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Бронхиальная астма с точки зрения гликомики

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АННОТАЦИЯ

Бронхиальная астма — широко распространённое заболевание, которое с каждым годом всё дороже обходится медицинской и финансовой системам развитых стран. Растущее бремя бронхиальной астмы обусловливает необходимость поиска наиболее эффективных методов диагностики и лечения различных, в том числе и относительно редких фенотипов данного заболевания.

С этой точки зрения гликомика является одним из самых интересных и перспективных направлений медицины. Данная отрасль изучает различные углеводные соединения и их роль в развитии заболеваний.

В контексте бронхиальной астмы представляют интерес мембранные рецепторы к конечным продуктам гликирования (RAGE) и их растворимые варианты. Помимо этого, ключевую роль в принципиально новых методах терапии могут играть иммуноглобулиноподобные лектины, связывающие сиаловую кислоту (Siglec): воздействуя на них можно добиться снижения провоспалительной активности иммунокомпетентных клеток и протекции стенок бронхов. Наконец, практически неизученными остаются N- и O-гликаны, потенциально способные играть роль не только в диагностике и верификации бронхиальной астмы, но и в изменении аллергенности отдельных молекул. N-гликаны интересуют учёных не только в диагностическом контексте, но и в роли молекул, воздействуя на которые можно снизить аллергенность, например, яичного белка вакцин.

Гликомика и гликопротеомика — современные, активно развивающиеся разделы медицинской науки, которые открывают новые перспективы в ведении пациентов с заболеваниями многих органов и систем, включая заболевания респираторного тракта в целом и бронихиальной астмы в частности. Несмотря на взрывной характер развития гликонауки, представления об участии изучаемых ею молекул в патогенезе заболеваний дыхательной системы только начинают формироваться.

Ключевые слова: гликомика; бронхиальная астма; рецепторы к конечным продуктам гликирования (RAGE); Siglec; N-гликаны.

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Bronchial asthma from the perspective of glycomics

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ABSTRACT

Bronchial asthma is a widespread disease that is becoming increasingly costly to the medical and financial systems of many countries with each passing year. The rising prevalence of bronchial asthma necessitates a search for the most efficient diagnostic and treatment strategies for various asthma phenotypes, including some that are relatively uncommon.

From this point of view, glycomics appears to be one of the most interesting and perspective branches of medicine. This research area studies various carbohydrate complexes and their roles in the development of various diseases.

Researchers are interested in the study of the receptors for advanced glycation end products and their soluble variants with regard to bronchial asthma. Furthermore, sialic acid-binding immunoglobulin-type lectins (Siglecs) may play a vital role in the principal novel strategies of the treatment. By affecting Siglecs, a decrease in the proinflammatory activity of immunocompetent cells results, and the bronchial walls are protected. Finally, N- and O-glycans remain almost unresearched. These molecules, on the other hand, have the potential to play a significant role not only in the diagnosis and confirmation of asthma but also in the allergenicity of various molecules. Scientists are interested in N-glycans, not only in the diagnostic context but also in their role as a molecule that can reduce allergenicity, for example, egg white vaccines.

Glycomics and glycoproteomics are cutting-edge disciplines of medical science that are opening up new perspectives in the management of patients with diseases of various organs and systems, including diseases of the respiratory tract in general and bronchial asthma in particular. Despite the fast-paced nature of the development of glycoscience, theories about the role of the molecules investigated in the pathophysiology of respiratory disorders are only beginning to emerge.

Keywords: glycomics; bronchial asthma; receptor for advanced glycation end products; Siglec; N-glycans.

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INTRODUCTION

Bronchial asthma is one of the most widespread noncommunicable diseases affecting more than 330 million people worldwide. The average asthma prevalence is about 4.3% with significant cross-country variations, from 0.2% in the People's Republic of China to 21% in Australia [1]. Patients with asthma annually cost the US budget of $56 billion according to medical and economic studies. The costs of managing such patients with asthma, as well as their number, are steadily increasing not only in the United States but also throughout the world [2]. The growing burden of asthma necessitates the search for more effective methods of screening, diagnosis, and treatment of the disease.

Glycomics and glycoproteomics are modern actively developing branches of medical science that open new prospects of identifying patients with diseases of various organs and systems, including respiratory tract diseases in general and asthma in particular [3]. Despite the explosive nature of the glycoscience development, concepts about the molecules involvement under glycoscience study in the respiratory tract diseases pathogenesis are just beginning to form.

This review reflects current ideas about the carbohydrates effects and their interactions with biomolecules on the asthma development as well as the potential for using molecules of interest as diagnostic biomarkers and therapeutic targets.

RAGE AND THEIR LIGANDS ROLE IN THE ASTHMA DEVELOPMENT

Glycation or nonenzymatic glycosylation is a reaction between reducing carbohydrates (glucose, fructose, etc.) and free amino groups of proteins, lipids, and nucleic acids of a living organism, proceeding without the enzymes participation. Glycation is a particular Maillard reaction case.

Membrane-bound receptors for advanced glycation end products (mRAGE) are surface proteins from the immunoglobulin superfamily capable of binding a wide range of ligands. These receptors are expressed in various tissues, both in the healthy population and in patients suffering from various diseases. In the lungs, however, an initially higher mRAGE level was found, which is localized mainly in type I alveolocytes. Apparently, in healthy people, these receptors perform not only homeostatic functions but also a number of other functions that have not been reliably determined [4, 5].

The receptors for advanced glycation end products (RAGEs) bind a wide range of ligands, including proteins calprotectin (S100A8/A9), calgranulin C (S100A12), and high-mobility group protein B1 (HMGB1). These molecules play an important role in the allergic asthma pathogenesis [6–8].

Amphoterin (HMGB1) is a nuclear nonhistone protein widely present in the tissues of the lungs, brain, liver, heart, etc. [9]. It has been established that amphoterin is involved in the diseases pathogenesis accompanied by chronic inflammation (especially respiratory system diseases) [10]. Elevated HMGB1levels are recorded in the sputum of patients with severe asthma. Apparently, this protein, through RAGE, can contribute to the allergic inflammation development of the upper respiratory tract, participating in the eosinophils migration. In addition, the HMGB1 level directly correlates with the tumor necrosis factor alpha (TNF-α) level and interleukins 5 and 13 (IL-5 and IL-13) in sputum [7].

The S100 proteins are calcium-binding proteins with low molecular weight. The calgranulin A (S100A8) and calgranulin B (S100A9) exist as homodimers for an extremely short time, quickly combining into the S100A8/A9 complex. Expressed on the neutrophils and monocytes surfaces as a calcium receptor, S100A8/A9 is involved in cytoskeleton changes and in arachidonic acid metabolisms, taking a significant part in the inflammatory response [11].

The S100A8/A9 complex is the main neutrophil cytosolic protein [8]. It has antimicrobial activity and has been found to directly correlate with the asthma severity. Thus, an elevated S100A8/A9 complex level is associated with severe, uncontrolled asthma course and can be used as biomarker to predict response to therapy [8].

In addition, calgranulin C (S100A12), interacting with RAGE, enhances mast cell degranulation and IgE-mediated inflammatory response in the lungs. The S100A12 and eosinophils levels expressing this protein are higher in the sputum of patients with asthma compared to healthy people [12].

Further studies on the RAGE interaction with the designated ligands are needed. Potentially, these data can open up a fundamentally new approach to asthma therapy through the correction of the described molecules' interaction intensity.

The RAGE role in asthma pathogenesis remains largely unclear. Apparently, mRAGE is one of the key mediators of respiratory tract hypersensitivity, increased mucus secretion, and bronchial wall remodeling in laboratory mice [13]. In addition, in animal models of ovalbumin-induced asthma, mRAGEs were found to be involved in ovalbumin-induced airway inflammation, which is adopted in this study as a human asthma model. This involvement is realized through the Th2-immune inflammation activation, pro-inflammatory cytokines stimulation (IL-5, IL-13, and TNF-α) synthesis of [14].

It is important to note that, in addition to membrane RAGE, researchers have detected soluble RAGE (sRAGE) in the blood [15–18]. A number of studies have found that sRAGE level is inversely correlated with the amount of eosinophils, IgE, and pro-inflammatory cytokines in sputum in both adults and children [15, 16]. Apparently, this receptor functions as a "trap-"binding mRAGE ligands and thus preventing their pro-inflammatory activities [17]. The HMGB1 expression inhibition in the lungs, which occurs with the sRAGE participation, mainly contributes to decrease in RAGE activities [15]. In addition, this soluble receptor helps to reduce the IL-17secretion [17]. Regarding the IL-17 levels,

an inverse synthesis correlation with the vitamin D level in the blood seems to be significant, which indicates this vitamin's anti-inflammatory role in asthma [18]. It appears that along with the effect on targets studied by glycoscience, the vitamin D levels correction may be important in the comprehensive asthma treatment.

In addition, sRAGE is inversely correlated with the neutrophilic airway infiltration severity and disease severity [19, 20]. Thus, local exposure to sRAGE can lead to decrease in asthma intensity through various effector pathways, opening up new possibilities for pathogenetic asthma therapy [15, 16, 19, 20].

Chinese researchers have identified characteristic haplotypes of genes encoding RAGE that increase the risk of developing asthma and chronic obstructive pulmonary diseases [21]. This study, however, was conducted among the Hanzu ethnic group living in the northeastern part of China. Therefore, further study of this issue in a larger sample of patients is necessary. In general, the issue of gene polymorphisms coding RAGE in the asthma development and course is studied insufficiently.

MODERN CONCEPTS OF THE SIGLEC ROLE IN THE BRONCHIAL ASTHMA PATHOGENESIS AND MANAGEMENT

Siglec (sialic-acid-binding immunoglobulin-like lectins are immunoglobulin-like lectins-binding sialic acid) is a molecules family mainly expressed on immunocompetent cells. Apparently, Siglec has an inhibitory effect on the cells expressing them, reducing the oxidative stress and inflammation intensities [22].

In the pathogenesis of asthma eosinophils, basophils, and mast cells, the action of which is activated through T-lymphocytes and IgE-mediated sensitization takes a significant part [23]. Ultimately, the most important role is played by eosinophils. The lifespan of which is prolonged in the pro-inflammatory factors (IL-3, IL-5, and granulocyte-macrophage colony-forming unit) presence in their microenvironment [24, 25]. In order to reduce the eosinophils life span in the focus, as well as the migration intensity, IL-5 inhibitors (mepolizumab, reslizumab, and IL-5R inhibitor benralizumab) can be used [24, 25]. In addition, antibodies, which activate the Siglec-8 protein which interacts with sialic acids, cause eosinophils and mast cells apoptosis, reducing the allergic inflammation intensity [24, 25].

The result of a number of studies confirming that the apoptosis intensity caused by Siglec-8 activation increases in the IL-5 presence is remarkable, which, on the contrary, usually prolongs eosinophils lifespan [26, 27]. Probably, this dependence may determine the rationale for the combined use of biological drugs that inhibit IL-5 and activate Siglec-8 in patients with severe eosinophilia; however, such treatment regimens have yet to be studied in detail.

It is important to note that the Siglec-8 expression level does not correlate with the absolute eosinophils number and the disease severity [28]. This fact may indicate that for the treatment with new drugs activating Siglec-8, determining the disease severity and the eosinophilia severity does not matter.

The Siglec-F, a molecule similar in expression pattern and ligands to human Siglec-8, was identified in laboratory mice. These data make it possible to determine that the aforementioned molecules have similar roles [29]. Genetic studies in allergic lung disease models showed that mice deficient in ST3Gal-3 (beta-galactoside alpha-2,3-sialyltransferase 3) protein had significantly higher eosinophilic airway inflammation levels. This pattern was associated with a lack of sialylated ligands to Siglec-F, resulting to a low eosinophil apoptosis intensity [30, 31]. It is likely that the presence of this gene's orthologue in humans may be the key to predicting the asthma severity.

Research in this direction is already underway. Thus, in the gene encoding Siglec-8, two single-nucleotide polymorphism variants, rs36498 and rs6509541 that apparently affect the Siglec-8 expression level, plasma IgE level, and the risk of developing asthma were found [32, 33].

The Siglec-8, among other things, is expressed on mast cells but does not induce their apoptosis. It exerts its inhibitory effect on these cells through inhibition of the FcεRI-dependent release of histamine and prostaglandin D2, as well as the calcium ions flow and bronchial contraction [34, 35].

Despite the eosinophils and basophils significant role in the asthma development, neutrophils should not be overlooked. Noneosinophilic asthma is characterized by local neutrophilic inflammation [8]. The complexity of managing patients with this asthma phenotype lies in the weak response to inhaled glucocorticosteroids with the pronounced systemic effects development from their use, in particular, an increase in the neutrophils number in the peripheral blood [36]. Diagnosis and treatment of noneosinophilic asthma constitute a substantial problem that is often patients are confined to take high inhaled or systemic glucocorticoids doses, which are long-acting beta-blockers [37, 38]. Such treatment regimens naturally lead to the development of serious side effects.

Within this framework, the use of Siglec-9 activating drugs seems promising in this group of patients with asthma. These molecules are expressed mainly on the neutrophils and monocytes surface and to a lesser extent on the natural killer cells membranes [39, 40]. The use of monoclonal antibodies that activate Siglec-9 leads to neutrophil apoptosis [40]. This group of drugs can potentially become the drug of choice in patients with severe non-eosinophilic asthma where neutrophils play a major role in inflammation.

Overall, the part of Siglec as targets for novel asthma therapies remains to be explored. However, it is clear from the available data that the potential of these molecules as targets for therapeutic intervention cannot be overestimated.

N-GLYCANS AND BRONCHIAL ASTHMA

The N-glycans are complex carbohydrates covalently attached to the protein by N-glycosidic bonds through asparagine residues. In mammals, the N-glycans biosynthesis is the most complicated, but it has been studied to a sufficient extent [41].

It has been determined that N-glycans expressed on the cell surface take part in the neutrophils and eosinophils migration to the allergic inflammation focus [42]. In addition, the epithelial glycoprotein MUC4β expression with a high N-glycosylation (sialylation) level is increased in patients with Th2-associated asthma [43]. At the same time, IgG N-glycans galactosylation plays a key role in the complexes inhibition formed by these immunoglobulins, which has anti-inflammatory effect in many pathological conditions and diseases, including allergic asthma [44].

Not only human N-glycans are of great interest. Many exoallergens have carbohydrate epitopes that provoke an immune response in humans [45–49]. For example, terminal carbohydrates removal from the N-acetylglucosamine structure of ovalbumin was found to reduce IgE hypersensitivity and Th2 immune response in sensitized mice [45, 46]. More than 150 different compositions of N-glycans were discovered in the venom and tissues of honey bee (*Apis mellifera*) larvae [49].

It is known that allergic asthma is the most common asthma phenotype, frequently associated with the exoallergens presence [50]. In this regard, the abovementioned studies of the allergen effects on N-glycome are of particular interest.

Thus, despite the increasing attention to N-glycome changes in patients with respiratory diseases, there is very little data on the role of such changes in the asthma pathogenesis.

Besides N-glycans, mammalian organisms contain O-glycans, which are extracellular proteins with attached serine or threonine residues [51]. The O-glycans definition and characterization are made complex by the lack of multipurpose enzymes for spectrometric and fluorescent analysis, as well as heterogeneity of these molecules group and a common glycan core absence [52]. Therefore, there is practically no data on the O-glycans role in the respiratory system diseases pathogenesis at the moment.

CONCLUSION

Glycomics is a relatively new and rapidly developing branch of medical science. Modern data indicate that molecules in the glycoscience area of interest play a crucial part in the diseases pathogenesis of many organs and systems. In this regard, it seems promising to use the glycomics achievements for asthma diagnosis, risk verification, and treatment.

For example, mRAGE, when activated, potentiates allergic airway inflammation by increasing the granulocytes activity and by the pro-inflammatory cytokines synthesis. On the contrary, soluble RAGE has anti-inflammatory effect, apparently by trapping RAGE ligands and preventing their association with mRAGE.

Siglec and mainly Siglec-8 and Siglec-9 are of particular interest in the context of asthma treatment since, when activated, they induce immunocompetent cells apoptosis and also have some protective effects on respiratory tract tissues.

Finally, N-glycans are of interest to scientists not only in relationship to diagnostics but also as molecules that, being manipulated, can reduce the allergenicity of, for instance, egg protein of vaccines.

Thus, the glycomics achievements can potentially have a significant impact on the allergic diseases course in general and asthma in particular.

ADDITIONAL INFORMATION

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