Mini Review

Rice Components with Immunomodulatory Function

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Summary Rice (Oryza sativa) is one of the most important food crops in the world, and the effect of its consumption on human health is of great concern. Evidence has accumulated that rice contains several components, such as γ-oryzanol and rice bran fibers, which modulate the immune system. In addition, rice has other immunologically beneficial characteristics. It has a low allergenic potential and is gluten-free, reducing the risk of development of food allergies and diseases related to gluten sensitivity such as coeliac disease. This review presents the recent advances in our understanding of the immunomodulatory function of rice components.

Key Words Immune modulation, γ-oryzanol, rice bran fiber, allergy, inflammatory diseases

1. Introduction

The prevalence of chronic inflammatory disorders such as allergies, inflammatory bowel diseases (IBD), and age-related diseases (e.g. diabetes and Alzheimer disease) has increased over the past decades. Our immune system has developed to eliminate harmful non-self-components such as pathogens and tumor cells. However, when the immune system is dysregulated, it leads to chronic inflammation, a strong disease-promoting factor in a variety of inflammatory disorders. Therefore, it is important to identify dietary components with immunomodulatory functions in order to establish dietary strategies for the prevention and treatment of such disorders.

In the immune system, the cells that first encounter foreign antigens are antigen presenting cells (APCs) such as dendritic cells (DCs) and macrophages. APCs capture allergens, process them into peptides, and present these peptides as complexes with major histocompatibility complex (MHC) class II molecules to CD4⁺ T-cells. Upon activation of naive CD4⁺ T-cells via the interaction of a complex of an antigenic peptide with MHC class II molecule with T-cell receptor, they are polarized into effector T cells (i.e. T helper type 1 (Th1) cells, Th2 cells, Th17 cells, Th22 cells), or regulatory T cells (T reg) (1, 2). Effector CD4⁺ T-cells play a central role in the induction of antibody production by B cells and in the activation of cytotoxic T cells (CD8⁺ T-cells) to cope with pathogens and tumor cells. In contrast, T reg play an important role in suppressing excess immune responses by producing anti-inflammatory cytokines (e.g. IL-10 and TGF-β), inducing lysis of target cells and exerting immune modulatory functions (1). However, in chronic inflammatory diseases, the balance between effector T cells and T reg is dysregulated (2). In addition, inflammation causes an increase in the production of pro-inflammatory cytokines (e.g. IL-6, IL-1, and TNF-α) in APCs. Notably, evidence has accumulated that several rice components possess immunomodulatory functions and thereby prevent immune dysregulation and suppress the development of inflammation (3–5).

2. Immunomodulatoly Components and Properties of Rice

2.1 Small compounds

The rice grain (rough rice or paddy) consists of the hull (an outer protective covering), bran, endosperm, and embryo at around 20%, 6%, 72%, and 2% of the rough rice weight, respectively (6). The most extensively studied rice component with immunomodulatory function is γ-oryzanol. It is present in the lipid fraction of rice bran. γ-oryzanol consists of a mixture of a ferulic acid ester of sterols and triterpene alcohols. Several studies have shown anti-inflammatory effects of γ-oryzanol and ferulic acid in allergies, IBD, diabetes, and neuroinflammation using murine models (3–5), γ-oryzanol and ferulic acid are capable of inhibiting the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). NF-κB is a transcriptional factor that is involved in gene expression of pro-inflammatory cytokines and inflammatory enzymes, e.g., inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2), in monocyte, macrophage, and microglial-like cell lines (7). Inflammatory stimuli (e.g. lipopolysaccharide and TNF-α) trigger the phosphorylation-induced proteasomal degradation of the inhibitor of NF-κB proteins (IκB). This triggers the activation and translocation of the NF-κB p65 protein into the nucleus, which leads to the expression of various kinds of inflammatory mediators. γ-oryzanol inhibits IκB-α degradation, resulting in the inhibition of NF-κB p65 nuclear translocation. This prevents the expression of inflammatory molecules.
and the subsequent development of inflammation. The anti-inflammatory effect of γ-oryzanol is considered to be dependent on its ferulic acid component since both compounds inhibit NF-κB activation similarly (3, 4). In addition, rice isoprenoids also possess potential to exert immune modulation (3). Geranylgeranyl diphosphate, which is contained in rice endosperm, could be converted to geranylgeraniol by intestinal alkaline phosphatase (8). Geranylgeraniol is capable of restoring the mevalonate pathway that is impaired in inflammatory status and thereby suppress inflammatory responses in macrophages (9, 10). Collectively, rice contains multiple small molecules with immunomodulatory function. Advanced knowledge about such molecules is essential for development of rice-based functional foods.

2.2 Dietary fibers

Rice bran makes up around 22.8% of the total fibers of rice bran. Multiple studies have shown beneficial effects of rice bran fibers including hypocholesterolemia, anti-diabetic, and anti-cancer effects (11, 12). In addition, recent studies have shown that dietary fibers possess immunomodulatory function (3, 13–15). The immunomodulatory function of rice fibers has been assessed using murine models of colitis, or obesity-inducing inflammation induced by macrophage polarization (13–15). Notably, Komiyama et al. showed that enzyme-treated rice bran, in which starch was removed but which still contained various dietary fibers, suppressed the development of colitis (13). This effect of enzyme-treatment of rice bran was accompanied with a concomitant reduction in the serum levels of pro-inflammatory cytokines and enhanced levels of short chain fatty acids (SCFAs) in the cecum. In addition, the enzyme-treated rice bran significantly suppressed the growth of a pathogenic Clostridium species.

SCFAs such as acetate, propionate, and butyrate are the end products of the gut bacterial digestion of food-derived components. It is now well known that SCFAs regulate innate and adaptive immune cell generation, trafficking, and function (16, 17). In particular, the effect of SCFAs on regulatory T cells (Treg) is important for immune modulation. Notably, macrophages and DCs express GRP109a (also known as hydroxycarboxylic acid receptor 2), which is a nicotinic acid/niacin, and (D)-beta-hydroxybutyrate receptor. The interaction between butyrate and GRP109a promotes the production of IL-10 and retinol dehydrogenases (enzymes producing retinoic acid) from macrophages and DCs, thereby inducing Treg generation (16–18) (see Fig. 1). Treg express GPR43, which is also a receptor for SCFAs (18). Engagement of GPR43 with SCFAs promotes Treg differentiation through epigenetic modifications by inhibiting histone deacetylase, which leads to the increased expression of Foxp3 (Forkhead box P3) (19). Foxp3 is a transcription factor that plays a critical role in the development and function of Treg. The severity of chronic inflammatory disorders including allergies, IBD, and rheumatoid arthritis is inversely correlated with gut microbial diversity and the abundance of butyrate-producing bacteria (20–22). Taken together, rice bran fibers potentially induce Treg and suppress the development of inflammatory diseases.

2.3 Low allergenic property

It is noteworthy that rice possesses beneficial properties, i.e. it is low allergenic effects and is gluten free when compared to wheat, another major staple food. The prevalence of food allergies has increased in westernized countries (23). Clinically important foods are often referred to as the big eight: which include milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat and soybean (23). The big eight account for about 80–90% of all food allergies in the United States, Japan and other westernized countries. These allergenic foods contain multiple allergens.

So far, only two rice allergens have been registered in WHO/IUIS (see http://allergen.org/), which is the official Allergen Nomenclature Sub-Committee, under the World Health Organization and the International Union of Immunological Societies (Table 1). In case of wheat, 28 allergens inducing food allergy, or baker’s asthma have been identified and registered in WHO/IUIS (Table 2). Junker et al showed that wheat contains allergens (α-amylase/trypsin inhibitors) with strong intrinsic immunogenicity for stimulating pro-inflammatory cyto-
Table 1. A list of rice (Oryza sativa) allergens registered in WHO/IUIS.

| Allergen | Protein family |
|----------|---------------|
| Ory s 1  | Beta-expansin  |
| Ory s 12 | Prollin A      |

Table 2. A list of wheat (Triticum aestivum) allergens registered in WHO/IUIS.

| Allergen | Protein family |
|----------|---------------|
| Tri a 12 | Prollin       |
| Tri a 14 | Non-specific lipid transfer protein 1 |
| Tri a 15 | Monomeric alpha-amylase inhibitor 0.28 |
| Tri a 17 | Beta-amylase  |
| Tri a 18 | Agglutinin isolecitin 1 |
| Tri a 19 | Omega-5 gliadin, seed storage protein |
| Tri a 20 | Gamma gliadin |
| Tri a 21 | Alpha-beta-gliadin |
| Tri a 25 | Thioredoxin |
| Tri a 26 | High molecular weight glutenin |
| Tri a 27 | Thiol reductase homologue |
| Tri a 28 | Dimeric alpha-amylase inhibitor 0.19 |
| Tri a 29 | Tetrameric alpha-amylase inhibitor CM1/CM2 |
| Tri a 30 | Tetrameric alpha-amylase inhibitor CM3 |
| Tri a 31 | Triosephosphate-isomerase |
| Tri a 32 | 1-cys-peroxiredoxin |
| Tri a 33 | Serpin |
| Tri a 34 | Glyceraldehyde-3-phosphate-dehydrogenase |
| Tri a 35 | Dehydrin |
| Tri a 36 | Low molecular weight glutenin GluB3–23 |
| Tri a 37 | Alpha purothionin |
| Tri a 39 | Serine protease inhibitor-like protein |
| Tri a 40 | Alpha amylase inhibitor |
| Tri a 41 | Mitochondrial ubiquitin ligase activator of NFkB 1 |
| Tri a 42 | Hypothetical protein from cDNA |
| Tri a 43 | Hypothetical protein from cDNA |
| Tri a 44 | Endosperm transfer cell specific PR60 precursor |
| Tri a 45 | Elongation factor 1 (EIF1) |

Conclusions

Rice contains multiple immunomodulatory components, which potentially exert anti-inflammatory actions. So far, the function of rice components has been assessed using murine models of inflammatory disorders. It is crucially important to assess whether these rice components are able to modulate inflammatory status in humans. For patients with food allergy and gluten-inducing intestinal disorders, rice is beneficial food. Rice serves as a gluten-free and low allergenic food. Further investigation in the immunological properties of rice components could contribute to establish nutritional intervention strategies for multiple inflammatory disorders and to deliver better health for society.

Disclosure of State of COI

The author declares no conflict of interest in relation to this work.

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