Lung microbiome – a modern knowledge

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Abstract

Recent studies have reported that commensal microorganisms are not just “passive occupants” but may play a crucial role in the immune system activation. It is well-known that in critically ill patients, the microbiome is modified and may be associated with the development of immunosuppression in sepsis, contributing to the development of acute renal injury, cardiovascular diseases, or more importantly, respiratory system disturbances. The conviction of lung sterility has gone down in history. The presence of characteristic gut microbiome, such as Bacteroidetes and Enterobacteriaceae, was demonstrated in lungs of critically ill patients. This bacteria’s translocation, especially in ischemia-reperfusion injury, results in increased concentration of inflammation response markers and may play a pivotal role in the pathogenesis of respiratory system disturbances, including acute respiratory distress syndrome. Recent studies have shown that ischemia-reperfusion injury is often observed in intensive care units (ICUs) and predispose to microbiome disturbances that are strictly connected with immune system activation and epithelial damage. Potential effects of dysbiosis treatment are under highly activated investigation. Therefore, it is possible that microbiota-targeted therapy may constitute the future therapeutic path in ICUs.

Key words: lung microbiome, ARDS, VILI, ICUs, immune system cells.

Introduction

The human body is colonized by millions of microorganisms. It is believed that their number is at least as large as the number of cells forming the host organism [1]. Recent years have brought an increased technical ability to identify the human microbiome [2]. There are reports that commensal microorganisms are not just “passive occupants” since they have a significant impact on the immune response of their host [3]. It is known that in critically ill patients, the microbiome is modified [4, 5]. Disorders of microbiome may be associated with the development of immunosuppression in sepsis and contribute to the development of acute renal injury or cardiovascular diseases [6–8]. Therefore, it is important to assess the existence of possible dependencies between the microbiome and genetic or environmental factors in the aspect of immune response in critically ill patients [9].

There are numerous reports documenting the composition and role of the gut, skin, or vagina microbiome [10-12]. However, the role of commensal organisms living in the lungs is relatively unknown. In 2013, the number of 401,000 European people died from respiratory diseases, which accounted for 8% of all deaths recorded [13]. It can be assumed that the assessment of pulmonary microbiome’s impact on the immune response of the host organism may indicate new therapeutic directions.

Lung microbiome

The conviction of lung sterility has gone down in history. By means of gastro-esophageal reflux or by micro-aspiration from the nasopharyngeal cavity, microorganisms constantly reach the alveoli [14]. The microbiome of healthy lungs consists mainly of bacteria from the Prevotella, Veillonella, and Fusobacterium species [15, 16]. Experimental studies have observed low density of pulmonary microbiome, with the value of the row 10^5-10^7 CFU/g of a lung tissue [17]. Its current composition is determined by the mutual ratio of microorganism immigration to the airways, their elimination, and reproduction of bacterial colonies forming the microbiome [18]. However, the assessment of human microbiome in healthy individuals presents some difficulties. Non-intubated patients samples taken during bronchoscopy could be contaminated by bacterial flora of the nasopharynx. Furthermore, difficulties in acquiring microbial material, which represents a reliable composition of the pulmonary microbiome, concern intubated patients; the collected bronchoalveolar lavage fluid (BALF) often more closely indicates the microbiome of upper respiratory tract than the lungs. Only strongly invasive methods, such as an open lung biopsy allow to obtain a reliable material for testing [19]. However, experimental studies have shown that pulmonary microbiome is different from that in the oral cavity or the gut [4].
Animal studies indicate the role of forming respiratory airways microflora in the first few weeks of life in the development of a proper immune response of the organism, through the appearance of Helios (-) Treg cells and a reduction in the response to allergens. It results in lowering of susceptibility to the development of allergic airway inflammation in adulthood [20]. It has been shown that the early formation of the microbiome is responsible for the subsequent stability of upper respiratory tract microflora and the reduction of susceptibility to pulmonary infections [21]. Lungs of germ-free (GF) mice contain 2.5 times more inreduction of susceptibility to pulmonary infections [21]. Consequent stability of upper respiratory tract microflora and the formation of the microbiome is responsible for the subse-quent inreduction of susceptibility to pulmonary infections [21].

In the absence of commensal microorganisms, the number of infiltrating TH2 lymphocytes and eosinophils in the lungs increased [23]. Pulmonary microbiome, by modulating the expression of innate immunity genes, causes an increase in the concentration of IL-5, IL-10, IFN-γ, and CCL11. In the lungs of murine SPF newborns, the level of expression of PD-L1 on CD11b+ DCs and the frequency of FoxP3+ CD25+ Treg cells are higher [20]. The composition of microbiome also affects the TLR4-dependent response of pulmonary macrophages [24]. Moreover, microbiota modulate the production of antibacterial peptides (AMPs) in the mucus and is responsible for inhibiting multiplication of bacteria and protecting the epithelium from these micro-organisms [25]. It has been shown that in the absence of microbiome in the lungs or when its number is low, there is a decrease in the production of protective mucus [26]. The GF mice are more susceptible to pulmonary infections caused by Pseudomonas aeruginosa, Streptococcus pneumoniae, or Klebsiella pneumoniae [27, 28]. Additionally, the number of pulmonary alveoli is greater in the lungs with normal microbiome [17].

**Effect of gut microbiome on the lungs**

Gut microbiome is the largest and the most diverse group of commensal bacteria of the human body [29]. Microbiota shapes the immune response of the host reducing its susceptibility to the development of inflammation or infection and improves the integrity of intestinal wall [30-32]. Unfortunatley, commensal bacteria are highly sensitive to environmental factors, including diet, antibiotics, allergens, and infectious pathogens, which can lead to microflora disorders, so-called “dysbiosis” [33]. Homeostasis disorders of the gut microbiome affect the distant organs, such as the brain, liver, vagina, or oral cavity [34]. Also, there is an evidence of interactions between the gut and the lungs in immunological aspect [14, 35]. Gut dysbiosis has been shown to be associated with the development of infection and inflammatory response to the allergic back-ground in the respiratory system [16, 36]. Both, the bacteria present in the gut and the products of their metabolism, may be the reason for immune stimation within the lungs [37]. The lymph and/or blood pass through the immune signals from the originally sensitized gut to the lungs [38].

It is known, however, that signals can also be transmitted in the opposite direction. The dysbiosis of pulmonary microbiome caused by tracheal administration of lipopolysaccharide leads to disorders in homeostasis of the gut microbiome [39]. Experimental studies documented the influence of pneumonia with etiology of a multi resistant drug to Staphylococcus aureus or Pseudomonas aeruginosa on the occurrence of gut damage [40]. For this reason, the reciprocal bi-directional relationship of these two local microbiomes is called the “gut-lung axis”.

**Lung microbiome in critically ill patients**

As a result of imbalance between the elimination and inflow of bacteria to the lungs during the disease, the composition of pulmonary microbiome is disturbed [41]. Disorders of the physiological flora of the lungs in asthma or chronic obstructive pulmonary disease have been documented [42, 43]. However, it is known that pulmonary dysbiosis also occurs in critically ill patients, in whom the primary pathology did not have a pulmonary source. The etiology of lung dysbiosis in critically ill patients is complex. First of all, such patients often undergo antibiotics therapy [44]. Schuijt et al. showed that in mice that received antibiotics, lung inflammation, organ damage, and mortality associated with Streptococcus pneumoniae infection was higher than in the control group [45]. Wienhold et al. documented that a wide-spectrum antibiotic therapy, which leads to microbial disturbances in experimental animals and ventilation with high tidal volume, increases the susceptibility to ventilatory-induced lung injury (VILI) development [46]. Secondly, endotracheal intuba-tion and mechanical lung ventilation favor the phenomenon of micro-aspiration and impair the mechanisms of natural cleansing of the airways, which promotes the dominance of opportunistic pathogens [15, 47]. In addition, the ongoing inflammatory process in septic patients or the nutrient-rich edema found in acute respiratory distress syndrome (ARDS) are responsible for the modification of metabolic and physicochemical conditions of the lungs [48, 49]. Furthermore, the presence of bacteria characteristic for the gut microbiome, such as Bacteroidetes and Enterobacteriaceae, has been demonstrated in critically ill lungs, which results in an increase in the concentration of inflammation response markers and may play an active role in the pathogenesis of ARDS [48, 50, 51]. Recent studies presented that ischemia-reperfusion injury, often observed in ICUs, predispose to microbiota disturbances strictly connected with immune system activation and epithelial damage. Elevated growth of Enterobacteriaceae...
promotes and perpetuates inflammation and trauma processes [52]. Hammer et al. showed that some elements of immune system can protect epithelial barrier during burn trauma. IL-22 and STAT3 signaling regulate the epithelial barrier, intestinal microbiome, and may prevent translocation of Enterobacteriaceae [53]. Importantly, interleukin 22 reduces inflammation in lungs. During mechanical ventilation, pH, free-radicals production, or oxygen tension changes, and alveolars are the potential target of pathogens growth. Some studies showed that intestinal typical bacteria are detected in the lung, serum, and mesenteric cells after ischemia-reperfusion injury. Intestine microbiome use activation of TLR 2, TLR 4, and myeloid differentiation primary-response 88 (MyD88) to tissue damage via nitric oxide synthase (iNOS) and reactive oxygen species (ROS) production.

A meta-analysis conducted by Manzanoares et al. evaluating the effects of probiotics in the treatment of patients hospitalized in intensive care units (ICUs) showed a reduction in the incidence of ventilatory-associated pneumonia (VAP); however, there was no effect on mortality or length of hospitalization [54]. Therefore, it is possible that microbiota-targeted therapy may constitute the future therapeutic direction in ICUs.

The authors declare no conflict of interest.

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