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COMMENTARY

Controlled modulation of all the arms of the immunity including innate immunity by biological response modifier glucans, a simple yet potential nutritional supplement strategy to fight COVID-19

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Abstract

Immune modulation, being one of the potential strategies to combat COVID-19 infection, emphasis has been laid on enhancing the innate immune response in a balanced manner. Beta (β)-glucans have been suggested as nonspecific immunostimulatory adjuvants to beneficially boost protective antiviral immunity. Through this article, we wish to emphasize that β-glucans not only enhance the innate immunity but also possess the capability to modulate all the arms of the immunity viz., innate, adaptive, TRIM at different sites including those postulated to be the entry site of the SARS-CoV2. Other than immune modulation capabilities, the beneficial metabolic- and coagulation-related effects of β-glucans, a simple nutritional supplementation strategy, make them be considered for larger clinical studies to validate their prophylactic vaccine adjuvant and nutritional-based therapeutic supplement activities to effectively fight the COVID-19 pandemic.

Practical applications

A 360° wholesome protection from viral infections is possible only when all the arms of the immune system function in a balanced and effective manner which is especially important in COVID-19. Nutritional supplementation using biological response modifier beta (β)-glucans (BRMGs) is worth considering for large-scale clinical studies based on their track record of safety and their beneficial regulation of all the arms of the immune system.

KEYWORDS
antiviral, beta (β)-glucans, COVID-19, immune modulation, innate immunity

The COVID-19 pandemic continues to wreak havoc and even after more than 2 years having passed since the report of the first infected patient, there has not been any approved treatment. Several vaccines, though approved, are not widely available for all age groups and those with different comorbidities (Vabret et al., 2020). In this scenario, immune modulation is considered as the major strategy to combat the infection, and different agents have been employed in this regard (Zhong et al., 2020). Immunotherapies are at various stages of development aiming at augmented anticoronavirus immunity with a particular focus on the innate immune response to not only enhance it but also modulate it in a balanced manner to prevent hyperimmune activation (Schijns & Lavelle, 2020). Beta (β)-glucans have been suggested to be potential nonspecific immunostimulatory adjuvants that can promote trained immunity (TRIM) to beneficially boost protective antiviral immunity apart from BCG vaccine (Geller & Yan, 2020), with clinical pilot studies have proven their efficacy

and safety in bringing down the inflammatory and immune biomarkers associated with cytokine storm and coagulopathy in COVID-19 patients (Pushkala et al., 2021; Raghavan et al., 2022).

We wish to emphasize that these β-glucans not only promote TRIM and innate immunity but also have capabilities to uniquely modulate all the arms of the immunity viz., innate, adaptive, TRIM at different sites, including those postulated to be the entry site of the SARS-CoV2, the mucosal and gut immunity (Ikewaki, Iwasaki, et al., 2020). Although yeast-based β-glucans have been proven clinically to be safe and effective vaccine adjuvants, especially an AFO-202-derived β-glucans against Avian Influenza virus (Le et al., 2011), the significance of this β-glucan as a wide-spectrum immune enhancement (β-WIFE) vaccine adjuvant strategy to COVID-19 (Ikewaki et al., 2021) deserves a mention.

Such β-glucans modulate all arms of the immunity in a controlled manner through the following postulated mechanisms:

1. Induce epigenetic reprogramming both at the peripheral and at the central level of bone marrow, leading to cellular activation of trained innate immune cells for antiviral activity, with a long-lasting innate memory (Geller & Yan, 2020).
2. β-glucans activate antigen-presenting dendritic cells (DCs), leading to stimulation of antigen-specific CD4 and CD8 T cells, and induce IFN-γ production (Netea et al., 2020).
3. Since the β-glucans act akin to pathogen-associated molecular patterns (PAMP), activating mucosal and gut immunity by binding with specific pathogen recognition receptors such as dectin-1, which is also a key receptor for beta (β)-glucan binding, this process induces adaptive and innate immunity in distant lymphoid organs as well (Li et al., 2010).
4. Acts on B cell-mediated adaptive immune response by increasing the immunoglobulins specifically those in the saliva (sIgM, sIgG, and sIgA), as they can mount effective anti-SARS-CoV2 response at the level of oral entry itself. Orally administered β-glucans also have been reported to stabilize IgG1 levels, maintaining anti-infective immunity (Richter et al., 2016).
5. A balanced immune modulation occurs after the administration of β-glucans with the enhancement of beneficial cytokines such as IL-7, IFN-γ, and sFAS while suppression of pro-inflammatory cytokine storm-inducing cytokines such as IL-6 (Netea et al., 2020). This balanced immune response is significant in COVID-19 as any immune-modulatory agent can be truly beneficial only if it induces this kind of a balanced response rather than an enhanced antiviral immune response alone.
6. Gut-microbiota alteration with β-glucans to modulate dysbiosis and lead to the enhancement of beneficial microbes has been documented (Jayachandran et al., 2018; Raghavan et al., 2021). Schijns and Lavelle (2020) have also suggested that aiming for microbiome balance to prevent dangerous immune hyperactivation is essential for an anti-COVID-19 response.
7. Metabolic beneficial effects of these β-glucans (Ikewaki, Iwasaki, et al., 2020) become critical in the context of prophylaxis and supportive therapeutics in COVID-19 as higher rate of inflammatory processes occurring in diabetic patients due to constant glucose recognition by C-type lectin receptors and immune-related coagulatory dysfunction pose individuals with these metabolic alterations at heightened risk of severe mortality associated with the disease (Ikewaki, Rao, et al., 2020).

Thus, by adopting a simple nutritional supplementation strategy based on β-glucans, not only the innate immune response is beneficially enhanced but all arms of the immunity including at the postulated sites of entry of the SARS-CoV2 virus are also modulated in a controlled and effective manner. Therefore, we suggest that this β-glucan-based controlled immune modulation strategy be considered for large-scale multicentric clinical trials for validation as a prophylactic vaccine adjuvant and nutritional-based therapeutic supplement strategy to effectively fight the COVID-19 pandemic, in a manner that has minimal adverse effects which are considered the major hurdle for several disease-fighting strategies under development for COVID-19.

CONFLICT OF INTEREST

Samuel Abraham is a shareholder in GN Corporation, Japan which in turn is a shareholder in the manufacturing company of the AFO 202 Beta Glucan product and an applicant to several patents of relevance.

AUTHOR CONTRIBUTIONS

Nobunao Ikewaki: Conceptualization; writing – review and editing. **Gene Kurosawa:** Writing – review and editing. **Tomohiko Kisaka:** Writing – review and editing. **Samuel JK Abraham:** Conceptualization; writing – original draft.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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