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Features of apoptosis and blebbing of the lymphocyte plasma membrane in bronchial asthma

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ABSTRACT

Given a persistent global trend towards an increase in the number of patients with bronchial asthma (BA) over the past decades, researchers are facing challenges related to a comprehensive study of the pathogenesis of BA. Numerous studies have shown that BA is associated with long-term persistence of leukocytes (lymphocytes, macrophages, and eosinophils) in the bronchial tissues. However, the causes of this phenomenon remain understudied. The article provides an overview of modern research on the mechanisms of disorders of lymphocyte apoptosis in patients with BA.

Our study considers the main mechanisms of molecular regulation of lymphocyte apoptosis, including transcription factors, the Fas/FasL system, and bcl-2/bcl-XL factors. We presented the data on the role of reduced lymphocyte apoptosis in the formation of a severe BA phenotype. Taking into account high prevalence of obesity among patients with BA, we analyzed a few existing articles on apoptosis of immunocompetent cells in obesity. In addition, the article highlights the key mechanisms of development of lymphocyte plasma membrane blebbing (PMB) with formation of microvesicles, as well as their influence on the course of pathological processes in BA.

The authors believe that further in-depth study of apoptosis, lymphocyte necrosis, and plasma membrane blebbing can help improve the principles of diagnosis and treatment of BA.

Key words: bronchial asthma, obesity, lymphocyte apoptosis, programmed cell death, caspase, plasma membrane blebbing.

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Особенности апоптоза и блеббинга цитоплазматической мембраны лимфоцитов при бронхиальной астме

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РЕЗЮМЕ

С учетом стойкой общемировой тенденции к нарастанию численности больных бронхиальной астмой (БА) за последние десятилетия перед исследователями встает задача всестороннего изучения патогенеза бронхиальной астмы. В многочисленных исследованиях доказано, что течение БА сопряжено с длительной персистенцией лейкоцитов (лимфоцитов, макрофагов, эозинофилов) в тканях бронхов. Однако остается открытым вопрос о причинах данного явления. В данной статье представлен обзор современных научных исследований, посвященных изучению механизмов нарушения апоптоза лимфоцитов у больных бронхиальной астмой.

Рассматриваются основные механизмы молекулярной регуляции апоптоза лимфоцитов, например транскрипционные факторы, система Fas/FasL, факторы bcl-2/bcl-XL и др. Приводятся данные об участии снижения апоптоза лимфоцитов в формировании фенотипа с тяжелым течением бронхиальной астмы. Учитывая высокую распространенность ожирения среди больных бронхиальной астмой, проанализированы немногочисленные статьи, касающиеся апоптоза иммунокомпетентных клеток при ожирении. Кроме того, в статье освещаются ключевые механизмы развития блеббинга цитоплазматической мембраны (ЦПМ) с формированием лимфоцитарных микровезикул, а также их влияние на течение патологических процессов при астме.

Авторы считают, что дальнейшее углубленное изучение процессов апоптоза и некроза лимфоцитов, а также блеббинга ЦПМ сможет помочь в улучшении принципов диагностики и лечения бронхиальной астмы.

Ключевые слова: бронхиальная астма, ожирение, апоптоз лимфоцитов, программируемая клеточная гибель, каспазы, блеббинг цитоплазматической мембраны.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Bronchial asthma (BA) is a chronic respiratory disease that places a serious social and economic burden on a patient and society as a whole [1, 2]. Experts of the World Health Organization (WHO) note that the number of patients with BA tends to increase [3].

Russia has also seen a continuing increase in the overall incidence of BA in recent years [4]. According to statistical data, the prevalence of BA among adult population of Russia accounts for up to 10.6% [5].

It is known that BA reduces the average life expectancy of women by 13.5 years and men by 6.6 years; it causes 1.4% of all hospitalizations and 1.5% of all disability cases. A financial burden associated with diagnosis and treatment of BA has a significant impact on the country's economy [6].

An equally important health and social problem worldwide is obesity. WHO sees this problem now as an epidemic which has affected millions of people. Since 1980, the number of obese people in the world has more than doubled. Excess body mass index (BMI) is observed in about 1 billion people among adult population of the world, and 475 million people are obese [7, 8].

Obesity is the most common comorbidity of BA. It was shown that obesity increases the prevalence and incidence of BA and raises the risk of exacerbations, aggravation of respiratory symptoms, and poor disease control. Precise mechanisms of the mutual effects of BA and obesity remain unclear. They are probably multifactorial and mediated by mechanical changes in the airways, systemic inflammatory response, and metabolic dysregulation [9, 10].

Quite recent studies emphasize the role of programmed cell death (PCD) and autoimmunity as

potentially important factors in the pathogenesis of chronic obstructive airway diseases. Currently, there are a few methods available for registering different PCD manifestations and analyzing molecular mechanisms [11], that are closely associated with mechanisms of other important phenomena (such as cell activation and biological signal transduction).

It is the study of apoptosis that is considered effective and useful for understanding certain significant processes, including immune homeostasis.

THE ROLE OF LYMPHOCYTES IN THE DEVELOPMENT OF BA

The course of BA is characterized by progressive chronic airway inflammation, which is based on production of proinflammatory cytokines (interleukin (IL) -4, -5, -9, -13, granulocyte-macrophage colony-stimulating factor (GM-CSF), etc.) [12], as well as long-term persistence of leukocytes (lymphocytes, macrophages, and eosinophils) in the bronchial tissues [13].

Lymphocytes are essential regulatory and effector cells of adaptive immunity. Together with antigen-presenting cells (APCs), T- and B-lymphocytes provide an immune response to pathogens and form long-term immunological memory [14].

The number of lymphocytes is regulated by a constant balance between production, proliferation, and death of cells. The equilibrium of these processes is characterized as lymphocyte homeostasis [15].

The number of effector T-lymphocytes in the immune response can increase by 1,000 times [16], but programmed cell death regulates accumulation of the total number of lymphocytes, also in BA [17].

Therefore, the constant presence of regulatory and effector immune cells in BA may be due not only to their accelerated migration to tissues, but also to restricted cellular elimination following PCD dysregulation.

TYPES OF PCD

Based on the physiological, morphological, and biochemical criteria, researchers distinguish three types of PCD: apoptosis (type I PCD), autophagy (type II PCD), and necrosis (type III PCD) [18, 19].

Autophagy and apoptosis

Autophagy is a process of *in vivo* elimination of the cytoplasmic contents changed by metabolites, that involves cell self-renewal. Extensive autophagy can lead to cell death [20, 21].

At the same time, natural, physiological, and programmed cell death (50–500 billion cells daily) mainly occurs through apoptosis: after plasma membrane blebbing, cell reduction, chromatin condensation, and DNA fragmentation, apoptotic cells are rapidly absorbed by phagocytic cells without any inflammatory response [22, 23].

Mechanisms of apoptosis

Type I PCD (apoptosis) occurs in several ways via the mechanisms that depend on both cellular characteristics and the impact of internal and external signals [24]. After the effects of toxic agents or unrepaired DNA damage, the mitochondrial (internal) signaling pathway is implemented in apoptosis. The main regulators of this process are the *p53* and *Bcl-2* genes (the main suppressor of apoptosis) with corresponding proteins [25, 26].

More often, the external or receptor-mediated pathway of apoptosis is implemented. It is initiated by a variety of extracellular triggers and is carried out with the participation of tumor necrosis factor (TNF) receptors. The most studied activator is Fas (APO-l or CD95), which stimulates cell apoptosis after the formation of a complex compound with its ligand Fas / FasL [27, 28].

The effector phase of apoptosis begins after transmission of inducing signals from triggers through adaptive proteins. The main participants in this phase are cysteine proteases (caspases), which quickly switch from the inactive (procaspase) to the active form, when apoptosis is initiated. This ensures cleavage of protein molecules at aspartic acid bases [29, 30].

The growing interest of experts in PCD issues [31] has led to an increase in the number of studies related to apoptosis. Methods for detecting apoptosis and analyzing its molecular and genetic mechanisms have emerged. It allowed researchers to identify the significant role of apoptosis in maintaining homeostasis of constantly regenerating tissues and understand the effect of PCD on the pathogenesis of many pathological processes [32].

The terminal deoxynucleotidyl transferase dUTP-biotin nick end labeling (TUNEL) method, or terminal deoxyuridine end labeling, was recognized as the most optimal method for determining apoptosis in cells [33], since numerous strand breaks occur in DNA during apoptosis under the action of

endonucleases, which results in formation of many 3'ends [34]. The TUNEL method is based on binding of biotin-labeled deoxyuridine triphosphate to the 3'-end of a DNA strand. The binding is implemented by deoxynucleotide transferase. There are other optimal biochemical, molecular, and genetic methods for determining apoptosis [35]. In the context of existing information about the abnormalities of lymphocyte apoptosis in systemic, autoimmune, and allergic diseases, the study of apoptosis in BA has become relevant and important.

Persistence of allergic inflammation in the airways is associated with excessive activation of immunocompetent cells (ICC), which, in turn, leads to accumulation of autoreactive clones with a simultaneous decrease in the activity of apoptosis (positive activation and absence of apoptosis) [36–38]. It is possible that lymphocyte apoptosis is closely related to their migration to the focus of inflammation as a result of allergen exposure. In this case, apoptosis acts as a mechanism of antigen-mediated selection of lymphocytes [39].

LYMPHOCYTE APOPTOSIS AND BA

In BA, several pathways of death are triggered in the ICC, and they are able to switch in the course of the disease [40]. In BA, marked inhibition of the mechanisms of lymphocyte apoptosis takes place, associated with an increase in the expression of IL-5 mRNA and the main anti-apoptotic factors (bcl-2, bcl-XL) inhibiting apoptosis via the receptor and mitochondrial pathways, which directly correlates with the severity of BA [41].

The molecular mechanisms playing an important role in the regulation of PCD include transcription factors, such as Janus kinases and signal transducer and activator of transcription (JAK-STAT), PAX-5, NF-KB, p53, etc. Transcription factors regulate expression of proteins (IL-4, -15, -13, IgE, Fas receptor molecules, etc.) and proliferation of cells, such as lymphocytes and eosinophils [42, 43].

It is proved that decreased gene expression, reduced activity of transcription factor p53, and stimulation of NF-kB activity have anti-apoptotic effects. High levels of STAT6 expression at reduced PAX-5 and elevated levels of NF-KB lead to development of BA and aggravation of its course [44].

The Bcl-2 / Bax ratio in patients with severe BA is much higher. This fact was confirmed by many studies demonstrating that NF-kB stimulates the expression and activity of Bcl-2, which itself acts as a powerful anti-apoptotic molecule and inhibits pro-apoptotic Bax molecules [45, 46].

Recent studies have found that the levels of Bcl-2 or the Bcl-2 / Bax ratio are higher in BA patients than in healthy people. The level of NF-kB expression positively correlates with the bcl2 / Bax ratio in patients diagnosed with BA [47].

It is remarkable that the Fas / FasL system that triggers the receptor-mediated pathway of apoptosis is less active in Th2 lymphocytes typical of BA, which suggests their evolutionary predisposition to a reduced apoptosis rate [48, 49]. According to the studies, steroids are able to enhance apoptosis but reduce the expression of Fas (CD95) and CD25 regulators, switching apoptosis to a different pathway [50].

A number of studies reported the association between the activity of apoptosis and the severity of BA [51]. Specifically, an inverse correlation was demonstrated between the number of apoptotic cells and BA severity [52]. It was noted in another study, that the number of lymphocytes in apoptosis was significantly lower in severe BA (compared to mild BA) against the background of 6-day incubation in the solution with the addition of an apoptosis inducer (dexamethasone). According to the authors, this may indicate inhibition of type I PCB in patients with severe BA [53].

Necrosis

Currently, an important role is assigned to the study of the consequences of not only apoptosis, but also of type III PCD (necrosis) for surrounding cells and the body as a whole. Necrotic cell death is accompanied by destruction of the cell membrane and entry of intracellular molecules into the extracellular space with alterations of surrounding cells and inflammation. Phagocytosis of dead cells is accompanied by development of a full-fledged immune response [54]. Necrotic death of lymphocytes is always associated with excretion of inflammatory mediators having cytotoxic and histochemical effects. It is also accompanied by active proliferation and migration of new effector cells into the airways, which aggravates airway inflammation [55].

According to A.P. Parakhonsky, the development of BA is closely associated not only with abnormalities in the implementation of apoptosis in blood ICC, but also with an increase in lymphocyte necrosis [56]. Few existing studies showed that necrotic death of lymphocytes prevails in patients with severe persistent BA [57].

PLASMA MEMBRANE BLEBBING (PMB) AND BA

During oxidative stress, apoptosis, and necrosis of lymphocytes, membrane microvesicles (MV) are formed as a result of intensive PMB [58, 59].

Development of PMB occurs following disruption of membrane-cytoskeleton interactions at the end of enzymatic reaction activation, electrolyte imbalance in the cell, and oxidative damage to the cytoskeleton. PMB is preceded by a disruption of actin-myosin interactions and externalization of phosphatidylserine, which is characterized by a bubble-like protrusion of the membrane. It is accompanied by migration of organelles and antigens into the resulting blebs, which acquire inflammatory and autoantigenic potential. For example, extracellular particles originating from T-cells carry CD4, CD3, or CD8 antigens [60, 61].

Microvesicles

Evidence for the role of ICC plasma membrane vesicles is still significantly limited. Their role in regulating homeostasis by transporting signals between cells, up to presentation of an antigen to immune cells, is still under discussion [62].

Microvesicles (MV) can affect cells in two main ways: interaction with receptors and microRNA transfer [63]. MV can regulate gene expression and cell differentiation, which involves them in the pathogenesis of many processes [64]. Many studies are devoted to MV microRNAs, which are highly conserved non-coding RNAs with a length of 18–24 nucleotides, as well as to their proinflammatory role [65].

Another factor affecting the inflammatory process can be the ability of MV to induce apoptosis of ICC. Apoptogenic activity of MV can be explained by the influence of caspases and other biologically active substances contained in them that induce apoptosis [66].

However, very few studies have been devoted to the pathogenic effect of lymphocyte microvesicles (LMVs) on the course of pathological processes, in particular, on the pathogenesis of BA. LMVs are known to induce activation of NADPH-oxidase, leading to activation of oxidative stress [67].

High content of circulating MV in patients with BA can serve as a useful biomarker of the activity of apoptosis and airway inflammation and a potential predictor of BA severity. It reflects the effect of an important element in the pathogenesis of BA and not just the appearance of inert “cell dust”, as it has been generally accepted for a long time.

APOPTOSIS AND OBESITY

There are very few studies and publications devoted to apoptosis of ICC (lymphocytes, in particular) in obesity. Metabolic changes in the white adipose tissue of obese people are known to lead to the persistence of ICC in the adipose tissue. Locally, elevated levels of proinflammatory cytokines and free radicals are observed that contribute to oxidative stress and progression of systemic inflammation [68].

In obesity, an increase in the intensity of lymphocyte apoptosis is noted, in which the interaction of the Fas receptor with FasL leads to activation of caspase-8, -10, and -3. In obese patients, the concentration of apoptosis inducer (p53 protein) is elevated, and its level directly correlates with the body mass index, waist circumference, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index [69, 70].

CONCLUSION

In terms of physiopathology, BA is a chronic inflammatory airway disease. The study of PCD, in particular, apoptosis, is determined by the essential role of lymphocytes in the pathogenesis of BA. Despite a large body of data on BA, the concept of apoptosis in the pathogenesis of BA is still contradictory. The findings of immunological studies provide evidence for changes in the functional state of lymphocytes in BA patients. Studies of apoptosis related to BA with comorbid obesity are especially relevant. It is worth noting that there is growing evidence that obesity has a causal association with BA. Better understanding of this association at the pathogenetic level may result in development of new treatment methods for the therapeutically resistant cohort of patients.

Therefore, further study of all aspects of apoptosis and lymphocyte PMB in BA and establishment of their cytological, molecular, and biochemical markers can contribute to more complete understanding of the mechanisms of BA pathogenesis, improve diagnosis, and create a new landmark for differential diagnosis. It can also serve as the basis for developing highly effective, modern methods for treatment and prognosis of treatment effectiveness in obstinate and treatment-resistant forms of BA.

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