdings, Inc., Japan

***Corresponding Author:** Shaw Watanabe, President, Asia Pacific Clinical Nutrition Society, Lifescience Promoting Association, Japan.

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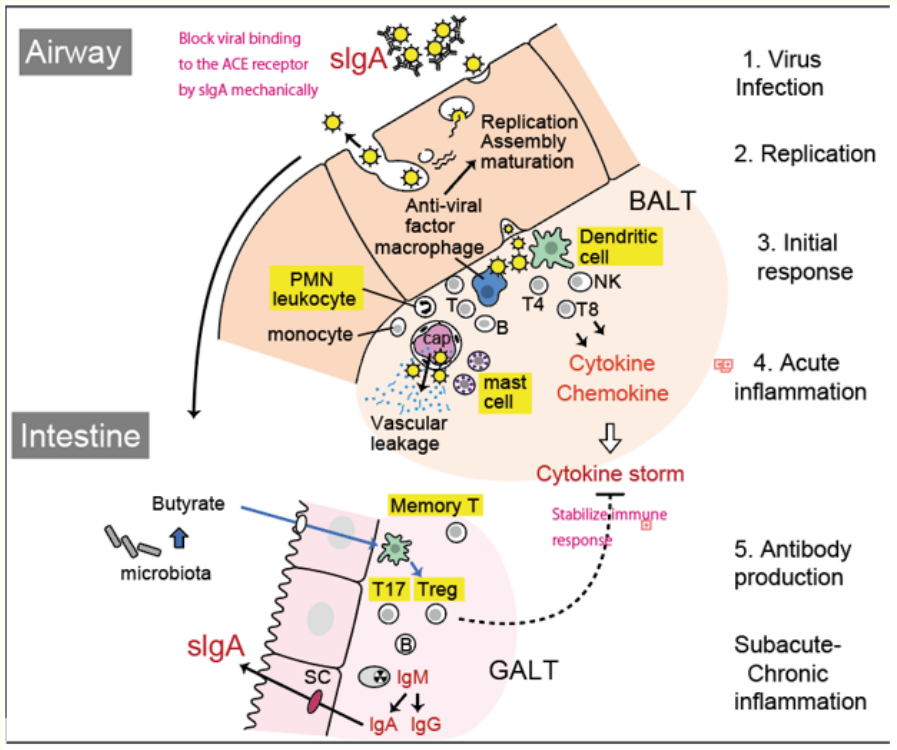
Japan experiences three waves of COVID-19 pandemic. The National Institute of Infectious Diseases has determined the COVID-19 first wave was derived from the Wuhan, and the second wave originated from a COVID-19 variant of the European type. Since October, the third wave causes the pandemic spread. The grim milestone of 100,000 COVID-19 cumulative cases reached at the end of October. On December 26, the cumulative number of PCR positive cases becomes 218,358. Even though, the total case/fatality rate is 1.4% or 2.45 death/100K population. Japan's death rate from COVID-19 is one of the lowest in the developed countries, despite its high risk aging population [1]. Factors explaining this low death rate are said to include cultural habits, such as bowing etiquette and wearing face masks, hand washing with sanitizing equipment, so far [2]. Still, we suspect an essential "X factor" is the strong innate immunity which explain the different mortality among countries.

Pathologically, the COVID-19 infection could be divided into 5 phases; (1) binding to ACE receptor, (2) viral replication inside the infected cells, (3) initial response of non-specific defense system, (4) acute inflammation, (5) antibody production in subacute-chronic phase leading to cure (Figure).

The CoV-2 virus itself is well studied, but host interaction is still insufficient. First step to bind to the ACE receptor could be mechanically blocked by the thick secretory IgA (sIgA) layer. Our findings that countries with high proportion of sIgA deficiency showed higher COVID-19 mortality than countries without sIgA deficiency like Japan and Korea support this hypothesis [3]. The second phase is an intracellular viral replication, which is interfered by many anti-viral factors [4]. At 3rd phase of an initial response, dendritic cells, macrophages, NK cells, other immature T-cells nonspecifically respond, and secrete various cytokines and chemokines. T cell lineage sees to work mainly, but still need more study. BCG vaccination in childhood may leave memory T cells that cause a legacy effect of cellular immunity. Dendritic cells and macrophages process antigen to T4, T8 lymphocytes, and these cells secrete cytokines and chemokines. A cytokine storm may occur If the secreted cytokines is overshooting. Any suppressive mechanisms to stabilize immune reaction should be present to avoid serious progression.

Then, infiltration of PMN leukocytes, monocytes and mast cells cause interstitial viral pneumonitis, making acute inflammation. Systemic viremia and microthrombus may occur when local capillaries are damaged. Antibody production started in the BALT and GALT lymphoid tissues, and IgM, IgG, and IgA are produced to lead to cure. sIgA is secreted into the lumen after binding with the secretory component in the epithelial cells, and join in the mucosal immunity.

The problem is how stabilize the initial immune response for avoiding cytokine storm.



Figure

Since we had found the negative correlation between the Covid-19 mortality and rice consumption per capita in OECD 20 countries (Coefficient of determination, 0.59), we considered why rice eating decreases the Covid-19 death [3]. We further focused on nine rice-producing countries, such as Vietnam, Myanmar, Thailand, Philippines, China, India, Japan, Indonesia, and Korea, and got a stronger inverse correlation, $R^2 = 0.662$. Looking at past rice consumption trends it weighs more than 200 kg per person per year in Vietnam and Myanmar, about 100 kg in Thailand and China, and 60-70 kg in South Korea and Japan. Wheat consumption per capita by the contrary showed a positive correlation on the contrary. These data suggest that the nature of staple foods strongly influences resistance to SARS-CoV-2 infection.

Our previous findings indicated that rice eaters had a specific composition of intestinal microbiota profile, which could prevent inflammation. So, we try to explain why rice eating habits protect from Covid-19 death. We have done the intervention study by a brown rice lunch, and the results suggest rice eating induce stable innate immunity by short chain fatty acids (SCFA) and regulatory T cells. In this study, brown rice *genmai omusubi* (rice cake) was provided 5/week as a business lunch for 12 weeks [5]. Participants practiced the pre-and post-questionnaires, including dietary habits and daily life records, monthly blood pressure, and body composition. Before and after the intervention, simultaneous measurement of intestinal microbiota and SCFAs was done on the fecal samples. We used biochemical data, including IL-6, CRP, and TNFa as inflammatory marker for correlation analysis with changes of microbiota.

After three months of eating brown rice lunch, the bodyweight decreased in about half of the participants, and bowel movements and stool status improved significantly [5]. Significant microbiotic change was an increase of Actinobacteria and decrease of Proteobacteria. *Blautia wexlerae, Collinsella aerofacience* and *Eubacterium hallii* significantly increased at species level. In SCFAs, acetate and propionate tended to decrease, while i-butyrate and i-valerate kept the same level, and capronate increased. Acetates and propionate positively correlated with IL-6. In addition, n-butyrate and n-val-

erate showed a positive correlation with both IL-6 and CRP. Isobutyrate and i-valerate negatively correlated with TNF-α. The upper tertial of *genmai* eaters tended to shaw low IL-6 and CRP, while TNFα is high.

Low IL-6 and CRP were results of the changes in SCFA affected by the changes of microbiota.

Genmai, unpolished rice, is characterized by rich dietary fiber, γ-oryzanol, GABA, and many other functional ingredients. It changed intestinal microbiota with increased diversity. They are positively or negatively associated with SCFAs. Butyrate is known to bind the GRP109 receptor of the epithelial surface, and the signal is transferred to the submucosal layer and stimulates proliferation and maturation of regulatory T cells. It may prevent cytokine storms in the acute phase of COID-19 virus infection.

Power up of the innate immunity is essential to suppress Covid-19 pandemic. Xi He et al. reported a substantial transmission potential of CoV-2 virus before symptom onset. They observed the highest viral load in throat swabs at the time of symptom onset and inferred that infectiousness peaked on or before symptom onset. SIgA in rice eaters may prevent mucosal infection at this stage by blocking attachment to ACE receptor.

In a rapidly expanding pandemic, contact tracing/quarantine and isolation are no longer feasible. Encouragement to change eating habits, in addition to the social behavioral change especially the promotion of brown rice food and rice bran, should be part of the national strategies to counter the COVID-19 pandemic. By recognizing the strong relationship between dietary habit and the Covid-19 infection, it is especially recommended to developing countries with no funds to buy the expensive vaccine and therapeutic drugs.

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- COI
- The authors have no COI to declair.

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