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AIM AND SCOPE

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INDEXING/ABSTRACTING

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EDITORS FOR THIS ISSUE

Lung microbiome in healthy and diseased individuals

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Abstract

The data on quantitative and qualitative microbial composition of the respiratory tract of healthy individuals revealed significant differences when compared with the microbiota of patients suffering from respiratory diseases. Possible etiological role of microbiota in pulmonary diseases as well as drug resistance development is of profound interest nowadays. Numerous studies have provided evidence confirming the relationship between gut microbiome and those of lungs. This relationship could explain how changes in the microbial communities in one organ may lead to pathological changes in the other. Till date, some progress has been made in the study of the biological properties of probiotic bacteria, considering their modulating effect on inflammatory immune response. The use of probiotics which exhibits an immunomodulatory potential looks promising.

Key words: Microbiome; Respiratory diseases; Probiotics; Prebiotics; Gut-lung axis; Synbiotics

Core tip: The role of the respiratory tract microbiota in a healthy state and in respiratory diseases is broadly discussed nowadays. There is also a big amount of data regarding contribution of gastrointestinal microbiota changes in respiratory diseases development. A gut-lung axis conception is of great interest. Perspective of prebiotics and probiotics application in lung diseases treatment looks very promising. Huge number of researches has been done on topics mentioned above. Our objective is to consolidate the current literature to summarize the most recent and most important data concerning this subject.

INTRODUCTION

Until recently, microbial structure of a human body remained poorly understood. Nowadays large-scale research conducted within the framework of the "Human Microbiome Project" (HMP 2007) provide us with novel knowledge on the diversity of human microflora. Previously lower respiratory tract supposed to be sterile, except when infection affects it. This concept existed due to limited experimental access to the respiratory tract of healthy individuals, and limitations of classical methods of culturing. Therefore, the study of lungs was initially not included in the original HMP. However later, molecular-genetic identification methods showed that native microbiome exists in lungs as well. Significant progress in the study of microbial ecosystems was associated with genomic analysis of 16S ribosomal RNA (16S rRNA). Currently more than 16000 sequences of bacterial 16S rRNA gene have been described. Preliminary data showed differences in the composition of respiratory tract microbiome in patients suffering from various respiratory diseases and relatively healthy volunteers. In comparison with the gastrointestinal tract (GIT) maintenance of the natural microbiome composition in the respiratory tract appears to be an important factor for protection against bronchopulmonary diseases.

Pulmonary microbiome

One of the earliest researches was focused on quantitative and qualitative analysis of the upper and lower respiratory tracts microbiome in relatively healthy volunteers, refuting the hypothesis of lung sterility[1-3]. The lower respiratory tract was found to contain bacterial 16S rRNA sequences. Thus, constant presence of unique symbiotic microbiota in a healthy lung was confirmed. The composition of the microorganisms in the lower respiratory tract was generally indistinguishable from those in the upper respiratory tract which explained their origin[2-4]. The respiratory tract was shown to contain 2000 bacterial genomes per cm[2]. Bacteroidetes (*Pseudomonas*, *Streptococcus*, *Prevotella*, *Fusobacteria* and *Veillonella*), particularly *Prevotella* spp. predominate in healthy individuals[5]. Despite the whole genome sequencing techniques do not provide firm conclusion of live microorganisms presence in the lower respiratory tract, there are some indirect evidences supporting the existence of an active, viable lung microbiome. For instance, a considerable variation was shown in both quantitative and qualitative composition of the microorganisms in the different regions of the respiratory tract of the same individual, suggesting growth inhibition of one type and active reproduction of another type of bacteria to be possible mechanism, depending on various local environmental conditions (temperature, pH, oxygen
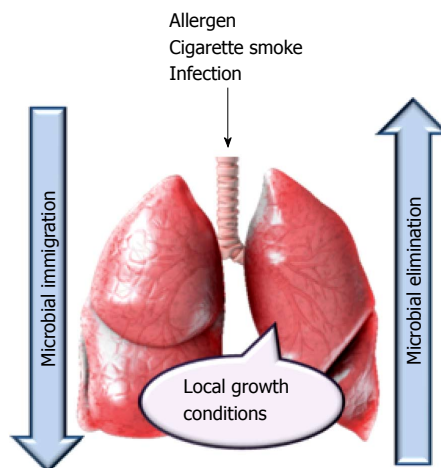
Figure 1 Ecological determinants of the lung microbiome. The respiratory microbiome is determined by three factors: Microbial immigration, microbial elimination (mainly in heathy individuals) and regional growth conditions (mainly in advanced lung disease) (adapted from Dickson RP 2015).

saturation, *etc*.)[6].

The composition of lung microbiome is determined by the balance of three factors: Microbial immigration, microbial elimination and local growth conditions (Figure 1)[4]. The respiratory microbiome is determined by three factors: Microbial immigration, microbial elimination (mainly in healthy individuals) and local growth conditions (mainly in advanced lung disease) (adapted from Dickson RP 2015). Therefore, any modifications in microbiome in pathogenic conditions occur due to changes in these factors. Potential sources of microbial immigration are: Air inhalation (contains 10^4-10^6 bacterial cells/mm^3), microaspiration (found in healthy individuals) and direct dispersion through the respiratory tract mucosa[4]. Thus high affinity of lung and oral cavity microbiome compared to air microbiome supports microaspiration and direct dispersion to be major microbial sources[7,8]. Clinical studies confirmed that the microbiome of lungs and oral cavity resemble each other more than the microbiome of the nasal mucosa[4,9]. Microbial elimination is determined by mucociliary clearance, cough and antimicrobial mechanisms - innate and adaptive immunity[4]. pO_2, pH, blood perfusion, alveolar ventilation, temperature, lung epithelium, mucociliary clearance and activity of inflammatory cells are major components of microbial local growth conditions[6]. Surfactant that covers distal alveoli has bacteriostatic activity affecting the reproduction of bacterial communities[10].

Lung pathology leads to both structural and microbial changes. For example, in destructive pulmonary diseases (emphysema, idiopathic pulmonary fibrosis) inner surface area of lungs is significantly reduced (up to 90%)[11]. Gastroesophageal reflux disease (GERD), which is often found in patients with progressive pulmonary diseases, increases microbial immigration and acts as an additional source of bacteria[12]. Chronic pulmonary diseases (cystic fibrosis, bronchiectasis, chronic bronchitis) lead to impairment of the mucociliary

Figure 2 Lung microbiome disturbances following respiratory diseases exacerbations (adapted from Dickson RP 2014). The triggers like virus, allergens, pollutants initiate airway inflammation with activation of alveolar macrophages, neutrophils, eosinophils, dendritic cells, lymphocytes, which alters growth c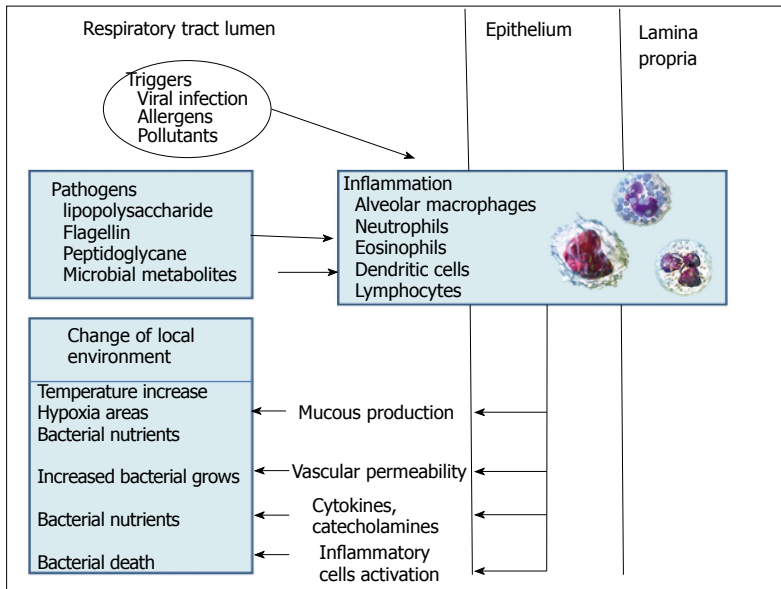onditions of airway microbiota. Altered growth conditions result in a disturbed microbiome, which promotes further airway inflammation *via* pathogen-associated molecular patterns and pattern recognition receptor interactions.

clearance, which in turn affects the microbial elimination. In addition, such conditions associated with increased mucus production contribute to bacterial growth and promotes formation of zones with low oxygen concentration and high temperature[13]. Exacerbation of chronic diseases results in microbiome alteration due to following mechanisms: Hyperventilation, cough, bronchoconstriction, overproduction of proinflammatory cytokines, catecholamines, glucose and reactive oxygen species, increased vascular permeability and mucus production[13-15]. The model of lung microbiome disturbances following respiratory diseases exacerbations has been proposed (Figure 2)[6].

Triggers (viral, bacterial infection, allergens, pollutants) upregulate a cascade of inflammatory reactions involving alveolar macrophages, neutrophils, eosinophils, dendritic cells and lymphocytes significantly affects microbial growth. Thus, for example, excessive production of proinflammatory cytokines [tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, 6, 8] directly activates growth of *P. aeruginosa*, *S. aureus, S. pneumonia*, *Burkholderia cepacia* and others[14,16,17]. Remarkably some microorganisms modify virulent factors making them more aggressive and hence increase immunogenicity. These factors promote further inflammation by increasing expression of pathogen-associated molecular patterns (lipopolysaccharide, flagellin), which in turn activate pathogens recognizing receptors [*e.g.*, toll-like receptors (TLR)][18].

Gut-lung axis
GIT appears to be the most bacterial populated organ of our body [up to 10^{14} colony-forming units (CFU)/mL in colon][5]. Microbiota plays an important role in health maintenance. In GIT it promotes formation of local and systemic immunity, induces intestinal angiogenesis and is supposed to be an important factor for normal digestion. In healthy individuals Bacteroidetes represent the most abundant phylum, followed by Firmicutes. The lower

respiratory tract has a much lower level of contamination, but Firmicutes and Bacteroidetes are predominants in the lung microbiome of healthy individuals as well as in the gut while Actinobacteria, Proteobacteria and Fusobacteria are presented in rather small numbers[19].

Gut-lung axis is of particular interest. While the gut and lungs are both mucosa-lined luminal organs with a shared embryological origin, their gross and micro-anatomical features are different. In the absence of emesis or gastroesophageal reflux, migration of microbes in GIT is unidirectional (from the mouth to the anus), and is serially interrupted by chemical and physical barriers. In contrast, the movement of air, microbes and mucus in the lung, is bidirectional, with no physical barriers between the larynx and the most distal alveoli. Consequently, the lung microbiome is more dynamic than the lower GIT[4]. The differences in the composition of lung and intestine microbiome are also associated with oxygen distribution and temperature, which represents a gradient from ambient temperature at the point of inhalation to core body temperature in the alveoli[4]. Trachea and bronchi like intestine are lined with glycosylated proteins of secreted mucus; the vast majority of the lung's surface area is lined with lipid-rich surfactant, which has bacteriostatic effects against selected bacterial species[18]. Intestinal microbiome greatly contributes to the regulation of the immune response, in particular directly in the lung (Figure 3)[20].

Commensal bacteria with their metabolic products interact with TLR inducing Tregs and dendritic cells activation; chemokines and cytokines production and expression of transcription factors therefore regulate immune response[20-22].

It is a well-known that asthma, chronic cough, COPD, and idiopathic pulmonary fibrosis can be associated with GERD. Acid-suppression medications, including proton pump inhibitors (PPIs), are some of the most prescribed medications in patients with GERD. Rosen *et al*[23]
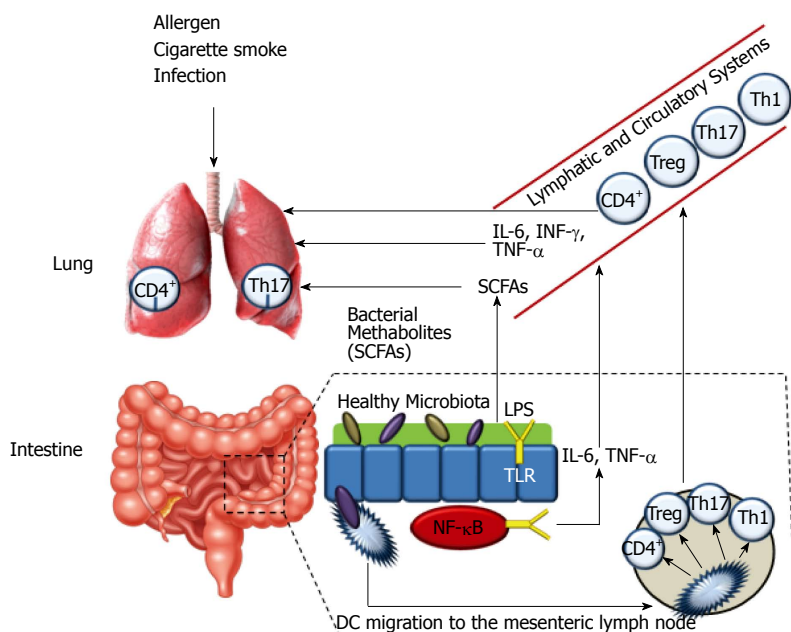
Figure 3 Model of intestinal microbiome effects on lung immunology (adapted from Samuelson DR 2015). Microbes in the intestine is sampled by dendritic cells (DCs) either directly from the lumen or following translocation through M-cells to the gut-associated lymphoid tissue. A combination of signals from the microbes results in phenotypic changes in the DCs. DCs promote activation of various T-cell subsets within the mesenteric lymph nodes (MLN) and production of regulatory cytokines. Following the immune challenge in the airways T-cells activated in the gastrointestinal associated lymphoid tissue (GALT) and MLN move to the respiratory mucosa where they promote protective and anti-inflammatory responses. Production of various bacterial metabolites (*e.g.*, SCFAs) also affects the gut-lung axis, as these products get to the lung, where they can alter the levels of inflammation. SCFA: Short chain fatty acid; IL: Interleukin; TNF: Tumor necrosis factor.

investigated the impact of acid-suppression medication in children ages 1 to 18 years with chronic cough on gastric and lung microbiome. No significant differences in the prevalence of various bacterial genera or the median concentration of total bacteria in the lungs between treated and untreated patients were shown. There were positive correlations between proximal nonacid reflux burden and lung concentrations of Bacillus, Dermabacter, Lactobacillus, Peptostreptococcus, and Capnocytophagia. These results could be evidence of reflux influence on lung microbiome, but further studies are needed.

The effect of the bacterial metabolites, in particular short chain fatty acids (SCFAs) on modulation of the immune response is one of the most discussed topics. SCFAs act directly on the epithelial and immune cells, contributing to powerful anti-inflammatory effects[20-22,24]. SCFAs were shown to modulate the activity of NFκB, reduce TNF-α production and downregulate the PRRs stimulation (pattern recognition receptors)[21,22]. Postulated that the ability of SCFAs to interact with certain G-binding receptors of neutrophils depend on their profile which defined by bacterial composition. Stimulation of Ffar2 (GPR43) receptor was associated with decreased level of eosinophils and reduced bronchoconstriction compared with the Ffar3 (or GPR41) stimulation, which was associated with increased production of pro-inflammatory mediators[25]. SCFAs were also shown to downregulate expression of CD-markers on the surface of tissue specific DCs[26]. Depressed expression of costimulatory molecules CD80, CD86 and CD40 modify the DCs ability to interact with regulatory T-cells (T-regs).

It was found that mice fed with low-fiber diet had decreased levels of SCFAs and higher prevalence of allergic reactions in the respiratory tract[27]. The administration of probiotics was associated with IL-10 secretion by DCs, which promoted T-regs differentiation, causing shift to the Th1 response[26]. Bacterial colonization

in sterile mice lead to stimulation of the secretory IgA and CD4+ T-cells, reducing the IgE levels[22].

There is a strong correlation between the bacterial composition of the GIT in infancy and asthma phenotype in childhood[27,28]. Low total microbiome diversity of the colon during the first month of life was shown to be linked with bronchial asthma development at the age of 7. Also decrease in Bifidobacteria and an increase in the number of Clostridia in the colon at the early ages were associated with the subsequent development of bronchial asthma[28]. In mice models it was found that the use of antibacterial drugs in the first 3 wk of life worsens the course of allergic respiratory inflammation in adulthood[29].

Microbiome and respiratory diseases
Currently, the role of lung microbiome in respiratory pathology is being discussed. Lung microbiome transformation, particularly reduction of probiotic species and potential increase of pathogenic bacteria appears to be the fundamental factor for susceptibility, chronization and progression of respiratory diseases. In recent study Bacteroidetes, mostly *Prevotella* spp., was significantly more common in healthy individuals, whereas Pseudomonas was frequently found in the lower respiratory tract of COPD patients[30]. A smaller diversity of bacteria in patients with COPD was also observed. Another study showed that Streptococcus, Prevotella, Fusobacterium and Veillonella were prevalent in individuals without COPD, while Pseudomonas and Haemophilus were dominated in COPD patients microbiome[31]. International research revealed that in COPD patients Streptococcus sp. and Haemophilus sp. were associated with decreased pulmonary function, while low level of FEV1 was a predictor of bacterial diversity reduction[32]. COPD exacerbation increases the number of Proteobacteria (Moraxellaceae, Pas-

teurellaceae, Pseudomonadaceae, Enterobacteriaceae) and reduces the amount of Actinobacteria, Clostridia and Bacteroidia[33]. It is interesting that Actinobacteria produces metabolites with antimicrobial activity and classes IV and XIVa Clostridia known to be inducers of anti-inflammatory T-regs[34]. Treatment strategy was shown to modify lung microbiome in respiratory diseases. Thus antibacterial therapy in patients with COPD exacerbation results in reducing number of Proteobacteria. Administration of corticosteroids increases their number, as well as the number of Bacteroidetes and Firmicutes, especially Enterobacteriaceae (more than 16 times), Lachnospiraceae, Burkholderiaceae and Neisseriaceae. Combination therapy with corticosteroids and antibiotics leads to increase of Proteobacteria[33].

An attempt to prove the etiological role of the microbial composition of the respiratory tract in COPD development was made. In mice models, reduction in the microbial diversity significantly increases the number of Pseudomonas genera, Lactobacillus, Chryseobacterium and reduction Prevotella. Also there was a marked enhancement of the inflammatory response which included the formation of lymphoid follicles in the lung tissue, increased production of IL-17A, which level was positively correlated with limited airflow and COPD progress[35]. Finally broncho-alveolar lavage fluid (BALF) of such animals was intranasally translocated to sterile and antibiotic-treated mice, as a result an increase in the number of cells producing IL-17A in the lung tissue, particularly CD4^{+} T cells in the recipients were noted[36].

One of the early studies confirmed the role of microbiome in the bronchial asthma development was done in Denmark. The presence of Moraxella cata-rrhalis, Haemophilus influenzae and Streptococcus pneumoniae in the oropharynx of children of 1-mo age significantly increased the risk of bronchial asthma development[37]. Pathologic role of mentioned bacteria in asthma development had been confirmed in more recent studies[38]. Asthmatic patients were found to have higher number of pathogenic proteobacteria (*e.g.*, Haemophilus) and significantly lesser Bacteroidetes, especially of genus Prevotella compared to healthy individuals[5]. The prevalence of families Comamonadaceae, Sphin-gomonadaceae, Oxatobacteraceae was shown to correlate with bronchial hyperresponsiveness. Inter-estingly, colonization with certain pathogenic bacteria is strictly associated with an immune response in newborns. Thus at high amounts of *M. catarrhalis* and *H. influenzae* production of IL-1, IL-17 increases. Also prevalence of S. aureus leads to overproduction of IL-17[39].

The microbiome composition varies in patients depending on the disease severity. Thus in patients with severe bronchial asthma when compared with those with mild to moderate severity, there is a significantly higher (7-8 times) number of Klebsiella[40]. In a recently published study healthy individuals when compared to patients with mild bronchial asthma were shown to have a decreased number of Bacteroidetes such as *Prevotella* spp.[41]. At the same time the number of pathogenic

Proteobacteria, including Neisseria and Moraxella spp., were 2-times higher in patients with mild bronchial asthma. Bacteroidetes (OR = 0.62) and Fusobacteria (OR = 0.38) were decreased in patients with severe bronchial asthma, compared to the control group. Significant increase in Firmicutes, consisting mainly of streptococci in comparison with healthy individuals and patients with mild bronchial asthma (OR = 2.15 for both comparisons) was observed. Also there was a positive association between the severity of bronchial asthma and the level of Streptococcus (*Streptococcus* spp., *Streptococcus*_23 and *Streptococcus*_155) and negative with the level of *Prevotella* spp.

Imbalance in the oropharyngeal flora was found to decrease resistance, increase bacterial colonization and dissemination of the potential pathogen in the airway and pneumonia development. Oropharyngeal microbiome of healthy individuals and patients with pneumonia in two age groups: 18-59 years old and group 60 years and older were compared. Three microbial profiles associated with pneumonia in both age groups were revealed: prevalence of bacteria genus Streptococcus, Rothia and Lactobacillus. At the same time in healthy individuals, the microbiome was dominated by Veilonella, Prevotella, Leptotrichia and Gemellales. Moreover, the overall number of viruses in the microbiome of patients with pneumonia significantly increased. The composition of the microbiome was less diverse, while bacterial load was significantly higher which was also correlated with the disease severity. Furthermore the number of Anaerobes, Bacteroides decreases with age, while overgrowth of lactobacilli was noted[42].

Several studies have shown protective role of the intestinal microbiota in the course of pneumonia. The role of normal gut microbiota in mice, particularly segmented filamentous bacteria (SFB) in the course of pneumonia caused by *S. aureus* was studied. It was shown that the number of CFU of *S. aureus* in the lungs and spleen were significantly higher in SFB-negative mice in comparison with SFB-positive mice and the clearance of pathogenic bacteria in SFB-negative mice was reduced. In addition, the bacterial load decreased in SFB-negative mice when they were co-housed with healthy mice and similarly after fecal transplantation from healthy mice. All SFB-negative infected mice died within 36 h, whereas the survival rate in mice with normal gut microbiota was 70%[43]. In another research the role of microbiota during the course of pneumococcal pneumonia was studied[44]. Microbiota-depleted mice were shown to have an increase in bacterial dissemination, inflammatory response, organ damage, higher mortality due to pneumonia, impaired phagocytic activity of alveolar macrophages, whereas after subsequent fecal transplantation from healthy mice, there were cytokines normalization (TNF-α, IL-6 and IL-10) and an accelerated elimination of *Str. pneumoniae*.

Place of probiotics, prebiotics, and synbiotics in respiratory pathology treatment
Several studies confirm that antibiotic administration

Table 1 Probiotics and synbiotics in respiratory diseases

Probiotics/synbiotics	Medical condition	Results	Source
Lactobacillus rhamnosus, Bifidobacterium breve	Smokers	Inhibition of nicotine -mediated IL-1β, IL-6, IL-10, TNF-α production, NF-KB, TLR4 and TLR9-induced expression of IL-8 activation	Mortaz *et al*[49], 2015
Lactobacillus rhamnosus, Bifidobacterium lactis, Bifidobacterium breve	Allergic asthma	Antigen-specific Tregs activation	Sagar *et al*[50], 2014 Jang *et al*[51], 2012
Lactobacillus reuteri ATCC 23272 Lactobacillus rhamnosus GG	Allergy	Significant reduction of inflammatory cells in BALF, increasing CD4+CD25+Foxp3+ Treg in spleen and mediastinal lymph nodes	Forsythe *et al*[52], 2007
Lactobacillus rhamnosus GG Lactobacillus casei (Sirota and DN 114001)	Acute infectious respiratory diseases	Increasing of IgA- secreting cells in bronchial mucosa	Tapiovaara *et al*[53], 2016
Enterococcus faecalis FK-23	Asthma	Suppression of T-cells and cytokines production	Zhang *et al*[54], 2012
Bifidobacterium longum	Klebsiella-induced pneumoniae	Increased production of IL-10, decrease of TNF-α and IL-6 levels	Viera *et al*[55], 2016
Acidic oligosaccharides	*P. aeruginosa*-induced infection	Increase in IL-10 production, decrease in cytotoxic T lymphocyte production	Bernard *et al*[62], 2015
Bifidobacterium breve M-16V galacto-oligosaccharides fructo- oligosaccharides	Allergic asthma	Significant increase in peak expiratory flow rate and reduction of IL-5 production	van de Pol *et al*[63], 2011

IL: Interleukin; TNF: Tumor necrosis factor.

can result in gut microbiota dysbiosis. Broad-spectrum antibiotics can affect the bacterial abundance in the gut causing rapid and significant decrease in taxonomic richness and diversity. Thus Jernberg *et al*[45] documented a decline in the clonal diversity of Bacteroides isolates, insurgence of antibiotic-resistant strains, and upregulation of antibiotic resistance genes in healthy volunteers treated for 1 wk with clindamycin. These effects persisted up to 2 years after treatment[45]. In another study vancomycin has been shown to cause long-lasting susceptibility to secondary infections in humans and mice. Vancomycin markedly disrupted the microbiota, leading to prolonged loss of resistance to *C. difficile* infection and dense colonization by vancomycin-resistant *Enterococcus*, *K. pneumoniae*, and *E. coli*[46].

In mouse models antibiotic administration during the perinatal period changes the lung microbial composition towards Th2 (vancomycin) or Th17 immune responses (streptomycin)[47].

However, some antibiotics like azithromycin could reduce pulmonary inflammation and exacerbations in patients with COPD. In the recent randomized, double-blind, placebo-controlled trial of 20 smokers (current or ex-smokers) with emphysema and CORD, administration of azithromycin 250 mg daily for 8 wk compared with placebo led to reduce *in-vivo* levels of chemokine (C-X-C) ligand 1 (CXCL1), TNF-α, IL-13 and IL-12 p40 in BAL, but increase levels of bacterial metabolites such as glycolic acid, indol-3-acetate and linoleic acid. Azithromycin treatment altered both lung microbiota and metabolome, affecting anti-inflammatory bacterial metabolites that may contribute to its therapeutic effects[48].

The relationship between respiratory pathology and the changes in the microbiome composition pre-disposed the use of probiotics. Anti-inflammatory effects of Lactobacillus rhamnosus and Bifidobacterium breve in smokers were evaluated. Both probiotic strains

significantly inhibited nicotine-mediated production of IL-1B, IL-6, IL-10, TNF-α, activation of the NF-κB as well as TLR4 and TLR9-induced expression of IL-8[49]. Use of Lactobacillus rhamnosus, Bifidobacterium lactis and Bifidobacterium breve in bronchial asthma resulted in reduction of allergic reactions[50,51]. Lactobacillus reuteri ATCC 23272 and Lactobacillus rhamnosus GG (LGG) administration leads to a significant reduction in the inflammatory cells of BALF[52]. The use of probiotic bacteria LGG and Lactobacillus casei (Sirota and DN 114 001 strain) showed high-potency for the prevention and treatment of both bacterial and viral infections of the respiratory tract[53]. The introduction of Enterococcus faecalis FK-23 in mice reduced the frequency of bronchial asthma exacerbations because of its ability to suppress T-lymphocytes and cytokine production[54].

Treatment of Klebsiella pneumoniae infected mice with Bifidobacterium longum, leads to more rapid resolution of inflammation, decrease in mortality, which has been associated with increased production of IL-10, lower levels of TNF-α and IL-6. Also in the group of mice, treated with probiotics, the ability of alveolar macrophages to produce reactive oxygen species was significantly higher when compared with the control group[55].

Probiotics are now used to treat and control a variety of gastrointestinal diseases including diarrhea, inflammatory bowel disease, irritable bowel syndrome, liver diseases. In rodent models, administration of probiotics prevents chronic stress-induced bacterial translocation[56], colorectal hypersensitivity[57], and restored intestinal barrier dysfunction[58].

The overall effects of prebiotics are similar to those of probiotics. It was shown that prebiotics provide optimal facilities for functional capacity of resident microbiota, stimulate different biochemical reactions within intestinal microbiome, promoting proliferation and renewal of

intestinal cells and therefore prebiotics appear to be an active and important part of gut-lung axis.

Prebiotics can ameliorate gut microbiota. Most prebiotics, including inulin and fructo-oligosaccharides are digested by Bifidobacteria and stimulate growth of their colonies[59]. These bacteria influence homeostasis of intestinal cells and inhibit the growth of pathogenic bacteria[60]. Moreover, SCFAs such as propionic acid, acetic acid, and butyric acid reduce the development of gastrointestinal disorders by inducing apoptosis[61]. Additionally SCFAs are important participants in macroorgsnism's immune system modulation as it was mentioned above[20-27].

As can be seen from the above prebiotics and probiotics are essentially different biological structures but their effects are mutually reinforcing.

The use of pre- and synbiotics in the treatment of the respiratory diseases was also studied. Effect of acidic oligosaccharides in the treatment of mice infected with P.aeruginosa was investigated. A significant reduction in mortality, an increase in IL-10 production was achieved. Diminished production of cytotoxic T-lymphocytes was revealed and as a result, reduction in the severity of inflammation and limitation of tissue damage was observed. In re-infected with Pseudomonas aeruginosa mice, the bacterial load in the lung tissue was lower when compared with the control group[62]. In the study on patients with allergic bronchial asthma treatment with synbiotic, containing Bifidobacterium breve M-16V showed a significant increase in peak expiratory flow rate and reduction in the production of IL-5 when compared with the placebo group[63]. Data summarized in Table 1.

CONCLUSION

The status of the lung microbiome is normally determined by the relationship between microbial immigration, elimination and local conditions of bacterial growth. The results of studies indicate changes both in the lung and the intestinal microbiome in patients with respiratory diseases, occurring due to imbalance between the factors mentioned above. The studies on human microbiome have aroused great interest in application of probiotics for the prevention and treatment of somatic diseases. However, there is a necessity of further studies to determine the appropriate dose, selecting an optimal bacterial strain, duration of treatment, as well as groups of patients that will provide desirable effect in the prevention and/or treatment of a particular disease. Studies on mice models have shown a positive effect of probiotics on the course of pneumonia, acute exacerbation of bronchial asthma and COPD, which dictates the need for its research on human population. It gives hope that the treatment of these diseases might be improved in the nearest future.

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