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Impact of gut microbiota on immune reactions relevant to lung pathologies

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Abstract

Bacterial microbiota of the gastrointestinal tract is known to prevent the invasion of pathogenic microorganisms and regulate intestinal permeability, digestion, metabolism, and immune response. It affects function, homeostasis, and disease outcomes in the gastrointestinal tract and extra-intestinal sites such as the lungs. This review summarizes the currently available knowledge regarding the gut-lung axis. The association of bacterial composition and/or dysbiosis in the gut with asthma, chronic obstructive lung disease, cystic fibrosis, recurrent respiratory tract infections, and lung cancer in humans is highlighted, as well as data obtained from animal models of pulmonary inflammation, which indicated that modulation of immune system activity lies at the base of this interaction. Additionally, the potential use of prebiotics, probiotics, and postbiotics in the treatment of lung inflammation is presented.

Key words: gut bacterial microbiota, gut-lung axis, lung inflammation

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Introduction

Although the term microbiota includes different microorganisms such as bacteria, viruses, fungi, and protozoa distributed over different body surfaces in humans and animals, bacterial microbiota of the gastrointestinal tract (GIT) is the most studied. There is a large amount of data regarding gut bacterial microbiota composition and their role in preventing the invasion of pathogenic microorganisms, intestinal permeability, digestion, metabolism, and immune response (1). The impact of gut microbiota composition and dysbiosis on homeostasis in the gastrointestinal tract and its relationship with various diseases in the GIT has been extensively studied. In recent years, the impact of gut microbiota on distal sites such as the brain (2), skin (3), or lungs (4) has been shown, leading to the coining of terms such as the gut-brain, gut-skin, or gut-lung axis. These new concepts investigate mechanisms by which bacterial microbiota in the GIT affects function, homeostasis, and disease in extra-intestinal sites. Examining the interaction between the gut and lungs might be interesting as these organs have the same embryonic origin (both alveolar and intestinal epithelia develop from the endoderm, and have physical, chemical, and physiological barrier functions), have specific microbiota, and are part of the common mucosal immune system. Additionally, due to their same embryonic origin, both the gastrointestinal and respiratory systems share an entrance (oral cavity) through which microorganisms from the external environment gain access to the host.

The respiratory system (and the lungs), besides gas exchange as its main physiological role, protects individuals from harmful substances present in the air (such as particles, pollen, dust, bacteria, viruses, etc.) by the production of mucus and the activity of cilia. Various xenobiotics to which lungs are continuously exposed might affect their function, resulting in many conditions and disorders of which some are minor and temporary, while others are chronic and more severe. The most common lung disorders include asthma, chronic obstructive lung disease (COPD), cystic fibrosis (CF), lung cancer, bacterial (*Mycobacterium tuberculosis*), viral (respiratory syncytial virus/RSV, influenza virus, severe acute respiratory syndrome coronavirus 2/SARS-CoV-2) or fungal (*Aspergillus fumigatus*) infections. The immune system is relevant for the development and/or progression of each mentioned disease. For example, childhood asthma develops in susceptible (atopic) individuals following an encounter with various environmental allergens that results in the activation of the T helper (Th) 2 response (production of interleukin (IL)-4, IL-5, IL-13), migration of the eosinophils to the lungs and production of immunoglobulin (Ig) E (5). The development of COPD is mainly associated with the immune response to chronic inhalation of cigarette smoke, characterized by an increased number of immune cells (macrophages, neutrophils, lymphocytes and dendritic cells) in the lungs, impaired macrophage function (reduced phagocytosis), increased production of reactive oxygen and nitrogen species, and increased proinflammatory response (interferon (IFN)-γ, and IL-17) (6). Inflammation (migration of neutrophils to the lungs, high production of cytokines and chemokines, etc.), in addition to the production of more viscous mucus resulting in impaired

mucociliary clearance, is noted in CF patients (7). Immune cells (Th lymphocytes, macrophages, dendritic cells and natural killer cells) are also important for lung tumor pathogenesis, and the production of proinflammatory cytokines by Th1 cells and increased cytolytic response contribute to the limitation of tumor progression (8). The activation of the immune response in the lungs is vital for the elimination of pathogens from this organ, but the characteristics of the response depend on the pathogen (9-11).

Bacterial microbiota in the gastrointestinal tract can affect immune reactions in the lungs, but on the other hand, pulmonary inflammation might cause gut dysbiosis (4). In this review, we presented only one aspect of bidirectional communication between the gut and lungs, limited to the papers investigating how bacterial microbiota composition in the gut affects inflammation in the lungs. Results from epidemiological studies are included to show an association of gut dysbiosis with human diseases, although from these studies it is generally not clear whether gut dysbiosis precedes the disease or is its consequence (except for asthma). Evidence from experimental models in which gut dysbiosis exists prior to lung inflammation (germ-free or antibiotic treated animals) or in which microbiota was targeted (by oral application of prebiotics, probiotics or postbiotics) indicate that the modulation of immune system activity is the main mechanism of the gut to lung axis.

Association of gut bacteria with lung diseases

The first indices of the gut-lung axis are co-occurrences of pulmonary abnormalities with inflammatory bowel disease (12). Currently, bacteria in the gastrointestinal tract have been associated with asthma (13-18), COPD (19-22), CF (23), recurrent respiratory tract infection (24), and lung cancer (25-28).

Asthma is a chronic lung disease affecting people of all ages that often starts in childhood, and increased risk for developing asthma in childhood is associated with less mature gut microbiota in the first year of life (13, 18). Early life application of antibiotics that results in decreased alpha diversity indices of gut microbiota (13) and a lower abundance of *Faecalibacterium prausnitzii*, *Roseburia*, *Ruminococcus bromii* and *Clostridium perfringens* (13), or reduction in *Lachnospira*, *Veillonella*, *Faecalibacterium,* and *Rothia* (14), were noted in asthmatic children. Early life colonization with *Bacteroides fragilis* (at 3 weeks of age) (15) and *Clostridium difficile* (1 month) (16) might contribute to the development of asthma. Other factors that can impact gut microbial colonization are also associated with asthma. For example, a higher risk of asthma at the age of six years was noted in children born by cesarean section that results in lower alpha diversity (at age one month and a year) and different microbial composition (differences were most obvious at early time points) when compared with vaginal delivery (17). However, children born by cesarean section have a high risk of asthma only if their gut microbiota remains less mature up to the first year of life. In another study that examined bacterial microbiota at different time points, the occurrence of asthma at the age of 5 years was related to different microbial compositions between healthy and asthmatic children born to asthmatic mothers at age 1 (18). Asthma in these

children is a consequence of the increased abundance of *Veillonella* and lower abundance of *Roseburia, Alistipes,* and *Plavonifactor*. Apart from microbial composition, the relevance of the metabolic activity of bacteria in this disease was also recognized. Asthma was shown to be connected with a lower level of lipopolysaccharide biosynthesis (14), decreased concentration of acetate (14), increased levels of histamine synthesis (29), and a higher level of 3-ketoshinganine (at 3-6 months of age) but a lower linoleic acid (at age one year) (30). In one study examining the impact of cesarean section on asthma development, a higher risk of asthma in children born by cesarean section (compared to naturally born infants) was associated with lower levels of metabolites (tryptophan, bile acid, and phenylalanine) early following birth (31).

Chronic obstructive pulmonary disease is an inflammatory chronic lung disease characterized by airflow blockage and breathing-related problems. A comparison of gut microbiota in COPD patients during the period of stable disease with healthy controls revealed differences in bacterial composition between the two groups, with a higher abundance of *Streptococcus*, *Rothia*, *Romboutsia,* and *Intestinibacter*, but a lower abundance of *Bacteroides*, *Roseburia,* and *Lachnospira* in COPD patients (19). Bacterial microbiota is correlated with disease severity as well (20). Although no differences were noted in alpha diversity and composition between patients with different stages of diseases (GOLD recommendations), the relative abundance of *Veillonella*, *Corynebacterium*, *Romboutsia* and *Aerococcus* was higher in patients with stages 3 and 4 of the disease, while *Megasphaera* was the lowest in patients with stage 1 disease (20). Associations were found between gut microbiota and better lung function in a patient population with a higher abundance of some *Streptococcus* and *Lachnospiraceae* species and a lower abundance of *Desulfovibrio*. Gut microbiota in COPD patients can affect disease progression, as a decline in lung function was correlated with an increase in alpha diversity indices, a decrease in the abundance of Firmicutes, and an increase in *Stentrophomonas* (21). In contrast to that, in patients with stable lung function a higher abundance of *Bacteriodetes* and *Alloprevotella* was noted. Bacterial products can also affect disease severity. Measurements of short-chain fatty acid (SCFA) in patients with COPD revealed lower levels of total SCFA, acetic, isobutyric and isovaleric acids in patients with COPD with stages 3 and 4 (compared to healthy controls) (22).

Cystic fibrosis is a genetic disorder characterized by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene resulting in viscous epithelial secretion. As this disease affects the function of different organs, including the gut, the association of gut dysbiosis with CF cannot be directly estimated. Data show that CF results in a different pattern of gut bacterial colonization compared to healthy controls (32). Regardless of the disease's impact on gut colonization, a significant association was found between disease exacerbation and gut microbiota composition (23).

Recurrent respiratory tract infections are the most frequent diseases in children under 5 years of age. An analysis of fecal bacteria revealed a decrease in bacterial diversity and distinct community structures in patients compared to healthy controls (24).

A higher abundance of *Enterococcus*, but lower *Eubacterium*, *Bacteroidetes,* and *Faecalibacterium* was noted in children with recurrent respiratory tract infections.

The examination of fecal microbiota in lung cancer patients and healthy controls revealed different bacterial compositions between these groups (25, 26), with higher *Bacteroides*, *Veillonella,* and *Fusobacterium*, and lower *Escherichia-Shigella*, *Kluyvera*, *Fecalibacterium*, *Enterobacter* and *Dialister* in cancer patients (25). Additionally, gut microbiota compositions were shown to correlate with different tumor biomarkers (27), tumor stages, and subtypes (28).

Based on the above data, a clear connection between gut dysbiosis and risk for disease development exists only for asthma, as dysbiosis was documented prior to the disease. Although for other diseases the role of gut microbiota composition in disease development is not so obvious (whether dysbiosis exists before disease symptoms or is a consequence of lung inflammation), gut bacteria might have an impact on disease course and stability (exacerbation, stable disease periods, etc.).

Experimental evidence of a gut-lung axis

Studies examining the impact of gut bacteria on inflammatory reactions in the lungs are based on a comparison of germ-free (GF) animals with conventional or GF animals colonized with specific bacteria, animals with different microbial compositions, or animals treated with antibiotics.

The presence of gut commensal bacteria is important for the control of allergic airway inflammation, as shown in GF mice that develop an exaggerated response to ovalbumin (OVA) administration compared to specific pathogen-free (SPF) mice (33). In the absence of commensal bacteria, a higher goblet cell hyperplasia, increased perivascular and peribronchial infiltration of inflammatory cells were noted, as well as a higher production of IL-4 and IL-5, and augmented IgE response. This exaggerated response can be reversed by the colonization of GF mice with commensal flora of SPF mice (33). Additionally, a comparison of airway inflammatory response to OVA in F1 generation of GF mice colonized with humanized microbiota (fecal microbiota from a patient that developed asthma at the age of 3 years) or with the same microbiota supplemented with *Faecalibacterium* spp., *Lachnospira* spp., *Veillonella* spp. and *Rothia* spp. (FLVR) pointed to beneficial role of FLVR in lung inflammation (14). These genera are decreased in the feces of children with asthma, and enrichment of microbiota with FLVR results in decreased infiltration of total lung cells, neutrophils, and lymphocytes in the lungs in response to OVA (14). The presence of commensal bacteria was shown to impact pulmonary response to bacterial infection also, indicated by higher mortality, higher infection rate in the lungs, and systemic dissemination in GF compared to conventional mice following *Klebsiella pneumoniae* infection (34). The absence of neutrophil infiltration and a lower tumor necrosis factor (TNF) and chemokine CXCL-1 response, but increased IL-10 response, were noted in infected GF mice (34). This aberrant pulmonary response to bacterial infection in GF mice can be reversed by

restoring gut microbiota, pretreating mice with bacterial product lipopolysaccharide, or neutralizing IL-10.

A comparison of animals that differ in the presence of segmented filamentous bacteria (SFB) in the GIT pointed to the role of these bacteria in Th17 cell differentiation, as a higher number of Th17 cells in the lungs was noted in mice colonized with SFB (35-37). The presence of SFB resulted in altered lung antifungal response to opportunistic fungal pathogen *Aspergillus fumigatus* (although the increase in fungal burden was not statistically significant) (35), increased resistance to *Staphylococcus aureus* infection (36), or induction of autoimmunity in prone mice (37). Besides its effect on a number of Th17 cells, SFB stimulates the expression of dual T cell receptors on the Th17 cell surface (for SFB and self-antigens) that contribute to the development of autoimmunity (37). These dual receptor-expressing Th17 cells migrate to the lungs and are responsible for lung pathology noted in rheumatoid arthritis (37). In this regard, it should be noted that many systemic autoimmune diseases have pulmonary manifestations (38). The presence of SFB also results in increased production of antimicrobial proteins (RegIIIγ and IL-22) in the intestine, leading to an increase in serum levels of IL-1α which augments Th17 cell accumulation (35).

A combination of antibiotics such as ampicillin, vancomycin, metronidazole, and neomycin, or gentamycin, in drinking water, is used to deplete gut microbiota. Using this approach, the role of gut microbiota in lung response to viral (39, 40) and bacterial (41-44) infections was investigated. Depletion of gut microbiota results in higher influenza virus titers (39, 40) and bacterial colonization (41-44) in the lungs, higher mortality of infected animals (39, 41-43), and more pronounced lung tissue damage (39, 41, 42). Increased susceptibility of antibiotic-treated animals to pulmonary infections was shown to be a consequence of diminished macrophage function (39, 41-43) and altered cytokine and chemokine production. In general, influenza infection in antibiotic-treated animals results in reduced production of IL-6, TNF, and chemokine MIP-1β (39). In contrast to viral infections, bacterial lung infections result in increased IL-6 and IL-1β, but decreased TNF (41, 42), as well as reduced IL-17A, granulocyte-macrophage colony-stimulating factor (GM-CSF), chemokine (C-X-C motif) ligand 2 (CXCL2), and CXCL1 (43). Besides innate immunity, adaptive immunity was also affected, as the reduction of pathogen-specific antibody titers (40, 44) and the number and activity of $CD4^+$ T cells (40) and $CD8^+$ cells (39) were noted in the antibiotic-treated group. Microbiota transfer in antibiotic-treated animals was shown to improve lung immunity (42, 43). Additionally, stimulation of receptors that recognize microbial patterns, Toll-like receptors (TLR) (40, 41), and NOD-like receptors (43) can improve immune response in antibiotic-treated animals, suggesting that signals from bacterial products may be sufficient to support immune priming in the lungs. Treatment of mice with a combination of antibiotics prior to exposure to cigarette smoke (CS) was shown to ameliorate lung inflammation (45). An increase in the relative abundance of *Parabacteroides goldsteinii* noted in these animals was shown to correlate with decreased symptoms, and oral treatment with *P. goldsteinii* had a protective effect in CS exposed

mice (45). The previously described models contributed to understanding the impact of gut bacteria on immune reactions in the lungs, but should be carefully interpreted, as a mixture of antibiotics significantly depletes both gut and lung microbiota (43, 44).

Several papers have examined the effect of antibiotics with poor oral absorption, such as neomycin, vancomycin, or colistin. The administration of neomycin solely has a similar effect on anti-viral immunity as an antibiotic mixture (40). The infection of neomycin-treated animals with influenza virus resulted in more pronounced lung tissue damage, which was associated with reduced expression of TLR7 receptor mRNA in the lungs and impaired signal transduction (lower NF-κB expression) (46). Additionally, a lower interferon (IFN)-γ and IL-17 but a higher IL-4 and IL-10 response was noted in the infected neomycin group compared to the infected control group (46). Gut dysbiosis caused by vancomycin application lowered the number of Th17 cells in the lungs, and this effect was associated with a decrease in SFB (35, 37). The application of vancomycin in early life aggravates airway inflammation in adulthood, as a higher number of eosinophils and IL-13 and IL-4 production was noted following OVA application in vancomycin-treated compared to control animals (47). Neomycin and vancomycin affect Gram-positive bacteria, pointing to the role of these bacteria in lung immunity. In one study, both Gram-positive and Gram-negative bacteria, solely in the gut, were depleted following the application of vancomycin (for Gram-positive bacteria) and colistin (for Gram-negative bacteria), which resulted in worse infection outcomes, a higher lung injury, and lower survival of antibiotic-treated animals (compared to controls) following *Pseudomonas aeruginosa* infection as a result of depression of lung cellular immunity (48).

In general, bacteria from the gastrointestinal tract are necessary for adequate lung immunity as the absence of bacteria (germ-free animals) or gut dysbiosis (following antibiotic treatment) results in increased susceptibility to both bacterial and viral infections and an exaggerated allergic response (summarized in Table I). Additionally, in the absence of gut dysbiosis, some bacterial species might also affect the immune response in the lungs, as suggested by more pronounced inflammation in animals containing SFB compared to animals without these bacteria in the gut.

Mitigation of lung inflammation by prebiotics, probiotics or postbiotics

Concurrently with an examination of the mechanisms of the gut-lung axis, there are attempts to modulate immune reactions in the lungs by affecting gastrointestinal microbiota using prebiotics, probiotics or postbiotics (summarized in Table II).

By definition, a prebiotic is a substrate that is selectively utilized by host microorganisms conferring a health benefit (49). In other words, prebiotics are compounds (such as fructooligosaccharides, galactooligosaccharides, oligosaccharides present in human milk, some dietary fibers and polyunsaturated fatty acid) metabolized solely by microorganisms in the gut, which modulate the composition and/or activity of gut bacteria resulting in the improvement of host health. Beneficial effects of omega-3 polyunsaturated fatty acids (ω3-PUFA) were noted in a model of lung injury induced by

Table I Overview of data regarding the impact of gut bacteria on immune reactions in the lungs obtained from animal models

Tabela I Pregled podataka o uticaju mikrobiote creva na imunske reakcije u plućima dobijenih u modelima na životinjama

	Model	Effect	Characteristics of response	Ref.
GERM-FREE ANIMALS				
	Allergic airway inflammation	Exaggerated response to allergen	↑Infiltration of inflammatory cells, ↑IL-4, ↑IL-5, ↑IgE	33
	Klebsiella pneumoniae infection	Increased susceptibility to infection	Absence of neutrophil infiltration, ↓TNF, ↓CXCL-1, ↑IL-10	34
ANIMALS CONTAINING SFB IN THE GUT				
	Aspergillus fumigatus infection	No effect on fungal burden in the lungs, altered immune response	↑IL-17, ↑IL-22, ↓IL-4, ↑RegIIIβ and RegIIIγ in intestine	35
	Staphylococcus aureus infection	Increased resistance to infection	↑IL-22, ↑IL-6, ↑Number of neutrophils	36
	Autoimmunity	Triggered lung pathology in susceptible strain	↑Auto-antibody-secreting cells, ↑Th17 cells, Expression of dual T cell receptors on the Th17 cell surface	37
ANIMALS TREATED WITH ANTIBIOTICS				
	Influenza virus infection	Increased susceptibility to infection	↓Number of virus-specific $CD8^+$ T cells, ↓Proinflammatory cytokines (TNF, IFN-γ, IL-2, MIP-1α, IL-1β, IL-17), ↑ IL-4 and IL-10, ↓Titers of specific antibodies (IgM, IgG), Defective innate immune response, ↓TLR7 signaling	39, 40, 46
	Escherichia coli infection	Increased susceptibility to infection	↓Bacterial killing by alveolar macrophages, ↑IL-6, ↑IL-1β, ↑MIP-2	41
	Streptococcus pneumoniae infection	Increased susceptibility to infection	↑IL-6, ↑IL-1β, ↓TNF, ↓IL-10, ↓Phagocytosis in alveolar macrophages, ↓IL-17, ↓Bacterial killing by alveolar macrophages, ↓GM-CSF, ↓CXCL2, ↓CXCL1	42, 43
	Klebsiella pneumoniae infection	Increased susceptibility to infection	↓GM-CSF, ↓CXCL2, ↓CXCL1, ↓IL-17, ↓Bacterial killing by alveolar macrophages	43
	Pseudomonas aeruginosa infection	Increased susceptibility to infection	Depression of lung immunity*, ↓Specific IgA, ↑CXCL2, ↑IL-1α, ↑IL-6	44, 48
	Allergic airway inflammation	Exaggerated response to allergen	↑Infiltration of inflammatory cells, ↑IL-4, ↑IL-13	47

Legend: ↑ - increase; ↓ - decrease; N/A - not available; *Immune response was examined following antibiotic application, but not during infection. Characteristics of the response are presented in comparison to relevant controls, i.e. specific-pathogen free animals for germ-free, animals without SFB, or animals not treated with antibiotics.

Table II Summary of the effects of application of prebiotics, probiotics and postbiotics on immune reactions in the lungs

Tabela II Pregled efekata primene prebiotika, probiotika i postbiotika na imunske reakcije u plućima

	Model	Effect	Mechanism	Ref.
PREBIOTICS				
ω3-PUFA	Lung injury (fine particulate matter)	↓Lung injury	↓TNF, ↓IL-1β, ↓IL-6, ↓IL-17, ↓Oxidative stress	50
Polysaccharides	Lung tumor	↑Antitumor response	↑$CD8^+$ T cells, ↓Treg cells, ↑SCFA, ↓L-kynurenine	51
Dietary fiber	Allergic airway inflammation	↓Lung inflammation	↓Cell infiltration, ↓IL-4, ↓IL-5, ↓IL-13, ↓IL-17A	52
A mixture of galactooligosaccharides and polydextrose	Rhinovirus infection in preterm infants	↓Incidence of viral respiratory tract infection and the incidence of rhinovirus-induced episodes	N/A	53
PROBIOTICS				
B. longum AH1206	Allergy	↓Allergic airway response	↓Number of eosinophils, ↓TNF, ↓IL-6, ↑Number of Treg	55
L. reuteri	Allergic asthma	↓Allergic airway response	↓Number of eosinophils and macrophages, ↓TNF, ↓MCP-1, ↓IL-5, ↓IL-13, stimulation of TLR-9	56
L. acidophilus LA-5, *L. rhamnosus* GG, and *B. animalis*	Allergic asthma	↓Allergic airway response	↓Number of eosinophils, ↓IL-4, ↓IL-5, ↓IL-13, ↓IL-17, ↓IL-25, ↓IL-33	57
L. rhamnosus GG strain	Lung injury (fine particulate matter)	Restored pulmonary function, ↓Pulmonary inflammation	↑Number of Treg, ↓Number of Th17 cells, ↓IL-6, ↓TNF, ↓IL-17A, ↓IL-1β, ↑IL-10, ↑TGF-β1	58
L. rhamnosus GG strain	Respiratory tract infection	↓Risk of respiratory tract infection, ↓Episodes of respiratory tract infection, ↓Severity of infection	N/A	59, 60
L. paracasei subsp. *paracasei*	Influenza infection	↓Duration of upper respiratory symptoms	N/A	61
L. casei	Cigarette smoke	N/A	↑Activity of NK cells, ↑Number of $CD16^+$ cells	62
SYMBIOTICS				
Vegetable and fruit concentrate, fish oil, and *L. salivarius* PM-A0006	Asthma	↓Medication use, ↑Pulmonary function	N/A	63
Galactooligosaccharides, fructooligosaccharides, and *B. breve* M-16V	Asthma	No effect on bronchial inflammation, ↑Peak expiratory flow	↓Th2-cytokines by peripheral blood mononuclear cells	64
Yogurt and high fiber intake	Lung cancer	↓Risk of lung cancer	N/A	65
POSTBIOTICS				
Inactivated non-typeable *Haemophilus influenzae*	COPD	↓Severity of COPD exacerbations	N/A	67
PMBL	COPD	↓Severity of COPD exacerbations	N/A	68
PMBL	Respiratory tract infections	↓Number of infectious episodes	N/A	69
Lantigen B	Respiratory tract infections	↓Number of infectious episodes	N/A	70

Legend: ↑ - increase; ↓ - decrease; N/A - not available.

fine particulate matter (PM2.5) exposure (50). Oral application of ω3-PUFA before induction of lung injury was shown to mitigate inflammation (TNF, IL-1β, IL-6, and IL-17 production) and oxidative stress in the lungs caused by PM2.5. This effect was associated with the attenuation of changes in the relative abundance of bacterial phyla in the gut induced by PM2.5, and with alteration in lung metabolic pathways that positively correlate with *Verrucomicrobiota* (50). In another study, supplementation with polysaccharides isolated from *Panax ginseng* was shown to result in potentiating the antitumor effect of anti-programmed cell death 1/ programmed cell death ligand 1 (anti-PD-1/PD-L1) therapy in a mouse model of lung tumor (51). Combined therapy resulted in higher activation of $CD8^+$ T cells and suppression of regulatory T cells compared with solely anti-PD-1 therapy. The application of ginseng polysaccharides altered microbial composition in the gut, which resulted in an increased concentration of short-chain fatty acids (SCFA) in plasma and a decrease in tryptophan metabolite L-kynurenine (51). The beneficial effect of prebiotics was also shown in a model of allergic airway inflammation (induced by house dust mite extract) in which a diet supplemented with readily fermentable fiber pectin reduced the infiltration of cells into the lungs and decreased IL-4, IL-5, IL-13, and IL-17A (52). The noted effect was mediated by an increased concentration of SCFA. In clinical trials, the application of prebiotic (1:1 mixture of galactooligosaccharides and polydextrose) was shown to lower the incidence of viral respiratory tract infection and the incidence of rhinovirus-induced episodes in preterm infants (53).

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer health benefits to the host (54). In the context of the beneficial role of probiotics in lung inflammation, *Bifidobacterium* spp. and *Lactobacillus* spp. were examined. Allergic airway response (induced by OVA administration) was attenuated with prior oral administration of *B. longum* AH1206 (55), *L. reuteri* (56), or a combination of probiotic strains (*L. acidophilus* LA-5, *L. rhamnosus* GG, and *B. animalis*) (57). Probiotic strains decreased the number of eosinophils (55-57) and macrophages (56) and reduced the production of TNF (55, 56), IL-6 (55), MCP-1 (56), IL-5 and IL-13 (56, 57), IL-4, IL-17, IL-25 and IL-33 (57). The noted effect is strain-specific and depends on live organisms, as *B. breve* AH1205 (55) and *L. salivarius* (56) or heat-killed *L. reuteri* (56) do not modulate the allergic airway response. The beneficial effect might be mediated by increased numbers of regulatory T cells (in Peyer's patch and spleen) (55) or stimulation of TLR-9 by *L. reuteri* (56). In the model of pulmonary injury, the oral application of *L. rhamnosus* GG strain restored pulmonary function that was decreased in response to PM2.5 exposure and ameliorated pulmonary inflammation (58). Probiotics increased the number of regulatory T cells and decreased the number of Th17 cells in comparison to PM2.5. Additionally, lower levels of proinflammatory (IL-6, TNF, IL-17A, and IL-1β) and higher levels of anti-inflammatory (IL-10 and TGF-β1) cytokines were noted following probiotic administration (58). The beneficial effects of probiotic administration were also examined in humans. In clinical trials, the prevention of respiratory infections with *L. rhamnosus* strain GG (53, 59, 60)

and *L. paracasei* subsp. *paracasei* (61) was investigated. These studies indicated that the application of probiotics reduces the duration of upper respiratory symptoms following influenza infection (61), the risk of respiratory tract infection (59, 60), the severity of infection (60), and episodes of respiratory tract infection that lasted over 3 days in hospitalized children (59). In another clinical study, supplementation with *L. casei* Shirota in smokers for three weeks was shown to increase the activity of NK cells and the number of $CD16^+$ cells (CD16 is a molecule that is expressed on NK cells, but also on other cell types) that are reduced in smokers (62).

Combined administration of prebiotics and probiotics (designated as symbiotics) on asthma (63, 64) and the incidence of lung cancer (65) was estimated. Daily supplementation with vegetable and fruit concentrate, fish oil, and *L. salivarius* PM-A0006 reduced medication use and improved pulmonary function in asthmatic school children (63), while a symbiotic containing galactooligosaccharides, fructooligosaccharides, and *B. breve* M-16V had no effect on bronchial inflammation, but reduced production of Th2-cytokines by peripheral blood mononuclear cells isolated from patients with allergic asthma (64). An analysis of the association between lung cancer risk and dietary fiber and yogurt (containing starter cultures of *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus*, but other *Lactobacilli* spp. and *Bifidobacteria* spp. may also be added) consumption revealed that the risk of lung cancer was reduced by more than 30% in adults with a high yogurt consumption and with the highest quintile of fiber intake, suggesting a protective role of symbiotics against lung carcinogenesis (65).

In the treatment of lung inflammation, postbiotics, which are defined as preparations of inanimate microorganisms and/or their components that confer health benefits to the host (66), might be used as well. Formalin-inactivated non-typeable *Haemophilus influenzae* was shown to reduce the severity of COPD exacerbations, proportions of episodes requiring corticosteroid therapy, and duration of episodes (67). A similar effect in patients with COPD was noted when a polyvalent mechanical bacterial lysate (PMBL) (of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Klebsiella ozaenae*, *Haemophilus influenzae* type b, *Moraxella catarrhalis* and *Streptococcus pneumoniae*) was added to regular treatment (68). Infection is one of the risk factors in COPD exacerbations, and the use of inactivated bacteria for stimulation of immune response against potential pathogens might be beneficial for these patients. In patients with recurrent respiratory tract infections, a reduced number of infectious episodes was recorded following the application of PMBL (69) and Lantigen B (chemical lysate of suspension containing *Streptococcus pneumoniae* type 3, *S. pyogenes* Group A, *Branhamella catarrhalis*, *Staphylococcus aureus*, *H. influenzae* type b, and *K. pneumoniae*) (70).

Additional perspectives

While this review summarized the effects of bacterial microbiota from the GIT on immune reactions in the lungs, the effect of other microorganisms (viruses, fungi, and protozoa) should not be neglected. For example, the overgrowth of *Candida* spp. in the gut following antibiotic treatment promotes allergic airway inflammation (71, 72) by increasing the level of prostaglandin E_2, which induces M2 macrophage polarization (72).

Another aspect that was neglected is the effect of lung microbiota on the immune homeostasis in this organ. The lungs of healthy individuals have long been considered sterile, but with the development of new technics (sequencing of 16S rRNA gene), it is now established that the lungs harbor a vast range of microorganisms. Bacterial microbiota in the lungs is involved in the regulation of homeostasis in this organ and can be altered during the disease (73). In this context, lung dysbiosis is noted in diseases such as asthma (74), COPD (75), and CF (76), in patients with tuberculosis (77), invasive pulmonary aspergillosis (78), and during influenza A virus infection (79). In recent years, the alteration of lung microbiota in various animal models of lung inflammation/injury has been investigated (80-86). Whether gut microbiota affects bacterial composition in the lungs, thus resulting in altered tissue homeostasis, is still not clear, but data indicate that lung microbiota is enriched in the GIT taxa (gaining access to the lungs through microaspiration) (73).

Communication between the GIT and the lungs is not a one-way interaction (with the GIT microbiota affecting lung immunity), as immune reactions in the lungs might affect the gut microbiome. Dysbiosis in the gut was documented during pulmonary viral (87-91), bacterial (92, 93), and fungal infections (94, 95), as well as in mice exposed to high oxygen levels (80). The effect of lung inflammation on gut dysbiosis is also mediated by the immune system (87, 88).

Conclusion

The bacterial microbiota of the gastrointestinal tract has numerous effects on tissue homeostasis both locally (in the gut) and in extra-intestinal sites such as the lungs. The association of gut bacteria with various pulmonary diseases in humans has been established, and experimental data on animal models confirmed the existence of a gut-lung axis that is mediated by the effect of gut bacteria on immune system activities (Figure 1). The existence of the gut-lung axis provides the basis for modulating pulmonary immune response by affecting gut bacteria with prebiotics, probiotics, or postbiotics.

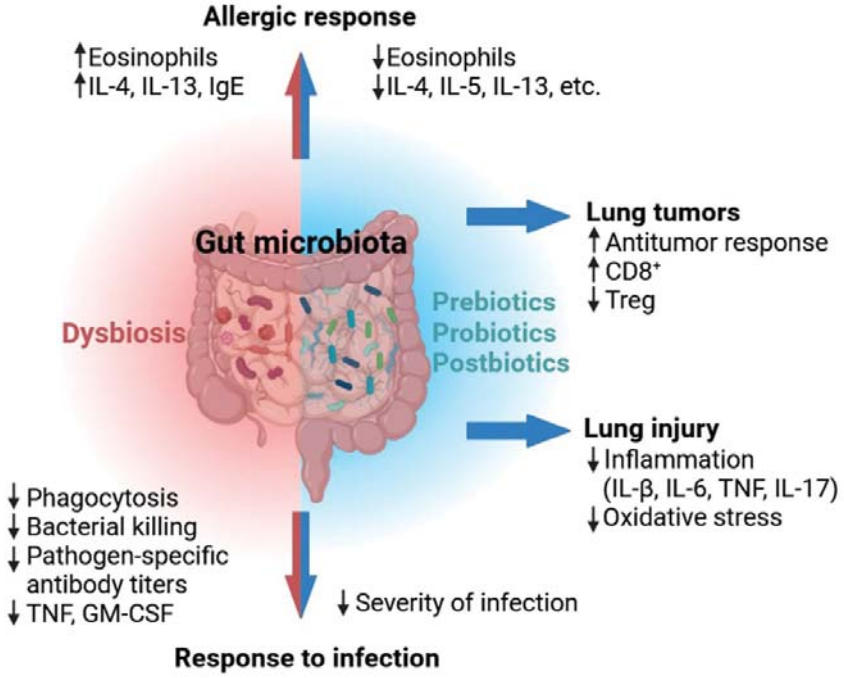

Figure 1. **Impact of gut microbiota on immune reactions in the lungs. While bacterial dysbiosis leads to an exaggerated response to allergen (by increasing the number of eosinophils and IL-4 and IL-13 production) and impaired response to infections (by decreasing activities relevant for pathogen removal), treatment with prebiotics, probiotics or postbiotics was shown to diminish allergies (decreasing the number of eosinophils and IL-4 and IL-13 production), increase antitumor response, decrease lung injury induced by xenobiotics (by lowering inflammation and oxidative stress) and severity of infections.**

Slika 1. **Uticaj mikrobiote creva na imunske reakcije u plućima. Bakterijska disbioza u crevima dovodi do intenzivnijeg odgovora na alergene (povećanje broja eozinofila i produkcije IL-4 i IL-13) i slabijeg odgovora na infektivne agense (smanjenje aktivnosti relevantnih za uklanjanje patogena). Sa druge strane, primena prebiotika, probiotika ili postbiotika smanjuje intenzitet alergijskog odgovora (smanjuje broj eozinofila i produkciju IL-4 i IL-13), potencira antitumorski odgovor, smanjuje stepen oštećenja pluća izazvan ksenobioticima (smanjenje inflamacije i oksidativnog stresa) i doprinosi smanjenju ozbiljnosti infekcija.**

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Uticaj mikrobiote creva na imunske reakcije relevantne za patologiju pluća

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Kratak sadržaj

Poznato je da bakterije prisutne u gastrointestinalnom traktu imaju ulogu u sprečavanju invazije patogenih mikroorganizama, regulaciji propustljivosti creva, varenju hrane, metabolizmu i imunskom odgovoru. Ove bakterije utiču na funkciju, održavanje homeostaze i ishod bolesti kako u gastrointestinalnom traktu, tako i u udaljenim organima kao što su pluća. Ovaj pregledni rad sumira trenutno dostupna znanja o osi creva-pluća. Prikazana je veza između bakterijskog sastava i/ili disbioze u crevima sa različitim bolestima kod ljudi kao što su astma, hronična opstruktivna bolest pluća, cistična fibroza, rekurentne infekcije respiratornog trakta i karcinom pluća, kao i podaci dobijeni u životinjskim modelima inflamacije pluća koji su pokazali da modulacija aktivnosti imunskog sistema leži u osnovi ove interakcije. Potencijalna upotreba prebiotika, probiotika i postbiotika u terapiji inflamacije u plućima je takođe prikazana.

Ključne reči: bakterijska mikrobiota creva, osa creva-pluća, inflamacija u plućima