

Vaccine therapy for dysbiosis-related diseases

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Abstract

Progress in genomic analysis has resulted in the proposal that the intestinal microbiota is a crucial environmental factor in the development of multifactorial diseases, such as obesity, diabetes, rheumatoid arthritis, and inflammatory bowel diseases represented by Crohn's disease and ulcerative colitis. Dysregulated gut microbiome contributes to the pathogenesis of such disorders; however, there are few effective treatments for controlling only disease-mediating bacteria. Here, we review current knowledge about the intestinal microbiome in health and disease, and discuss a regulatory strategy using a parenteral vaccine with emulsified curdlan and CpG oligodeoxynucleotides, which we have recently developed. Unlike other conventional injectable immunizations, our vaccine contributes to the induction of antigen-specific systemic and mucosal immunity. This vaccine strategy can prevent infectious diseases such as *Streptococcus pneumoniae* infection, and control metabolic symptoms mediated by intestinal bacteria (e.g. *Clostridium ramosum*) by induction of high titers of antigen-specific IgA at target mucosal sites. In the future, our vaccination approach could be an effective therapy for common infectious diseases and dysbiosis-related disorders that have been difficult to control so far.

Key words: Dysbiosis; IgA; Microbiome; Mucosal immunity; Pathobiont; Vaccine

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Core tip: How to control intestinal pathogenic bacteria that mediate multifactorial diseases is a major concern worldwide. There are few methods for controlling only

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intestinal pathogenic bacteria; therefore, we have developed a prime–boost type, next-generation mucosal vaccine, and have used it for control of bacterial intestinal diseases. This vaccine can contribute to prevention of *Clostridium ramosum*-mediated obesity. Thus, this approach might be useful for protecting against microbe-associated disorders of the intestine.

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INTRODUCTION

With the rapid progress of next-generation sequencing and genome analysis technology, human genome analysis has ended, and the focus has shifted to research on commensal microbiomes^[1-8]. Body sites that are exposed to a wide variety of external antigens through mucosal sites, such as the respiratory organs and gastrointestinal tract, are constantly colonized with microorganisms, resulting in a symbiotic relationship. If this relationship is broken, the host immune response to microorganisms is distorted, sometimes causing disease. Dysbiosis, which is defined as an imbalance in the repertoire of the intestinal microbiota, is associated with many disorders in humans^[9-11]. Therefore, novel strategies to control dysbiosis-associated diseases by attenuating the function of related microorganisms are necessary.

Antibiotics, which were first deployed in 1910, have drastically changed our lives^[12]. In particular, penicillin discovered in 1928 contributed to the discovery of naturally occurring antibiotics. Antibiotics have extended our lifespans by > 20 years. However, a rapid increase in multidrug-resistant bacteria has arisen because of overuse and inappropriate consumption and application of antibiotics, which reveals that antibiotics are not a panacea for infectious diseases^[13,14]. In addition, antibiotics sometimes cause dysbiosis and can lead to diseases such as *Clostridioides difficile* (*C. difficile*) infection^[15]. Thus, although antibiotics are available for killing disease-specific commensal bacteria, they are not suitable for eliminating only pathogens.

Fecal microbiota transplantation (FMT), an effective therapy for dysbiosis-related diseases such as *C. difficile* infection, has been shown to improve aberrant intestinal microbiota^[16,17]. Feces from healthy individuals, which are considered relatively safe, are usually used for FMT. However, it was recently reported that antibiotic-resistant bacteria from donor feces were transferred to recipients and induced bacteremia^[18]. This is an emergency issue and FMT is not now a recommended regimen. In fact, elimination of only pathobionts through the intestinal mucosa is difficult; therefore, development of novel methods to control dysbiosis-related diseases by attenuating the function of pathobionts is strongly desired.

In this review, we present current knowledge about the intestinal microbiome in health and disease, and discuss a prime–boost type, next-generation mucosal vaccine that we have recently developed and reported for control of disease mediated by intestinal bacteria.

INTESTINAL MICROBIOME IN HEALTH AND DISEASE

Intestinal commensal microbes have primarily been analyzed through single bacterial species isolation. Since most enteric bacteria do not like aerobic conditions, it has been difficult to culture them. However, advances in culture-independent technologies such as next-generation sequencing have shown the dynamics of the human intestinal microbiota^[9,19]. For example, trillions of intestinal microbes reside in the gastrointestinal tract and dysbiosis is correlated with diseases such as obesity^[20-22], diabetes^[23-25], rheumatoid arthritis (RA)^[26-31], and inflammatory bowel diseases (IBDs) including Crohn's disease and ulcerative colitis^[32]. Therefore, in addition to the current best treatment, it is suggested that controlling dysbiosis may improve these diseases.

It is widely accepted that metabolic diseases, such as obesity and diabetes, are intimately correlated with diet and dysbiosis^[22,33]. Germ-free (GF) mice do not develop western-diet-induced obesity^[34-36]. It was also shown in 2006 that colonization of GF

mice with intestinal microbiota from obese mice led to a significantly greater increase in total body fat than colonization with microbiota from lean mice^[21]. This suggests a strong association between the intestinal microbiota and host metabolism. The intestinal microbiome from obese mice and humans has a significantly higher ratio of Firmicutes to Bacteroidetes (F/B ratio) than that from their lean counterparts^[21,37-40]. In addition, the bacterial diversity is lower in the microbiota from obese than lean individuals^[39,41]. However, other studies have shown no difference in the F/B ratio between obese and lean individuals^[42-46]. Therefore, although the diversity in obese individuals is low compared with that in lean individuals, the correlation between obesity and the F/B ratio is unclear.

There is an increased risk of developing type 2 diabetes in obesity; therefore, dysbiosis might also influence type 2 diabetes. Previous reports have shown that disorder of intestinal carbohydrate metabolism and low-grade gut inflammation cause insulin resistance^[47-49]. A reduced abundance of short chain fatty acids such as butyrate is associated with type 2 diabetes^[50]. Vrieze *et al*^[51] showed that FMT improved insulin resistance in individuals with metabolic syndrome by altered levels of butyrate-producing intestinal bacteria, indicating that gut microorganisms might be developed as therapeutic tools in the future.

RA is a systemic inflammatory disorder including in polyarthritis that leads to joint destruction. Although both genetic and environmental factors are involved in the pathogenesis of RA, intestinal microbiota analysis has recently attracted much attention, along with single nucleotide polymorphism analysis. When mice are reared in GF conditions, arthritis does not develop, indicating that intestinal microbiota is related to onset of arthritis^[28,52-54]. Abdollahi-Roodsaz *et al*^[53] showed that interleukin-1 receptor antagonist knockout mice do not spontaneously develop T-cell-mediated arthritis under GF conditions. However, they do develop arthritis under specific-pathogen-free conditions, and monoclonization of the mice with *Lactobacillus bifidus* induces arthritis^[53]. Matsumoto *et al*^[55] also showed that K/BxN T-cell receptor transgenic mice develop arthritis under specific-pathogen-free conditions, but not GF conditions, and monoclonization of the mice with segmented filamentous bacteria induces arthritis. Previous studies have shown that composition of the microbiota is altered in early RA^[26,28,56]. In the preclinical stages of RA, *Prevotella* species such as *Prevotella copri* (*P. copri*) are dominant in the intestine. Maeda *et al*^[28] showed that microbiota isolated from RA patients whose fecal bacteria contained high levels of *P. copri* contributes to the development of Th17-dependent arthritis, and monoclonization of SKG mice with *P. copri* is sufficient to induce arthritis. Thus, although more precise investigations are needed to determine which bacterium is a target for RA treatment, it is strongly suggested that there are intestinal pathogens that are related to the pathogenesis of human RA.

IBDs are increasing in incidence worldwide^[57]. Also in Japan, the numbers of IBD patients have rapidly increased over the past 30 years, suggesting that in addition to genetic predisposition, environmental factors such as dysbiosis are more involved in the development of IBDs^[58]. Various changes in the intestinal microbiota have been reported in IBD patients^[59-61]. The advent of next-generation sequencing has revealed a range of altered microbiota in the intestine. However, a common problem is that it is unclear whether the dysbiosis observed in IBD patients is a cause or a consequence of intestinal inflammation. Given the complicated relationships between the intestinal immune system and gut microbiota, further studies are needed to elucidate the pathogenesis of IBDs and develop more effective treatments.

PRIME-BOOST TYPE MUCOSAL VACCINE

Conventional injectable vaccines, including subcutaneous vaccines, have the ability to induce antigen-specific IgG, maintain antigen-specific immune memory, and contribute to prevention of severe infection^[62-64]. Pediatric vaccination is a key factor in protection against many life-threatening infections^[64]. However, despite progress in vaccine technology, many infections remain incompletely controlled in both humans and animals worldwide.

Mucosal immune responses are thought to be effective for prevention of infection because foreign antigens, such as microorganisms and food antigens, enter the host through mucosal surfaces^[65-69]. In the mucosal sites, secretory IgA (SIgA) plays an important role in regulating intestinal health and disease prevention^[70-78]. The major functions of IgA are (1) prevention of adherence, colonization, and invasion of pathogenic microorganisms that invade the mucosal surface; (2) neutralizing effect on toxins and enzymes produced by pathogenic microorganisms; (3) capturing pathogenic microorganisms in the mucus layer; and (4) antimicrobial activity. Only

limited numbers of mucosal vaccines are available to date; therefore, a new mucosal vaccine strategy is strongly desired for induction of beneficial systemic immune responses.

IgA is the most abundant antibody in mucosal secretory components. In the intestinal mucosa, there are two types of IgA production mechanisms, represented by T-cell-dependent and T-cell-independent immune responses^[79-82]. In the gut, T-cell-dependent antibody responses are involved in activation of B cells by antigen in the organized lymphoid tissue of Peyer's patches, mesenteric lymph nodes and isolated lymphoid follicles^[82-84]. It has been shown that both CD40L and transforming growth factor- β 1 are essential for the induction of T-cell-dependent IgA class switching^[85]. In contrast, T-cell-independent IgA class switch recombination occurs in B1 cells of the gut-associated lymphoid tissue (GALT), where IgA is constitutively induced by stimulation with commensal bacteria^[82].

GALT, such as Peyer's patches and isolated lymphoid follicles, is the primary site for IgA induction^[86,87]. It has been reported that antigen-specific IgA-producing B cells develop in GALTs with the aid of GALT-dendritic cells (DCs). It is notable that retinoic acid synthesized by GALT-DCs can contribute to IgA synthesis^[87-89]. GALT-DCs are also able to imprint gut-homing chemokine receptors such as α 4 β 7 integrin and C-C chemokine receptor type 9 on B and T cells, which is an essential process for lymphocyte migration to the intestines^[90].

Intestinal lamina propria DCs (LPDCs) are also crucial inducers of SIgA-producing B cells in a T-cell-independent manner. We have previously reported two subsets of small-intestinal LPDCs based on their differential CD11c and CD11b expression patterns: CD11c^{hi}CD11b^{lo} LPDCs and CD11c^{hi}CD11b^{hi} LPDCs^[91-93] (Figure 1). CD11c^{hi}CD11b^{hi} intestinal LPDCs express the gene encoding the retinoic-acid-converting enzyme, *Raldh2*, and are able to induce antigen-specific SIgA as well as systemic immunity mediated by Toll-like receptor (TLR) 5 or 9 stimulation^[91] (Figure 1). In contrast to CD11c^{hi}CD11b^{hi} LPDCs, CD11c^{hi}CD11b^{lo} LPDCs express TLR3, TLR7 and TLR9, which recognize dsRNA, ssRNA, and CpG oligodeoxynucleotides (ODNs), respectively^[93] (Figure 1). They do not express *Raldh2* and are not involved in IgA synthesis in the small-intestinal lamina propria^[93]. In addition, high titers of antigen-specific IgA were detected in fecal extracts from antigen-loaded CD11c^{hi}CD11b^{hi} LPDC-immunized mice^[93]. Accordingly, CD11c^{hi}CD11b^{hi} LPDCs are considered to be an ideal target for a mucosal vaccine, but it has thus far been technically difficult to induce antigen-specific mucosal immunity using conventional injectable vaccines.

We have recently reported that splenic DCs stimulated with both curdlan, dectin-1 ligand, and CpG-ODN, TLR9 ligand, successfully induced antigen-specific fecal IgA as well as antigen-specific serum IgG and splenic Th1 and Th17 responses in mice^[94]. This indicates that combination of curdlan and CpG-ODN is available as an adjuvant of parenteral vaccination to induce broad functional immunity against mucosal antigens. We found that intramuscular immunization with the combination of curdlan and CpG-ODN emulsified with incomplete Freund's adjuvant induced antigen-specific fecal IgA as well as serum IgG and splenic Th1 and Th17 responses^[94] (Figure 2). However, although antigen-specific IgG in serum was continuously detected after prime injection, antigen-specific IgA production in feces was only transiently detected by parenteral immunization with curdlan + CpG-ODN^[94]. Therefore, additional immunization, for example, boosting, to induce more durable mucosal immunity at targeted mucosal sites is thought to be necessary. We have demonstrated that after oral, nasal or vaginal antigen administration, high titers of long-lasting antigen-specific intestinal, lung or vaginal IgA are inducible^[94] (Figure 2). Also, this prime-boost vaccine is effective against cholera-toxin-induced diarrhea and *Streptococcus pneumoniae* (*S. pneumoniae*) infection^[94]. Thus, we established intramuscular antigen injection adjuvanted with curdlan + CpG-ODN and subsequent antigen administration on target mucosal sites (prime-boost vaccination) as a new vaccine strategy capable of inducing strong and durable systemic and mucosal immunity.

FUTURE REGULATION OF DYSBIOSIS-ASSOCIATED DISORDERS

Intestinal dysfunction has been correlated with multifactorial diseases^[9], suggesting that the mucosal immune responses provide a solid causal link between pathological symptoms in the host and disease-associated dysbiosis. Several studies have identified some pathobionts, such as *Clostridium ramosum* (*C. ramosum*)^[95], *P. copri*^[26,28], *Helicobacter pylori*^[96], adherent invasive *Escherichia coli*^[97], *Clostridium scindens*^[98], and *Enterococcus gallinarum*^[99]. Therefore, regulating the function of disease-associated

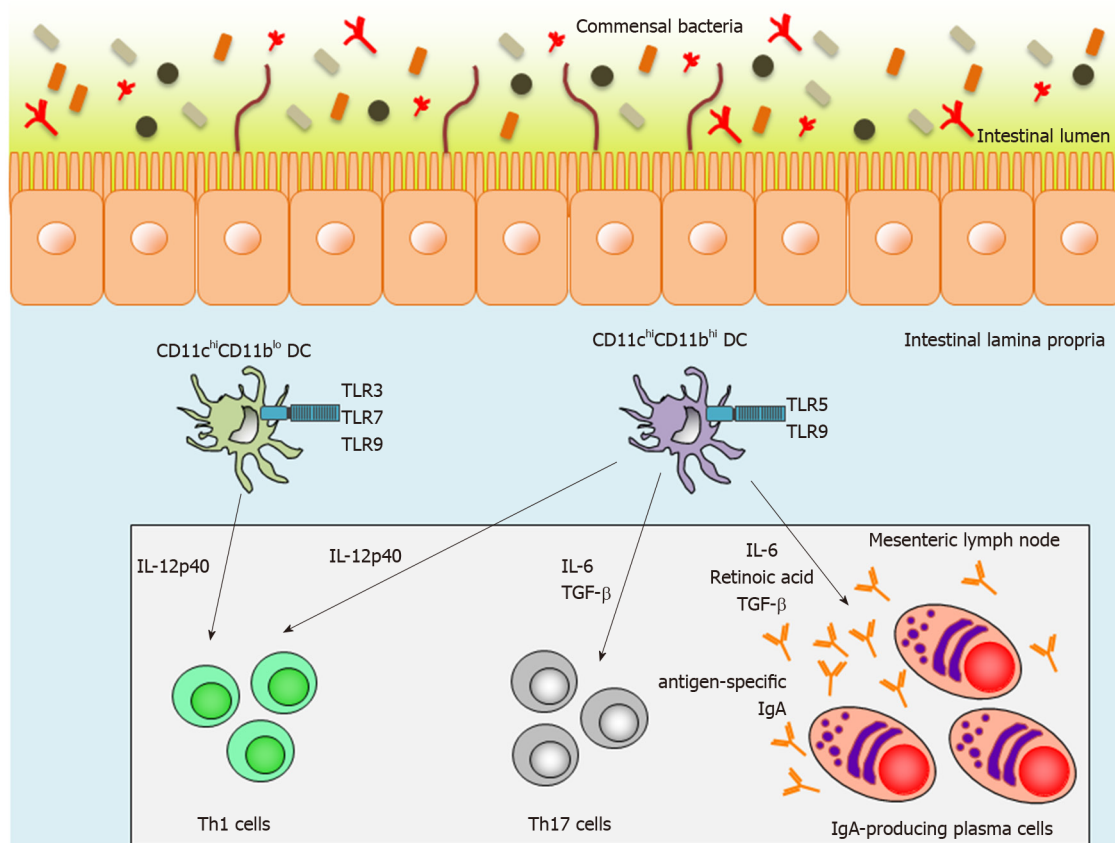


Figure 1 Function of two distinct lamina propria dendritic cells in the small intestine. Mouse small-intestinal lamina propria dendritic cells (LPDCs) are divided into two subsets on the basis of CD11c and CD11b expression. CD11c^{hi}CD11b^{lo} LPDCs express Toll-like receptor (TLR) 3, TLR7 and TLR9, whereas CD11c^{hi}CD11b^{hi} LPDCs express TLR5 and TLR9. After TLR stimulation, activated CD11c^{hi}CD11b^{lo} LPDCs can produce interleukin (IL)-12p40, IL-6, transforming growth factor-β and retinoic acid, and subsequently induce antigen-specific Th1 and Th17 responses and antigen-specific-IgA-producing plasma cells. In contrast to CD11c^{hi}CD11b^{hi} LPDCs, activated CD11c^{hi}CD11b^{lo} LPDCs can induce antigen-specific Th1 responses, but not antigen-specific Th17 responses and antigen-specific-IgA-producing plasma cells. TLR: Toll-like receptor; TGF: Transforming growth factor; IL: Interleukin; DC: Dendritic cell.

pathobionts can lead to prevention or treatment of dysbiosis-related disorders. However, antibiotics are not suitable for eliminating only pathogens because they have the possibility to induce dysbiosis or multidrug-resistant bacteria^[100].

C. ramosum is an obligate anaerobic bacterium first identified in an appendicitis patient in 1898 and widely inhabits the human gastrointestinal tract. Increased levels of *C. ramosum* are associated with human obesity and diabetes^[20,23]. *C. ramosum* is also associated with clinical symptoms of metabolic disorders in gnotobiotic mice colonized with *C. ramosum* alone and a simplified human intestinal microbiome containing *C. ramosum*. Furthermore, it has been shown that the numbers of *C. ramosum* are higher in mice fed a high-fat compared with normal-fat diet, and this results in increased expression of *Slc2a2* in the small-intestinal mucosa^[95]. Therefore, we recently applied our prime-boost vaccination to control *C. ramosum*-mediated diseases. Our vaccine for *C. ramosum* significantly inhibited body weight gain and the increased levels of *C. ramosum* in the intestinal mucosa under a high-fat diet^[94]. It also resulted in decreased expression of *Slc2a2* and subsequently ameliorated glucose intolerance^[94]. It is notable that this immunization strategy did not induce dysbiosis^[94]. Thus, it might be effective for preventing *C. ramosum*-associated obesity and diabetes.

Until now, there have been few methods that can induce high titers of antigen-specific IgA at target mucosal sites using an injection-type mucosal vaccine. It is noteworthy that we have developed a next-generation prime-boost mucosal vaccine using curdlan and CpG-ODN, and used it for control of diseases such as *S. pneumoniae* infection, and other diseases mediated by intestinal bacteria^[94]. With the advent of gnotobiotic technology, function of the intestinal microbiome has been revealed. However, since there are few methods for specifically attenuating the function of intestinal bacteria, many diseases mediated by intestinal bacteria are still not fully elucidated. Our vaccination is the world's first immunization strategy, and has the potential to be an excellent technique for functional analysis of intestinal bacteria.

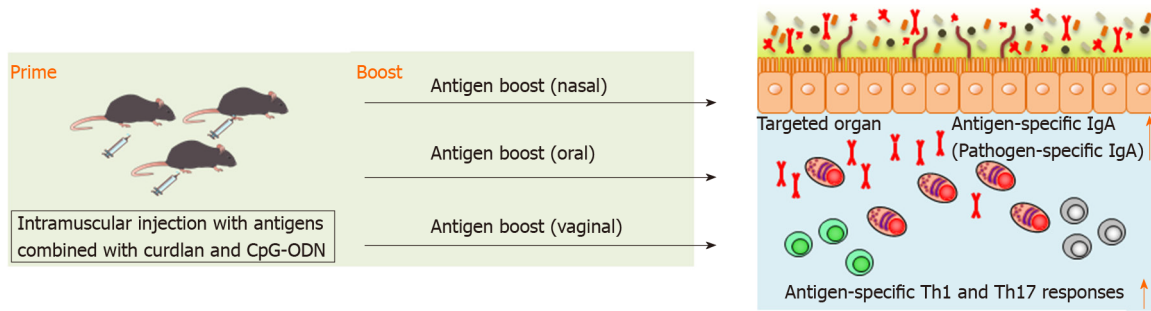


Figure 2 Scheme of antigen-specific immune responses by prime–boost vaccination. Parenteral immunization with antigen emulsified in curdlan and CpG-oligodeoxynucleotides induces antigen-specific fecal IgA as well as serum IgG and splenic Th1 and Th17 responses. Once primed, high titers of long-lasting antigen-specific lung, intestinal, or vaginal IgA are induced after nasal, oral, or vaginal antigen administration, respectively. Also, antigen-specific Th1 and Th17 responses are induced at the targeted organs. CpG-ODN: CpG oligodeoxynucleotides.

CONCLUSION

As the link between various diseases and aberrant intestinal microbiota becomes apparent, there is an urgent need to develop and disseminate control strategies for dysbiosis in addition to existing effective treatments. Antibiotics are not specific to pathobionts and may induce dysbiosis that can lead to disease. Attempts have also been made to control diseases mediated by intestinal bacteria using FMT or probiotic treatments, but these are established and effective treatments. An important treatment for diseases mediated by intestinal bacteria is to improve the underlying disease without inducing new dysbiosis. Vaccination with curdlan + CpG-ODN and antigens and subsequent antigen administration can effectively induce antigen-specific systemic and mucosal immunity. This prime–boost vaccine method has been patented in Japan and prime–boost vaccines targeting various infectious diseases are being developed for future human prescription. There is no doubt that the vaccine technology discussed in this review will become a new treatment in the next generation of antimicrobial strategies. Further analysis of the gut microbiota is necessary, but we are eagerly looking forward to developing pathobiont-specific treatments for human diseases in the future.

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