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Investigation of the relationships among respiratory syncytial virus infection, T cell immune response and intestinal flora

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Abstract. – The aim of this work was to evaluate the relationships among respiratory syncytial virus infection, T cell immune response and intestinal flora.

Peer-reviewed papers published in English were collected through extensive searches performed in PubMed, Web of Science, Google Scholar, and China National Knowledge Infrastructure databases. The articles were reviewed to extract relevant information on the immune responses of Th1/Th2 and Treg/Th17 to respiratory syncytial virus infection in the body.

RSV (Respiratory syncytial virus, RSV) infection leads to imbalance between Th1/Th2 and Treg/Th17 immune cells, resulting in Th2 or Th17 dominant immune responses, which can generate immune disorder and aggravate clinical symptoms. Intestinal micro-organisms play very important roles in maintaining stable immune environment, stimulating immune system maturation and balancing Th1/Th2 and Treg/Th17 immune systems in children. In our review of various papers from around the world, we speculated that the steady state of intestinal bacteria was disturbed after children got infected with RSV, resulting in intestinal flora disorder. Then, the imbalance between Th1/Th2 and Treg/Th17 immune cells was increased. Both intestinal flora disorder and RSV infection could cause cellular immunity imbalance of Th1/Th2 or Treg/Th17, eventually leading to disease deterioration and even a vicious cycle. Normal intestinal flora can maintain immune system stability, regulate the dynamic balance of Th1/Th2 and Treg/Th17 and prevent or mitigate adverse consequences of RSV infection.

Because probiotics can improve intestinal barrier function and regulate immune response, they can effectively be used to treat children with recurrent respiratory tract infections. Using conventional antiviral therapy strategy supplemented with probiotics in the treatment of clinical RSV infection may be better for the body.

Key Words:
Respiratory syncytial virus, T-helper 1/T-helper 2, Regulatory T cells/T-helper17, Intestinal flora, Cellular immunity.

Introduction

As the most common pathogen of viral pneumonia among children, respiratory syncytial virus (RSV) can cause interstitial pneumonia and bronchiolitis[1,2]. Based on statistics, more than 30 million children < 5 years old are infected with RSV in the world each year, of which 3-4 million need hospitalization and 0.1-0.2 million hospitalized children experience serious adverse consequences and even death[1,3]. 70% of children are infected with RSV at the age of about one year and 100% have RSV infection in the age range of 2 to 3[2,4,5]. Although most children present only mild upper respiratory symptoms, 2-5% develop severe bronchiolitis and require further treatment[5-7]. In addition, these children have a high risk of repeated wheezing and asthma[8,9]. Reasonable treatment strategies for children with RSV infection are of great significance in the efficacy and prognosis of therapy.

Immune responses help the immune system of body to identify themselves, eliminate alienation and maintain the balance of body environment.

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The physiological function of the immune system is mainly fulfilled by immunizing lymphocytes. Immune response is also described as the process of antigen recognition by immune lymphocytes, based on their own activation, proliferation and differentiation to exert their effect. In immune response, immunogen only contribute to the selection and triggering of immune lymphocytes. During antigen recognition, immune lymphocytes are activated to form B cell-mediated humoral immunity and T cell-mediated cellular immunity, and are mediated in non-activated state to form immune tolerance[10,11].

As a research hot topic in recent years, gut microbiota greatly affects human health mainly in regulating digestion, physiology, nutrition and immunity. Imbalance of intestinal flora can disturb the regulation of the immune system of body, damage intestinal mucosal barrier, and induce chronic inflammatory diseases. Different gut bacteria might be involved in the differentiation and functional regulation of various immune cell subsets. It is believed that RSV not only causes lung inflammation, imbalances the development of T cells in lungs and releases related inflammatory agents, but also affects intestinal immune cell differentiation and intestinal flora homeostasis. Therefore, this paper reviews the relationships among the mechanisms of RSV infection, T cell immune response, and intestinal flora, and provides a theoretical reference for clinical prevention and treatment of RSV, as well as new drug development.

In this research, a detailed review of published studies was performed on the works published in PubMed, Web of Science, Google Scholar, and China National Knowledge Infrastructure databases using RSV as a search term. Considering technological progress and recent reports, focus was placed on the last 30 years and articles published from January 1st, 1992, to January 1st, 2022, were considered. The search returned 176,262 articles. Peer-reviewed papers published in English language were adopted with no restrictions in terms of article type and geography. Papers related to RSV infection, T cell immune responses and intestinal flora were retrieved. To complement this review, electronic search was supplemented with a manual search of the references of these papers. The papers extracted from electronic databases were screened by reading their titles and abstracts and the full texts of those considered likely to be relevant were retrieved. The retrieved papers were reviewed and critically analyzed.

RSV Infection and T Cell Immune Response

T cell-mediated immunity (CMI) is also known as cellular immune response. Initial T cells (naive T cell, Tn), also known as non-sensitized T cells, migrate to peripheral lymphoid tissue after maturation in thymus. Tn cells are gradually differentiated into Th1, Th2, Th17, regulatory T (Treg), effector T and similar types of cells through antigenic stimulation or dendritic cell delivery. Th cells are mainly divided into Th1 and Th2 cells[11]. Th1 cells, so-called inflammatory T cells, secrete interleukin-2 (IL-2), interferon-α (IFN-α), IFN-γ, tumor necrosis factor-β (TNF-β), etc. These substances mediate cytotoxicity and local inflammation-related immune responses, assist antibody production, participate in cellular immunity, delay hypersensitivity and play an important role in body anti-intracellular pathogen infection[11,12]. Th2 cells mainly secrete IL-4, IL-5, IL-6, IL-10 and IL-13, which help the differentiation of B cells into antibody-secreting cells, regulate humoral immune response and play a key role in the induction of allergic reactions[11,13]. Treg cells are a subpopulation of T cells with immuno-suppressive function. The most important function of Treg cells is the suppressing the activation and survival of effector T cells, avoiding tissue damage and maintaining the immune balance of body by eliminating IL-2 and producing IL-10 and TGF-β during anti-infective immune responses[14-16]. Th17 cells are specific pro-inflammatory cells that produce IL-17, and their main function is the stimulation of inflammatory responses, enhancement of the acquired cellular immune responses, and resisting bacterial, fungal and viral infections[17,18]. IL-17 can also induce pro-inflammatory cytokine and chemokine expression. The activation of IL-17 receptor, which is extensively present in epithelial cells, endothelial cells, monocytes and macrophages, induces infiltration and destruction in tissue cells[19]. The coordination of various T cells plays a critical role in body protection against external stimuli.

RSV-infected children can cause cellular immune responses and imbalance Th1 and Th2 immune responses, especially Th2-dominant immune responses. The severity of clinical symptoms is correlated with increased degree of Th2 response[20,21]. Animal experiments showed that in T cell immune response, Tn cells are induced to differentiate into Th1 cells by RSV virus F protein and Th2 by RSV virus G protein[22,23]. NS1 protein of RSV virus can inhibit Th1, Th2 and

Th17 cell differentiations, while NS2 protein inhibits Th2 and Th17 cell differentiations[16]. Th1 response could produce IFN-γ, TNF-α, IL-2 and activate cytotoxic T and NK cells to promote effective virus removal, which is the most expected auxiliary T cell response mode after RSV infection[2,20]. However, Th2 cells secrete IL-4 and IL-5 which arise obvious and unfavorable inflammatory responses after re-infection with RSV.

Furthermore, Th1 and Th2 can restrain and lower the activation level of each other[24]. Thus, Th2 superior immune response after RSV infection decreases the efficiency of virus removal increasing its damage to body[2,25,26]. Clinical examination[27] revealed that newborns re-infected with RSV generated Th2-dominant immune responses, but this phenomenon is not generally observed in adults. Detecting sera and nasopharyngeal aspirate samples in RSV-infected children increased IL-4 concentration and decreased IFN-γ concentration, suggesting Th2-dominant immune response[20,26,28]. A correlation was also found[26] between IL-4/IFN-γ ratio and disease severity. In 1960s, the trial of FI-RSV vaccine failed since the vaccine not only could not prevent infants from being infected by RSV, but also aggravated and worsened original disease[29]. In FI-RSV-vaccinated cases, immune response was Th2-dominant response and Th1/Th2 ratio was one of the important indicators in measuring the severity of clinical symptoms after RSV infection[25]. It should be noted that, using Th1/Th2 balance to explain the pathogenesis of RSV infection is not absolute. For example, in the severe infection of RSV-induced bronchiolitis various types of immune cells exist.

Disequilibrium of Treg and Th17 immune cells leads to inflammation and autoimmune diseases[17,30]. Treg cells differentiation was relatively weakened and Th17 cell differentiation was increased, resulting in intensified inflammation response after RSV infection. Research[31-33] on RSV-infected mice showed that Treg cells promoted RSV clearance and significantly reduced inflammation degree in mice lungs[34]. Treg cells can modulate immune microenvironment and avoid excessive inflammatory T cell responses, including the inhibition of Th2-dominant immune responses[35]. The number of Treg cells was decreased and that of Th17 cells was increased in IL-10 knock out mice[36]. After IL-10 knock out RSV-infected mice, more severe disease development, increased pro-inflammatory and chemokines levels and increased pathological changes in lungs were observed[34,36].

Breakage between Th1/Th2 or Treg/Th17 also affected immune response to Treg/Th17 or Th1/Th2. In RSV-infected mice, the IL-10 produced by Treg cells can control inflammatory responses to ensure effective virus removal, maintain appropriate immune level of the body and reduce clinical symptoms by inhibiting Th2-based immune responses[31,35,37]. Th17 cells and IL-17 produced by them enhance Th2 response, preventing effective virus removal and enhancing inflammatory responses, eventually leading to more serious clinical symptoms[38]. In addition, the IL-17 produced by Th17 cells could up-regulate the level of Th2 cytokines in Th2-dominant immune environments, demonstrating that Th17 immune response is coordinated with Th2 immune response[38,39]. Wang et al[40] showed that OVA (Ovalbumin, OVA)-sensitized mouse asthma model had increased Th17 and insufficient Treg immune responses, then induced Th2-mediated respiratory inflammation.

The imbalance of Th1/Th2 and Treg/Th17 immune cells resulted in corresponding clinical phenotypes. Th1/Th2 and Treg/Th17 have a complex and intimate relationship. The imbalance of any system can lead to immune system disorders, eventually resulting in the occurrence of diseases.

Intestinal Flora and Immunity

Intestinal flora is a stable microbial community in the intestine of host by long-term evolution, capable of resisting pathogen stimulation and invasion and regulating a series of physiological and metabolic processes[41]. Normal intestinal flora and its metabolites contain a great number of immune stimuli including antigens, toxins, etc., while intestinal immune barrier can generate appropriate responses to different antigens from intestinal mucosal surface such as immune clearance and rejection to pathogens. Research has shown[42] that intestinal mucosa could induce immune responses of different CD4+ T cell subsets after colonization and formation of Treg, Th1, Th2, Th17 and T follicular helper (Tfh) cells, revealing the accurate regulatory mechanism of intestinal immunization. Intestinal flora not only is important to the development and activation of intestinal mucosal immune system, but also is significant for extra-intestinal immune system. Constant stimulation of immune system by normal intestinal microbes is required for its maturation. For example, lactic acid bacteria could stimulate the

secretion of IL-12, IL-18, IFN-γ and other cytokines by peripheral blood cells[43]. Nicaise et al[44] also suggested that intact intestinal flora was the basis for IL-12 production in spleen, which was an important link to innate immunity and acquired immunity. IL-12 effectively improves cellular immune defense function and promotes the differentiation of CD4+ T cells into Th1 cells. In recent years, research[45-47] on intestinal microflora effects on immune environment stability has made great progress. Host microbiota can participate in adaptive modulation of intestinal mucosa to maintain normal intestine state while suppressing immune response, resulting in the generation of inflammatory diseases. Furthermore, microbial composition could affect the susceptibility of immune-mediated diseases, such as autoimmune and allergic diseases[48-50]. Intestinal flora could regulate the reactivity of immune system through immune cells and vice versa. Kawamoto et al[51] showed that intestinal immunosuppressive receptor PD-1 affected the composition of intestinal flora. Under such conditions, intestinal bacteria lose control resulting in excessive breeding and bacterial translocation when intestinal immune activity is reduced. That is, intestinal immune system is inextricably related to systemic immune system.

Flora Imbalance and T Cell Immune Response

The type, number and distribution of intestinal flora are not constant and are affected by several factors such as eating habits, diseases and drugs[52]. Under normal circumstances, intestinal flora and host are in a dynamic equilibrium state through precise regulatory mechanism. When the number, type and proportion of normal intestinal flora are changed, the original stable state of intestinal flora is broken causing flora imbalance[41,53]. The main reason for flora imbalance is irrational application of antibiotics, especially broad-spectrum antibiotics. Experiments have revealed the correlation between intestinal flora imbalance due to the application of antibiotics and occurrence of immune diseases[41,53]. Antibiotics-induced intestinal flora imbalance can generate Th2 and Th17 cell-dominant immune responses and lead to the deficiency of Treg cells immune response[54]. Therefore, antibiotic-induced intestinal flora imbalance might be a risk factor for asthma and other lung diseases. Immune system could be regulated by probiotics through balancing Th1/Th2 ratio[55]. For example, *lactobacillus pentosus* produces IL-10 exerting an anti-allergic effect by regulating Th1/Th2 balance[56]. Studies[57-59] have shown that application of probiotics to newborn asthma mice induced the generation of Treg cells, inhibiting allergic and respiratory diseases. Normal intestinal flora could induce Th1 immune response and inhibit Th2 immune response, reducing the occurrence of allergic diseases. However, intestinal flora imbalance can prevent the maturation of Th1 cells and promote Th2 cell differentiation increasing the risk of respiratory allergies and infectious diseases. Therefore, probiotics can prevent inflammation by retrieving immune imbalance[43,60].

The relationships among RSV, T cell immune response and intestinal flora are shown in Figure 1.

Discussion

Based on the above discussion, it was concluded that intestinal microflora possessed regulatory ability to develop and activate immune system. If the normal colonization process of neonatal intestinal flora is damaged, abnormal reactions occur causing lung allergic immune response when exposed to allergens through ingestion or inhalation[61,62]. Children, especially infants and young children, are prone to the establishment of normal microbes. During these periods, the flora with poor stability and diversity are fragile and susceptible to various unwanted factors. However, the establishment of normal microbes is closely affected by some important physiological functions, such as development and maturation of immune, metabolism, and nutrition systems. If the formation of normal microbes is disturbed during this period, acute and chronic diseases and even some adult diseases could occur. Both intestinal flora disorder and RSV infection cause cellular immunity imbalance in Th1/Th2 and Treg/Th17, eventually resulting in disease deterioration and even a vicious cycle. Normal intestinal flora can maintain the stability of immune system, regulate Th1/Th2 and Treg/Th17 dynamic balance and prevent or mitigate adverse consequences of RSV infection. Therefore, application of conventional antiviral therapy strategies supplemented with probiotics to clinical RSV infection treatment may achieve better treatment results.

Conclusions

Intestinal dysbiosis can aggravate RSV airway inflammation by altering local immune

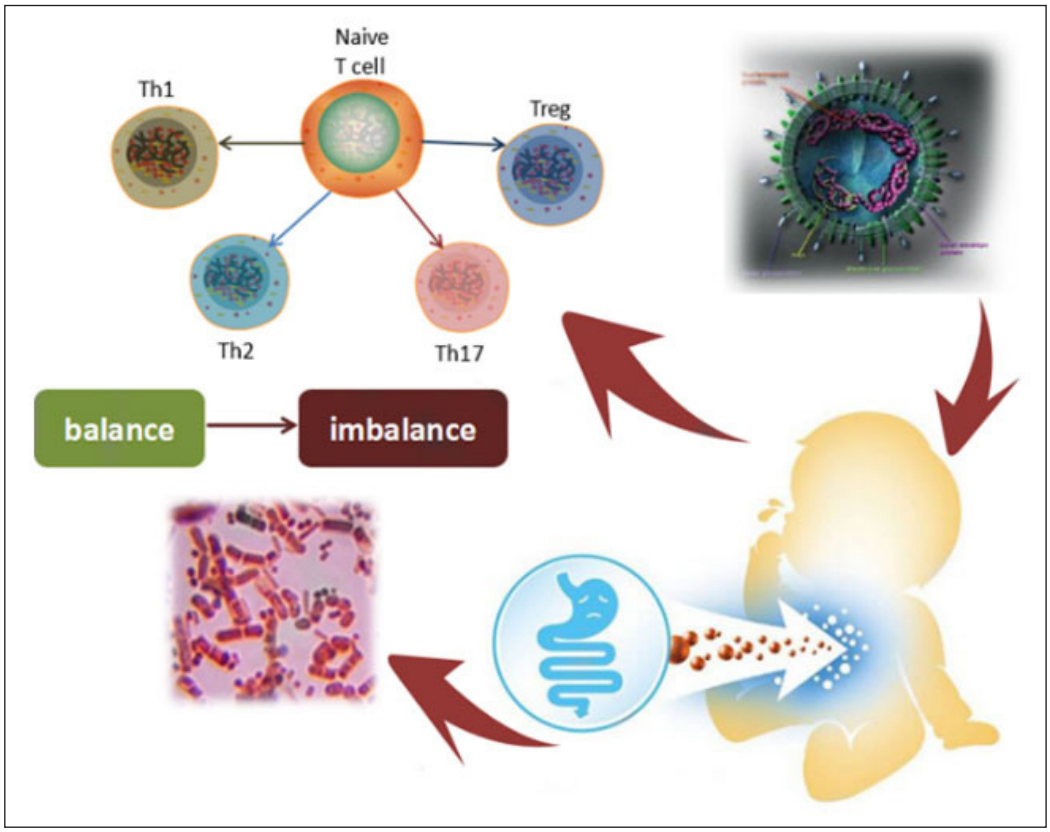

Figure 1. The relationships among RSV, T cell immunity and intestinal flora.

response in lungs. Supplementation with beneficial bacteria can restore immune dysbiosis induced by intestinal dysbiosis and reduce RSV airway inflammation.

Conflict of Interest

The authors declared that they have no conflicts of interest to this work.

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Informed Consent

Not applicable.

Authors' Contribution

HTZ YBY and BY participated in study conception, design, and preparation of the manuscript. QYZ, YD, SXM, WXC, JLQ, XFL, XXS and YJZ reviewed the manuscript. HTZ YBY and BY revised the manuscript and coordinated the whole project. All authors read and reviewed the final manuscript.

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