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Review Article

The Effect of the Microbiome on Vaccine Efficacy

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Abstract

Microbiomes are related to various factors such as geographical location, ethnicity, age, environmental and genetic factors, especially diet and lifestyle. More exposure to germs in childhood appears to be associated with greater expression of TLR5 in the blood. The opposite is true of TLR4, with more exposure to germs and poor hygiene producing fewer cytokines in response to TLR4 stimulation, which affects the response to vaccines. There is also the effect of the intestinal microbiome on the greater immunogenicity of influenza vaccine, so that for the production of antibodies after influenza vaccine, microbiota-related flagellin is detected by TLR5. The interaction of the gut microbiome and the immune system in early infancy is important in the immune response to vaccines because the gut microbiome and the immune system evolve together. Nutritional interventions in infants to increase the effectiveness of vaccines will be more unstable. In adults, microbiomes can further profile and manipulate and design for potentially beneficial changes to it. Greater stability of these changes may be due to the longer shelf life of vaccines.

Keywords: *Microbiome; TLR; Vaccine; Gut Microbiota*

Abbreviation

TLR: Toll Like Receptors

Introduction

A microbiome is a collection of microbes (living organisms) such as bacteria and fungi that live on the surface or inside the tissues or fluids of the human body. These organisms are useful to the human body and disturb the adjustment of substances inside the body tissues or their brokenness in liquids and tissues leads to pathogenic [1]. The human gut microbiome, comprised of approximately 1800 different species and 40,000 bacterial species, has been implicated in numerous aspects of human health and disease [2].

From birth, the body and gastrointestinal tract are colonized by a complex microbial population called microbiota. Most of them are colonized in the intestinal tract (gut microbiota). Gut microbiota is considered an assortment of microorganisms that inhabit the gastrointestinal tract. Since birth to adulthood, the gut microbiota matures from a simple community dominated by a few major bacterial groups into a highly diverse ecosystem that provides both benefits and challenges to the host. The composition of this microbial community depends on the host, but it can also be modified by exogenous and endogenous events but microorganisms are also present in other

areas of the human body such as the skin, airways and genitourinary tract. These bacteria play a major role in various functions of the body, including digestion, synthesis of essential vitamins, and protection against pathogens. One study in humans demonstrated a strong positive association between fecal and mucosa-associated microbial communities for some genera (e.g. *Bifidobacteria spp*.), while other studies have revealed relevant differences between the microbial populations in feces and mucosal biopsy samples. The composition of microbiomes is influenced by various factors such as ethnicity, geographical location, lifestyle, and diet that differentiate the microbiota of different populations [2,3]. We explore here the potential role of the microbiome in vaccine responses in the context of the relationship between the gastrointestinal microbiota and systemic immunity.

The human microbiota in health

The human microbiota affects host physiology to a great extent. Trillions of microbes colonize the human body, including bacteria, archaea, viruses, and eukaryotic microbes. The body contains at least 1000 different species of known bacteria and carries 150 times more microbial genes than are found in the entire human genome [4]. Breast milk is a rich source of maternal antibodies, which provide the first source of adaptive immunity in the newborn's intestinal tract. For breastfed infants, maternal antibodies provide the first source of antigen-specific immunity in the intestinal tract. The predominant type of antibody in breast milk is secretory (S)IgA, which is transported across mammary gland epithelial cells by the polymeric immunoglobulin receptor (pIgR) [3]. Over time, host-bacterial associations have developed into beneficial relationships. Symbiotic bacteria metabolize indigestible compounds, supply essential nutrients, defend against colonization by opportunistic pathogens, and contribute to the formation of intestinal architecture [5].

The human microbiota in disease

Numerous studies have demonstrated the intimate relationship between infection and dysbiosis of the microbiota and have shown that infection is associated not only with the microbiome, but also with viruses [6,7] (Figure 1). For example, according to the study that investigated the differences in the composition of intestinal microbiota between adult patients with *Clostridium difficile* infection (CDI) or *C. difficile*-negative nosocomial diarrhea (CDN) and healthy control subjects using sequence analysis of the V3 hypervariable region of 16S rRNA gene and real-time qPCR. The results are demonstrated that fecal microbiota provides a high curative rate for recurrent *C. difficile* infection (CDI). In this study, they identified CDI-associated key taxa by comparing the fecal microbiota composition of 15 adult patients with CDI with those of 18 individuals with *C. difficile*-negative nosocomial diarrhea (CDN) and 25 healthy control subjects. All healthy controls were free of malignancy or gastrointestinal disease without any history of antibiotics or chemotherapeutic drugs for at least 3 months before sample collection [8]. Microbiota is also associated with the progression of the human immunodeficiency virus (HIV) and gut microbiota may be tightly linked to the increase in microbial translocation and systemic inflammation in patients with human immunodeficiency virus 1 (HIV-1) infection [9]. On the other hand, patients with chronic liver disease have varying degrees of intestinal microflora imbalance with a decrease of total *Bifidobacterial* counts.

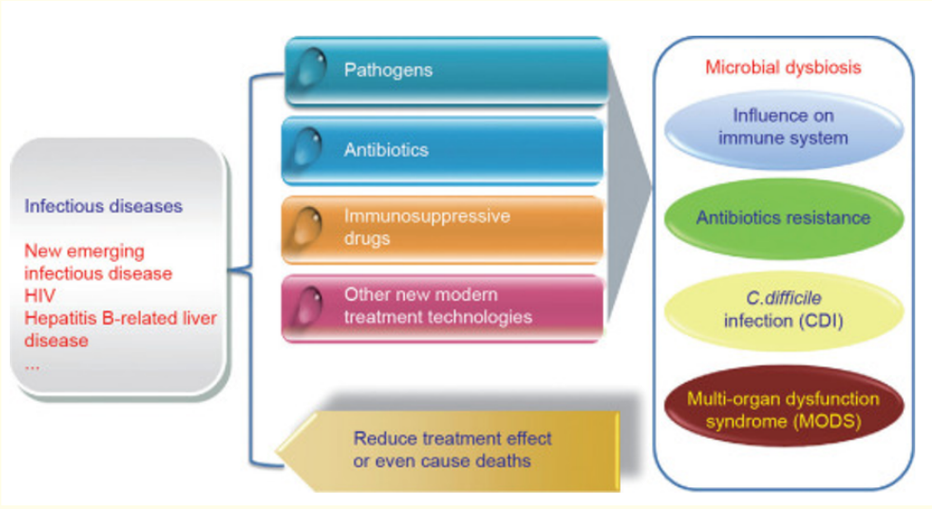

Figure 1: *Infectious diseases have a profound impact on the human microbiota. The wide use of antibiotics, immunosuppressive drugs, and other new treatment technologies for infectious diseases such as frequently emerging infectious diseases, HIV infection, and CDI has a profound impact on the human microbiota, which in turn determines the outcome of the infectious disease in the human host [4].*

Since different properties have been attributed to different Bifidobacterium species and there is no information available for the detailed changes in the genus Bifidobacterium in patients with chronic liver disease heretofore and HBV, it is meaningful to investigate the structure of this bacterium at the species level in these patients [10].

Microbiota balance and immune system

The intestinal microbiota is known to influence the development and balance of the host immune system and has been implicated in the prevention of damage induced by opportunistic microbes, in the repair of damage to the mucosal barrier, and in influencing systemic autoimmune diseases [11,12]. In recent years, according to research, the microbiota can affect the immune response to vaccination [13,14]. Some studies demonstrate in developed and developing countries host factors, such as genetics, nutrition, and host-microbiome, have affected vaccination response [15,16]. An increasing amount of evidence suggests that inflammatory bowel disease (IBD) arises from dysregulated control of host–microorganism interactions. In support of this hypothesis, several IBD risk alleles compromise intestinal immune mechanisms that maintain homeostasis with the microbiota [17,18].

Intestinal bacteria are involved in a wide range of vital reactions in the body, such as the digestion of food molecules and tissue repair. They are effective in safety. Disruption of the balance of immune system cells or disruption of the balance of the microbial population causes various diseases such as intestinal inflammation, diabetes, asthma, and various cancers, and among them, Immune cells, TCD4 + lymphocytes with a large population in the intestine are among the most important cells of the immune system that play a role in establishing and maintaining homeostasis and are considered as the goal in the study of diseases such as inflammatory bowel disease that can be converted. T cell subtypes such as Th1, Th2, and Th17, each of which is involved in cellular and humoral immunity, are important regulators of immune responses. Binding of specific microbes to the intestinal wall or damage to the intestinal epithelium provides antimicrobial antigen-presenting cells (APCs) to antigen-presenting cells, activating Tcell-specific responses. shows the evolution of the immune system with the microbiome and the two-way relationship of the immune system with common bacteria [19,20].

The microbiome plays the role in the development, function, and balance of the immune system. It leads to chronic inflammatory disorders, autoimmunity, allergies, and metabolic syndromes [21]. Selective interventions in the microbiome provide researchers with therapeutic capabilities in infectious diseases, treatment of tumors, improvement of vaccine results, and control of antibiotic-resistant bacteria [22,23]. Whereas antibiotic resistance is becoming to increase and antibiotics have been very successful and over the past decade the increase in antibiotic resistance has generated considerable medical problems [24]. By affecting the function of the intestinal barrier, microbiota affects the immune system's response to vaccines. For example, in germ-free mice that were exposed to antibiotics that lacked TLR5, the injection of the trivalent influenza vaccine produced low levels of IgG and plasma cells, and after inoculation of the microbiota in these mice, immune responses were returned to protective level [25] (Figure 2). However, there have been cases of negative and reducing effects of microbiota in the development of immune responses to antigens, especially in vaccines. This is because vaccine antigens are similar to common bacterial antigens [26].

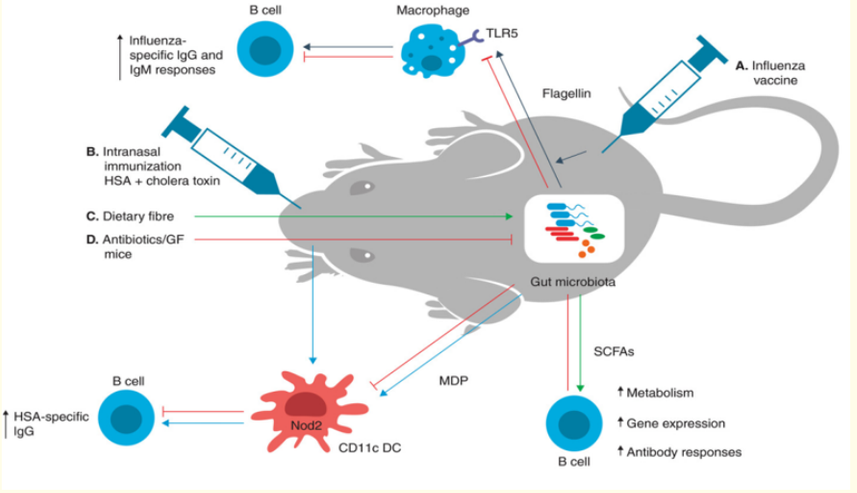

Figure 2: *In germ-free mice that were exposed to antibiotics that lacked TLR5, the injection of the trivalent influenza vaccine produced low levels of IgG and plasma cells, and after inoculation of the microbiota in these mice, immune responses were returned to protective level.*

Then in 2014, flagellin-knocked mice were injected with the flu vaccine, which produced fewer antibodies to the flu than controls. The research team suspected that the decrease was due to a flagellum receptor in the gut microbes of animals. Therefore, in separate experiments, the microbiota of mice was emptied with antibiotics before vaccination and vaccinated against aseptic mice. Both groups of mice, like the control group whose microbiomes were intact, did not respond to the flu vaccine. They concluded that the gut microbiota was involved in producing an optimal antibody response to the influenza vaccine [27,28]. In the absence of the microbiome, lethal T lymphocytes did not survive like memory T lymphocytes. The production of more specific metabolites by microbiomes increases the ability of lethal T lymphocytes to survive and produce memory T cells [29,30].

Vaccine

Vaccines are the most effective way to prevent infectious diseases. Vaccine-induced immune responses vary from person to person, population, and region [31]. The history of the discovery of the vaccine dates back to the 18th century, which was one of the most brilliant periods in medical science. More vaccinations are given to children to raise the level of immunity and the reason for their vulnerability and susceptibility to infection. Immune effects of vaccination are produced by the production of antibodies produced by B lymphocytes that bind to the toxin and pathogen [32,33]. Research shows that various factors such as genetic background, antigen exposure due to infection, diet, and microbiome affect the effectiveness and efficiency of the vaccine [34]. Also, Vaccines display a protective effect against a broad range of diseases including infection, cancer, and allergy. However, vaccine efficacy varies at an individual level. Multiple reports have shown that people in developing countries exhibit reduced responses to oral vaccines [35,36], the efficacy of trivalent oral polio vaccine (OPV) [37,38] and cholera [39] Lack of response or poor response to vaccines is considered to be the most challenging issue in vaccine production, and several studies have been conducted to find potential causes. Furthermore, growing evidence suggests that the gut microbiota, which is known to be different in children from developed and developing countries [35,40].

Since the intestinal microbiome plays an essential role in the regulation and development of the immune system, it seems that the composition and diversity of microbiota in different individuals and on the other hand upsetting the balance of intestinal microbial population dysbiosis can be the most influential factors on immune reactions considered in response to different vaccines. Oral vaccines against *Vibrio cholerae*, *Rotavirus* and polio are less effective in populations with poor hygiene and exposure to fecal-oral infections [41,42]. Changes that occur in populations can affect the effectiveness of vaccines. Because the immune system and the microbial population develop in parallel from birth, it is also when most vaccines are administered that the composition of the primary microbiota can potentially play an important role in the immune response to vaccines. In recent years, the role of diverse microbial populations in the development of the immune system in infancy, in the immune system's response to vaccines, and response to various drugs has been recognized. In response to vaccines, studies show that humans with more diverse and complex bacterial communities respond better to vaccines. Imbalance at birth to accept and tolerate the accumulation and classification of microbes in the affected areas are influenced by various regulatory factors. It can be the prelude to some diseases in adulthood [43]. In recent years, the importance of microbiota in activating the innate immune system has been recognized. Short-chain fatty acids such as butyrate, which is the end product of the fermentation of dietary fiber in the gut, increase the function of T-reg lymphocytes by inhibiting the histone deacetylase enzyme. Lactobacillus is also involved in the regulation of intestinal homeostasis by converting the amino acid tryptophan ligand-receptor (AHR) to the metabolite indole3-aldehyde, which is a ligand for the AHR receptor (aryl hydrocarbon receptor) [44-46]. It is involved in the immunity of intestinal mucosa against microbes [47]. Bacterial lipopolysaccharides also affect the immune system by inducing TLR4 signaling and activating the innate immune system by inducing the expression of inflammatory cytokines. It may have different effects and results [44,47,48] polysaccharide A in *Fragilis bacteroides* directly differentiates Tregs through TLR2 receptors and activates dendritic cells [49].

Gut microbiota

Gastrointestinal microbiomes play an important role in the efficacy and effectiveness of the vaccine. Factors such as age, type of antigen, type of antibody response, and type of microbiome affect the efficacy of the vaccine [50]. 70% of human microbiota reside in the gas-

trointestinal tract. It contains 10^3--10^4 bacteria per gram that reach their maximum values with an increasing gradient of concentration from the gastric lumen to the small intestine to the colon and rectum, creating a dynamic and multilayered ecosystem. Primary intestinal microbiomes include optional anaerobic microbes such as *Enterobacter* and *Enterococci*, and absolute anaerobic microbes such as *Bifidobacterium, Bacteroides*, and *Clostridium* [51,52]. Studies show that populations of some common intestinal bacteria such as Bifidobacterium are involved in inducing an effective immune response to oral vaccines by inducing sIgA production in saliva and mucosa According to studies, there are differences in the microbiome of the body of people in developed and developing countries. In a study by Zheng., *et al*. common gram-negative bacteria in intestinal equilibrium induce systemic IgG responses that protect humans and mice against *Salmonella enterica* and *E. coli* infections [28,53]. Also, the number of *Bacteroides fragilis* bacteria is inversely related to the production of inflammatory cytokines produced by the stimulation of the immune system by bacterial lipopolysaccharides, such as CCl4 and IL-6 [54]. Research by Fadrosh., *et al*. in 2013 showed that the presence of *Clostridiales* and the families *Lachnospiraceae* and *Ruminococcaceae* led to better responses to vaccines. The microbiome has also been recognized as the best natural adjuvant for improving the immune system. Studies have shown that the higher presence *of Acinetobacteria* phylum in oral and injectable vaccines and *Firmicutes* population in oral vaccines have been associated with higher humoral and cellular immune responses. *Bacteroidetes* in oral vaccines has been associated with a weaker immune response [55].

A 2014 study in Bangladesh, examining the effect of the gut microbiome on vaccine response in infants vaccinated against polio, tetanus, BCG, and hepatitis B, showed that the prevalence of *Acinetobacteria phylloxera* in *Bifidobacterium* and *Corynebacterium* was better. *Tetanus* is related [15]. In relation to the response to hepatitis B vaccine in neonates, *Rothia* was significantly and significantly associated with a higher level of humoral immune response than IgG class against this vaccine, while *Pseudomonadales* was associated with a reduced response to this vaccine The effect of the intestinal microbiome on the effect of rotavirus vaccine has also been studied [13,55].

According to a study in France, 20 infants who were vaccinated with the diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis *Haemophilus influenza* type b vaccine were tested for polio-specific IgA levels in their feces. According to experiments performed in the feces of infants with high IgA levels, high levels of *Bifidobacterium longum* and *infantis* subspecies were found [55]. A 2013 study by Harris., *et al*. in adults on the response to the *Salmonella* ty21a oral vaccine in adults found that the vaccine was attenuated live and used orally. The researchers found that differences in microbial composition or its temporary stability observed in individuals induced multiphasic cellular responses. They found that people who had multiphasic cellular responses had temporary differences or stability in microbial composition, but those who were able to respond positively to the vaccine showed no difference in the study, which was performed on 17 adults in the United States. The immune response to *Salmonella typhi* oral vaccine was assessed from one week before vaccination to 2 months thereafter. Measurements were performed at two months of vaccination and included measurements of serum levels of typhoid-specific IgG and IgA immunoglobulins. This study showed that the development of multiphasic cell-mediated immune responses was associated with more complex and diverse bacterial populations in individuals (mostly including the order *Clostridiales* and the family *Lachnospiraceae*), which is associated with better responses to the *Salmonella typhi* oral vaccine [56]. A 2014 study by Huda., *et al*. on the association of microbiota with response to OPV, BCG, TT (Tetanus toxoid) and HBV (Hepatitis B virus) vaccines. In this study, the high frequency of *Acinetobacteria* and *Bifidobacterium phylloxera* increased the efficacy of oral and injectable vaccines in neonates. According to this study, induction of *Bifidobacteria* in the gut improves vaccine response if it is possible to minimize imbalance or dysbiosis in infancy. In the case of oral vaccines, the findings were that in response to the oral polio vaccine, infants who showed a Tcell-specific poliovirus response, as well as higher levels of specific serum IgG at a given time (one week after the fourth dose of the vaccine), had Higher frequencies of the families Coriobacteriaceae and Bifidobacteriaceae were B. longum (subspecies longum and infantis) of Acinetobacteriaceae. Neonates with low levels of serum polio-specific Tcell response and IgG levels had a relatively higher relative frequency than Pseudomonads, and this association was reported to be negative [15]. At 15 weeks of age, neonates with higher Tcell responses were associated with higher relative frequencies of *Bifidobacterium* and *Corynebacterium*. *Acinetobacteria phylloxera* was associated with a higher hemorrhagic response and high levels of tetanus-specific IgG. In the cellular response to the HBV vaccine, no association was found with the composition of the intestinal microbiome [13]. However, the higher relative frequency of *Rothia* genus was associated

with higher levels of hepatitis B-specific serum IgG. In this study, the relationship between the intestinal microbiome and BCG vaccine was investigated and it was found that higher cellular immune response to PPD antigen with a higher frequency of *B. longum* subspecies *Infantis* and PPD skin test responses with a higher frequency of *Rothia* genus *Actinomycetes* and higher frequency of *Pseudomonas* Lower specific Tcell was associated with PPD and higher relative abundance of *Enterobacteriales* with lower responses was associated with PPD cutaneous testing [15].

Effect of the microbiome on nanovaccine

One of these recently confirmed cases is the body's response to drugs, especially nanovaccines designed to treat metabolic syndrome. This syndrome is the cause of many secondary diseases. One way to treat metabolic syndrome is to use poly lactic-co-glycolic acid (PLGA) nanoparticles in the vaccine. New studies show that this nanovaccine is less effective in cases where the gut microbiome is disrupted. Subsequent studies show that the replacement of PLGA nanoparticles with poly-hydroxyethyl methacrylate) will return the efficiency of the nanovaccine to normal.

Although the relationship between the microbiome and the efficacy of nanovaccines has not been definitively determined, researchers reporting the event believe that the nanoparticles used will restore the gut microbiome balance [57-60].

Effect of microbiome on corona vaccine

Studies show that people with high microbial diversity in the gastrointestinal tract have a stronger immune system and a milder severity of Covid-19 disease. Exercise, following a varied diet rich in fiber and antioxidants, taking probiotics, prebiotics, and symbiotic, and avoiding stress in modulating the diversity of microbiota in the human body reduce the effects of respiratory diseases such as coronary heart disease. Also, the role of intestinal microbiomes in increasing the function of the immune system is to increase the intestinal epithelial barrier, compete with pathogens in nutrient uptake, attach to the intestinal epithelium and produce antimicrobial substances and balance the innate and humoral immune system [61-64].

Conclusion

The mammalian intestine is colonized by trillions of microorganisms that have co-evolved with the host in a symbiotic relationship. Although the influence of the gut microbiota on intestinal physiology and immunity is well known, mounting evidence suggests a key role for intestinal symbionts in controlling immune cell responses and development outside the gut [65]. According to this belief, gut microbiota would have crucial role on vaccine efficacy.

There are many studies on the effect of microbiome on immunity. There are several methods to study this effect, including bacterial culture, Multiplex PCR for *Bifidobacteria* [5,25] and 16 srRNA gene sequencing techniques Roche454 [26].

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