Lipid Metabolism Disorders and COPD

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Exacerbations largely determine the character of the progression and prognosis of chronic obstructive pulmonary disease (COPD). Exacerbations are connected with changes in the microbiological landscape in the bronchi due to a violation of their immune homeostasis. Many metabolic and immune processes involved in COPD progression are associated with bacterial colonization of the bronchi.

COPD exacerbations immune response inflammation lipid metabolism phagocytosis lipid rafts

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease, the prevalence and social significance of which is of increasing concern to clinicians and researchers [1][2][3][4]. It is shown that COPD is among the leading causes of morbidity and mortality worldwide [5][6]. As forecasts predict, the medical and economic burden of the disease will only grow.

Despite the available advances in COPD research, the keys to understanding all the pathophysiological mechanisms underlying both the disease itself and its comorbid interactions are still unknown. It is also not fully understood how one major etiological factor—cigarette smoking—can initiate the development of differences in clinical characteristics variants of COPD course.

Exacerbations are considered an important part of the clinical heterogeneity of COPD, they can modulate the nature of the course and mediate the relationship with comorbid diseases [7]. Exacerbations are events in the natural course of COPD, which are characterized by an increase in the severity of chronic respiratory symptoms (shortness of breath, cough, and sputum production) that go beyond their daily variability [8][9]. Exacerbations are associated with a deterioration in the quality of life and prognosis [10]. Taking into account the influence of exacerbations on the character of the course of the disease, some authors suggest that frequent exacerbations should be considered as a separate phenotype of COPD [11][12][13].

The mechanisms whose disorders are associated with exacerbations of COPD are of great clinical and research interest [14]. Exacerbations can be caused by many different factors, including viruses, bacteria, and aeropollutants [9][15][16]. It is shown that bacterial colonization of the bronchi makes a significant contribution to the progression of COPD [17].

The data accumulated in recent years leave no doubts that lipid metabolism disorders are widely involved in the pathogenesis of COPD [18][19][20]. These disorders occur at different levels and participate in both the development of inflammation and the formation of pulmonary and extrapulmonary clinical heterogeneity of the disease [21]. It is shown that lipid metabolism is connected with the development of COPD phenotypes, such as emphysema [22]. Interestingly, dyslipidemia causes multidirectional effects on innate immunity in the lungs and in the body in general, which is associated with the unique lipid biology of the lungs [23].

2. Participation of Lipids in Phagocytosis Disorders in COPD

Phagocytosis is the most important mechanism that ensures the purification of tissues from foreign particles, microorganisms, and dead cells and is carried out by both professional and non-professional phagocytes [24][25]. The process of absorbing dead cells is called efferocytosis [26][27][28]. Macrophages are professional phagocytes and by their origin form two separate subpopulations in the lungs. Their number in the lungs in patients with COPD increases, which may be associated with increased recruitment of blood monocytes [29][30][31][32]. At the same time, both alveolar macrophages and macrophages differentiated from blood monocytes are characterized by defective efferocytosis and phagocytosis regarding a number of bacteria [33][34]. The phagocytic abilities of alveolar macrophages and macrophages derived from blood monocytes in COPD patients may differ, as was shown for *H. influenzae*, which provides an immunological basis for colonization of the respiratory tract by the bacterium in COPD [35][36] and may be one of the causes of exacerbation development [37]. In addition, the phagocytosis defect in COPD is mainly characteristic of bacterial pathogens, but not of inert microspheres [34].

Defective phagocytosis of bacteria is one of the factors leading to colonization of the lower respiratory tract and the development of infectious exacerbations of the disease [33]. Violation of phagocytosis by macrophages is associated with the frequency of exacerbations [37] and the severity of COPD, determined by indicators of pulmonary function [34][38]. Tobacco smoke is known to reduce the ability of alveolar macrophages to phagocytosis and efferocytosis [39][40]. Cells that died due to apoptosis and were not subjected to timely efferocytosis may be the cause of chronic inflammation [41]. Lipids oxidized under the influence of cigarette smoke make a significant contribution to local immune responses. It has been shown that exposure to cigarette smoke causes the production of antibodies against oxidized lipids in the lungs of mice, which may contribute to limiting the response to damaged lipids [42]. Interestingly, the phagocytic function of macrophages was dose-dependent suppressed by the presence of oxidized epithelial lipids [43].

Exposure to cigarette smoke leads to the accumulation of lipids in lung macrophages, with the formation of a foam cell phenotype [44]. It should be noted that the accumulation of cholesterol in macrophages may be facilitated by a decrease in the expression and functional activity of the ABCA1 transporter during smoking. The function of ABCA1 in phagocytosis is to remove excess cholesterol that is formed during uptake, for example, of apoptotic cells. At the same time, cholesterol-loaded macrophages are less effective phagocytes, which corresponds to data on a decrease in the phagocytic activity of ABCA1 deficient macrophages. In addition, ABCA1 participates in the “find-me” and “eat-me” signals, which are necessary for phagocytosis and efferocytosis [45].

Thus, phagocytosis is closely related to lipid metabolism. Active phagocytosis leads to an increase in the rate of lipid metabolism, which may reflect the general metabolic stimulation accompanying this process [46]. The increased synthesis of phospholipids during phagocytosis [47] is associated with the need for their use for the formation of membranes of phagocytic vesicles [48].

It is shown that the phagocytic activity of macrophages is determined by the composition of the plasma membranes of cells. At the same time, the ratio of saturated and unsaturated fatty acids in phospholipids is important [49]. Experiments with the cultivation of macrophages in the presence of various fatty acids have shown that they are well incorporated into the composition of plasma membranes, affecting phagocytic activity, while its greatest increase is observed in the presence of cis unsaturated fatty acids [50].

Some bacteria have developed certain strategies that allow them to avoid death during phagocytosis [51]. There is strong evidence that *K. pneumoniae* survives phagocytosis by macrophages by regulating phagosome maturation. *K. pneumoniae* controls the maturation of phagosomes by regulating the PI3K-Akt-Rab14 axis, so that the bacterium does not die in macrophages, but is located in a special intracellular compartment that does not merge with lysosomes [52].

In addition, *K. pneumoniae* can disrupt efferocytosis, so that neutrophils infected with the bacterium are excreted through efferocytosis less efficiently than uninfected neutrophils [53]. For this purpose, *K. pneumoniae* can use several mechanisms, including reducing exposure to phosphatidylserine (PtdSer) by increasing flippase activity [53][54]. The localization of PtdSer on the outer sheet of the plasma membrane is known to be the «eat-me signal» for macrophage receptors that provide uptake of apoptotic cells [55]. In the plasma membranes of living cells flippases are responsible for the transport of PtdSer from the outer leaf to the inner leaf, whereas, in apoptosis, PtdSer moves in the opposite direction [56]. *K. pneumoniae* contributes to the shift of the cell death pathway from apoptosis to necroptosis of infected neutrophils [53][57]. Thus, disruption of apoptosis due to PtdSer translocation modulation and activation of necroptosis are independent mechanisms of disruption of neutrophil efferocytosis in *K. pneumoniae*. This allows the bacteria to enter the interstitium, avoiding uptake by macrophages [53][54].

Thus, in COPD there is a violation of various phagocytosis mechanisms that can use bacterial pathogens for colonization.

3. Participation of Lipids in the Resolution of Inflammation in COPD

The information accumulated in recent years allows us to re-evaluate the variety of functions of lipids in various phases of inflammation. More and more evidence suggests that lipids are involved not only in the initiation of inflammation, such as prostaglandins and leukotrienes formed from arachidonic acid, but are also mediators of the highly organized phase of inflammation resolution [58][59][60]. Recently identified new families of mediators, called “specialized pro-resolving mediators” (SPM) play a key role in the active resolution of inflammation [61][62][63][64]. This class of endogenously produced bioactive lipids includes lipoxins, resolvins, protectins, and maresins, which

are formed by oxygenation of ω-3 and ω-6 PUFA [65][66]. Moreover, lipoxins are synthesized by a series of enzymatic reactions from arachidonic acid [67][68], resolvins of the E series from eicosapentaenoic acid, and resolvins of the D-series and protecins, as well as maresins, are formed from docosahexaenoic acid [69][70][71]. Thus, PUFAs, if necessary released from membrane phospholipids, are an important source of not only pro-inflammatory, but also anti-inflammatory mediators [70][71][72][73].

The function of SPM is being studied actively, but the data available to date allow us to emphasize their significant role in inflammation, which is provided by the regulation of many lower signaling pathways [58][61][73][74][75]. SPM affect the decrease in the secretion of pro-inflammatory cytokines, and on the contrary, they contribute to an increase in the number of anti-inflammatory cytokines, through switching macrophages to the M2 phenotype, and also increase phagocytosis, which is important, taking into account that tobacco smoke stimulates macrophages pro-inflammatory [73][75][76][77].

Taking into account the importance of SPM in the resolution of inflammation, and the violation of this process in COPD, the role of lipid mediators is of great clinical interest [76][78][79][80][81][82]. The participation of resolvin RvD1 in tissue regeneration in emphysema caused by smoking has been shown [83]. It has also been determined that resolvins inhibit the production of pro-inflammatory cytokines TNF-α and IL-6 by alveolar macrophages in COPD, weakening the inflammatory effects caused by cigarette smoke [84][85]. SPM also improves bacterial clearance by activating phagocytosis, such as RvD1, which enhances phagocytosis of *P. aeruginosa* by neutrophils and macrophages [85][86].

Lipid mediators demonstrate dysregulation of concentrations in various biological substrates of COPD patients, including exhaled air condensate, bronchoalveolar lavage fluid, and blood serum. It was found that the levels of anti-inflammatory lipoxin LXA4 decrease in sputum in COPD patients during exacerbation, while there is an increased ratio of pro-inflammatory leukotriene B (4) (LtB (4)) to LXA4 (LtB (4)/LXA (4)) [87].

Taking into account the role of SPM in providing bacterial clearance in acute infection, it is interesting to consider the relationship of SPM with chronic persistent infection, which is characteristic of COPD [86]. In this regard, it should be noted that there are currently known examples of the use of local SPM production by some pathogens as a strategy for evading host immunity and survival [75][76][88]. It is shown that *P. aeruginosa* participates in the biosynthesis of SPM by activating cytosolic phospholipase A2, thereby increasing the available pool of arachidonic acid and then metabolizing it with the help of functional 15-lipoxygenase (15-LOX) [88][89][90][91].

Thus, taking into account the biological role of lipid mediators and experimental data on the effectiveness of SPM in resolving inflammation, overcoming immunosuppressive effects caused by tobacco smoke [81], this group of lipid mediators is of great interest from the point of view of finding new effective therapeutic strategies and developing drugs for the treatment of COPD [84][85].

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