Sialic Acid-Binding Lectins as Potential Pathophysiological Targets in Treatment of Chronic Bronchopulmonary Diseases (Review)

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The article is devoted to the problem of finding the pathophysiological targets for optimizing the treatment of common and socially significant chronic respiratory diseases — bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD). The balance between pro-inflammatory and anti-inflammatory mechanisms determines the nature of inflammation in these diseases. Among the regulators of inflammation there are siglecs — sialic acid-binding immunoglobulin-like lectins able to interact with terminal sialic acid present in all cells. Siglecs are involved in regulating cell proliferation, differentiation, apoptosis and implementing cell-cell interactions. The key role in modulating the regulatory activity of siglecs is in their ability to interact with ligands.

Although research on the structure and biological functions of siglecs in the body has only recently started, the prospects for this research are promising, especially with respect to BA and COPD treatment. Siglecs are mainly expressed by immune and peripheral blood cells. Pathophysiological mechanisms of BA and COPD are implemented with participation of eosinophils, mast cells, neutrophils, and macrophages. The siglecs expressed on them play a particular role in the severity of tissue damage caused by the influence of these cells and therefore can be attractive targets for treatment of chronic inflammatory diseases of the respiratory organs.

Siglec-8 and Siglec-10 molecules expressed on eosinophils have been actively studied in BA pathogenesis. However, given the importance of not only eosinophils, but also other cells in the disease pathogenesis, it seems challenging to investigate the role of Siglec-3, Siglec-5, Siglec-6, and Siglec-14 expressed on mast cells and basophils. In recent years, the role of Siglec-3, Siglec-9, and Siglec-5/14 has been studied in the pathogenesis of COPD. The use of antibodies against Siglec-15 described recently may be relevant in treatment of osteoporosis often associated with COPD.

Based on scientific literature data, this article reviews the role of siglecs as possible regulators of inflammation in patients with chronic bronchopulmonary diseases.

Key words: chronic bronchopulmonary diseases; sialic acid-binding lectins; siglecs.

In many countries all over the world, chronic bronchopulmonary diseases occupy leading positions in terms of prevalence, disability, and mortality with the negative prognosis of a steady increase in the number of patients [1]. Bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) are the most common and socially significant diseases due to a lifelong necessity for patients to use medications [2, 3].

One of the most complex and unexplored problems of modern science is finding new pathophysiological targets for the therapy of chronic respiratory diseases [4, 5].

Despite the differences in etiopathogenetic mechanisms, the pathophysiological basis of BA and COPD is inflammation [6]. The nature of systemic and local inflammation in these diseases determines the balance between pro-inflammatory and anti-inflammatory

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mediators [7]. The regulators of the level of inflammation include siglecs, i.e. sialic acid-binding immunoglobulin-like lectins able to interact with terminal sialic acid [8]. Siglecs (Siglec-1, or CD169$^+$, and Siglec-2, or CD22$^+$) were first detected on sialoadhesin [9]. Subsequent findings of Siglec-3 (CD33$^+$) and Siglec-4 (MAG, a myelin-associated glycoprotein) led to introduction of the siglec family [10, 11].

So far, 16 siglecs have been identified in humans and 9 in mice. Siglecs are conventionally divided into two groups according to the degree of their identity in rodents and humans [12]. The first group is represented by Siglec-1, Siglec-2, Siglec-4, and Siglec-15 found in rodents and humans (25–30% identity). The second group includes Siglec-3 (CD33$^+$) and siglecs homologous to it (50–85% identity). Siglecs of this group are expressed in humans and numbered using Arabic numerals (Siglec-3, Siglec-5, Siglec-6, Siglec-7, Siglec-8, Siglec-9, Siglec-10, Siglec-11, Siglec-12, Siglec-14, Siglec-16); in mice (except Siglec-3) — with the English alphabet letters (Siglec-E, Siglec-F, Siglec-G, Siglec-H).

Siglecs, except for Siglec-4 and Siglec-11, are mainly expressed by immune and peripheral blood cells identified in cells of the central and peripheral nervous system [13, 14]. For example, Siglec-1 is expressed by macrophages [15]; Siglec-2 — by B lymphocytes [16]; Siglec-3 — by CD34$^+$ cells, mast and dendritic cells, neutrophils, macrophages, and basophils [17]; Siglec-4 is expressed by glial cells [14]; Siglec-5 — by neutrophils, monocytes, macrophages, basophils, CD34$^+$ cells, and B lymphocytes [18]; Siglec-6 is expressed by basophils, placental trophoblast, and B lymphocytes [8]; Siglec-7 — by CD8$^+$ lymphocytes, monocytes, dendritic cells, and NK cells [19]; Siglec-8 — by eosinophils, basophils, and mast cells [20]; Siglec-9 — by neutrophils and monocytes, T and B lymphocytes, NK cells [21]; Siglec-10 is expressed by dendritic cells, monocytes, eosinophils, B cells, CD34$^+$ and NK cells [22]; Siglec-11 — by monocytes and resident macrophages of the central nervous system [23]; Siglec-12 is expressed by epithelial cells [8]; Siglec-14 — by granulocytes and monocytes [24]; Siglec-15 — by macrophages and monocytes [25]. Siglec-16 has been found in many cells and tissues [26].

Siglecs are involved in regulating cell proliferation, differentiation, apoptosis and implementing cell-cell interactions [27]. According to the mechanism of their biological action, siglecs can be classified into three groups. The first group of siglecs (Siglec-8 (Siglec-F) is the most studied representative) is characterized by the presence of immunoreceptor tyrosine-based inhibitory motifs (ITIM) in their cytoplasmic domain, which allows regulating and limiting the excessive activation response of the immune system during inflammation through exogenous and endogenous ligands of Toll-like receptors (TLRs) [28]. Exogenous ligands include pathogen-associated molecular patterns (PAMP) of infectious agents and endogenous ligands include damage-associated molecular patterns (DAMP) [29]. Antigen-presenting cells can be activated by PAMP and DAMP signals, which is important for understanding the mechanisms of initiation and regulation of immune responses.

The second group comprises siglecs (Siglec-1 and Siglec-4), which have no immunoreceptor tyrosine-based inhibitory motifs in the cytoplasmic domain.

The third group is represented by siglecs (in humans — Siglec-14, Siglec-15, and Siglec-16; in mice — Siglec-3, Siglec-H, and Siglec-15), functioning through DAP12 (DNAX activating protein of 12 kDa) [30]. DAP12 is a cell membrane protein able to both enhance and attenuate innate inflammatory responses in infectious and non-infectious processes due to the involvement of various DAP12-associated receptors in signaling [31].

The expression of DAP12 in cells located in the lungs regulates transendothelial migration of neutrophils during inflammation [32]. DAP12 deficiency in macrophages penetrating the tissues is accompanied by the production of inflammatory cytokines. There are studies showing that some siglecs are paired receptors (Siglec-5 and Siglec-14, Siglec-11 and Siglec-16) [33]. It has been suggested, if one representative of the pair has ITIM and the other has DAP12, these receptors possess inhibition and activation potential providing signal balance in the interaction with the pathogen. It is the specific mechanism of the biological action of siglecs, which allows classifying them as regulators of inflammation levels.

The key role in modulating the regulatory activity of siglecs is associated with their ability to interact with ligands [34]. Since sialic acids are present in all cells, glycan ligands of siglecs are effective markers [35]. Discovering specific selective ligands for siglecs will make it possible to transport medicinal substances into the cell [36]. Although researchers have only recently started to explore the structure and biological function of siglecs in the hematopoietic system and in the whole body, the prospects for these studies are promising, especially with regard to treatment of BA and COPD.

Eosinophils, mast cells, neutrophils, and macrophages are involved in the implementation of the pathophysiological mechanisms of BA and COPD [37, 38]. Siglecs expressed on these cells play a particular role in the severity of tissue damage due to the influence of these cells and therefore can be attractive targets for BA and COPD treatment.

Eosinophils, mast cells, and basophils play a dominant role in BA etiopathogenesis [39]. Eosinophils or eosinophilic polymorphonuclear granulocytes are fully differentiated non-dividing cells. They develop from progenitor stem cells in the bone marrow under the influence of interleukins (IL-3, IL-5) and granulocyte-macrophage colony-stimulating factor (GM-CSF) [40]. On the surface of eosinophils, there

are marker molecules $CD9^+$ and $CD35^+$; the major histocompatibility complex class I and II (MHC-I, MHC-II) molecules; receptors for Fc-IgG (FcγRI ($CD64^+$), FcγRII ($CD32^+$), FcγRIII ($CD16^+$)), Fc-IgA (FcαRI ($CD89^+$)), Fc-IgE (FcεRI, FcεRII ($CD23^+$)); receptors for IL-3, IL-5, GM-CSF, and CCR3; β2, β1, and β7 integrins and their receptors [41]. Eosinophils secrete a wide range of cytokines (including pro-inflammatory, anti-inflammatory and immunosuppressive mediators involved in the regulation of Th1- and Th2-mediated immune responses), chemokines, eicosanoids, and neuropeptides [42, 43]. Antiparasitic and antibacterial functions of eosinophils are mediated by the toxic effect of the main component of their specific granules, the major basic protein (MBP), expressed as MBP1 and MBP2 homologs [44]. This protein has a damaging effect on the cells of the respiratory tract in BA patients with eosinophilic infiltration of the bronchial mucosa [45]. Eosinophil-derived neurotoxin (EDN) is another component of specific eosinophil granules. It is able to change the nature of bronchial tree muscle innervation, which leads to its hyperreactivity [46]. Thymic eosinophils express indolamine 2,3-dioxygenase (IDO) involved in the oxidative metabolism of tryptophan and, therefore, can perform an immunoregulatory function due to increased apoptosis of Th1 lymphocytes [47]. Lee et al. [48] have studied the role of eosinophils as immunoregulators and participants in allergic inflammation (Th2 pathway). Experiments in mice have allowed this team to put forward the LIAR hypothesis, according to which, eosinophils are involved not only in the immune response, but also in regulation of many physiological and pathological processes. Eosinophils have been found to affect glucose metabolism in adipose tissue [49], they are also involved in transplant rejection reactions, etiopathogenesis of multiple sclerosis, and skin diseases [50]. Their role in the etiopathogenesis of eosinophilic gastrointestinal disorders has been shown [51]. In recent years, the role of Siglec-8 and Siglec-10 molecules expressed on eosinophils in the pathogenesis of chronic bronchopulmonary pathology has been actively studied [52].

Siglec-8 (Siglec-F) is involved in the pathogenesis of BA [53]. It exists in two isoforms: a short (431-aa) and a long (499-aa) one, containing identical extracellular and transmembrane regions. The long form of Siglec-8 has a membrane-proximal immunoreceptor tyrosine inhibitor similar to the classic ITIM, and the membrane-distal one. This form is the main functional inhibitor of human eosinophil receptors as its activation triggers the mechanism of eosinophil apoptosis via reactive oxygen intermediate formation, decreased mitochondrial membrane potential, and caspase cleavage [54, 55]. Siglec-8 and Siglec-F recognize the sialoside ligand 6′-sulfo-sialyl Lewis X (6'-su-sLex) and the benzyl glycoside Neu5AcaBn [56]. Expression of Siglec-8 and Siglec-F ligands in the epithelial cells of the respiratory tract increases with inflammation of the bronchopulmonary system. This allows the use of Siglec-8 as a pharmacological target in eosinophilic diseases such as BA [57].

Siglec-10 (Siglec-G) is expressed on dendritic cells, which are the main antigen-presenting cells in the lungs [58, 59]. Different subclasses of these cells cause either immune tolerance or a Th1- or Th2-type response. Siglec-G plays a key role in suppressing DAMP-mediated innate immune responses [60]. Sialoglycoprotein $CD24^+$ can bind to Siglec-10 in human innate immune cells. Siglec-G has been shown to suppress T cell responses *in vitro* and *in vivo* [61]. The autonomous role of this siglec in the T cell is crucial for modulating the severity of immunopathology mediated by this cell [62]. Today, there are very few studies devoted to the role of Siglec-10 in BA pathophysiology [52].

Since not only eosinophils, but also other cells (mast cells and basophils) play an important role in BA pathogenesis, the study of Siglec-3, Siglec-5, Siglec-6, and Siglec-14 expressed on these cells is challenging.

Neutrophilic segmental leukocytes (neutrophilic granulocytes or neutrophils, which are mediators of innate immune responses) are significant in the pathophysiology of COPD [63]. On the surface of neutrophils, there are $CD13^+$, $CD14^+$, MHC class I and class II molecules, β2-integrins (LFA-1, Mac-1, p155/95), complement receptors (CR1, CR3, CR4) and chemotactic factor receptors (C3aR, C5aR), receptors for Fc-IgG (FcgRII ($CD32^+$), FcgRIII ($CD16^+$)) [64]. Due to the presence of Fc receptors, neutrophils have antibody-dependent cellular cytotoxicity [65]. Releasing destructive proteases and being a source of IL-8, neutrophils are able to damage the lung tissue [66–68]. Human neutrophils express three inhibitory siglecs — Siglec-3, Siglec-5, Siglec-9, and activating Siglec-14, while mouse neutrophils express inhibitory Siglec-E and Siglec-F. In recent years, Siglec-3, Siglec-9, and Siglec-5/14 have been actively studied in COPD pathogenesis [61, 69].

Given the fact that Siglec-3 ($CD33^+$) inhibits production of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-8) through phosphatidylinositol-3-kinase (PI3K) and mitogen-activated p38 protein kinase (MAPK) [70–72], we consider it necessary to carry out further studies to determine the role of this siglec in chronic bronchopulmonary pathology.

Siglec-9 (Siglec-E) is involved in the induction of apoptosis, inhibition of cell activation and migration, modulation of oxidative stress, and regulation of pro-inflammatory cytokine secretion [73, 74]. Expression of Siglec-9 by monocytic cells leads to secretion of the immunosuppressive cytokine IL-10 [75]. The level of Siglec-9 increases in patients with COPD and correlates with the frequency of this disease exacerbation and emphysema development [76, 77]. Enhanced migration of neutrophils into the lung tissue blocked by integrin alpha-M/beta-2 (αM, $CD11b/\beta_2$, $CD18^+$) has been observed in the model of lipopolysaccharide-induced

pneumonia in mice [78]. At the same time, the integrin action can be modulated using Siglec-E. Siglec-E has been found to promote β2-integrin-dependent reactive oxygen intermediate production by neutrophils *in vitro* and *in vivo*. This is exactly what is necessary to inhibit the mechanism of neutrophil recruitment into the lungs [79]. As sialic acid receptors, siglecs can recognize the carbohydrate chains of cell membrane glycoproteins and glycolipids, providing endocytosis [80]. Siglec-9 mediates rapid endocytosis of the specific bound antibody and therefore can become a new therapeutic target for inflammatory diseases [81].

Mucus obstruction is the most important cause of airflow restriction and high mortality rates in patients with COPD [82, 83]. In this disease, a number of mucins expressed in the respiratory tract have been found to have overexpression (MUC1, MUC2, MUC4, MUC5 AC, MUC5B, MUC6, MUC7, MUC11, MUC15, MUC16, MUC20) [84]. The studies carried out by Fischer et al. [85] show the effect on chronic inflammation in the bronchopulmonary system. Although the function of MUC1 in COPD is unknown, Ishikawa et al. [86] have reported the level of this mucin to increase in patients with COPD and contribute to airway remodeling, bacterial colonization, and impairment of epithelial integrity. The level of MUC7 also changes in COPD [87].

MUC16 expressed on the surface of epithelial cells and participating in their protection occupies a special place among the proteins of interest as potential therapeutic targets [88]. Although the level of MUC16 is known to increase in patients with COPD [89], the function of this mucin in the airways remains understudied. However, MUC16 has been found to be a ligand for Siglec-9 and ligation of the mucin with this siglec promotes immunosuppression [90]. This finding provides further possibilities to study in detail the molecular mechanisms leading to immunosuppression induced by this mucin. In order to understand the pathophysiological mechanisms of COPD better and develop new therapeutic strategies, it is necessary to continue research on the individual function and regulatory signaling of each mucin in the respiratory tract.

Siglec-14 contains three Ig-like domains, while Siglec-5 contains four, of which the first two are almost identical to Siglec-14 [91, 92]. In the study carried out by Pillai et al. [93], the null allelic polymorphism of neutrophils activating Siglec-14 has been identified. In humans, the siglec gene cluster has the *Siglec-14* and *Siglec-5* genes, while the Siglec-14 null allele contains the *Siglec-5/14* fusion gene. Imbalance in *Siglec-5/14* expression promotes initiation of inflammatory mechanisms in COPD [94]. The level of Siglec-14 affects the frequency of COPD exacerbations [95]. The study by Angata et al. [96] has demonstrated that non-typable strains of Haemophilus influenzae (NTHi) interact with Siglec-14 to enhance the production of pro-inflammatory cytokines and, therefore, the absence of Siglec-14 due to the homozygosity of the Siglec-14 null allele reduces the risk of COPD exacerbation. Obviously, siglecs affect COPD progression through their regulatory influence on cells involved in the implementation of immune response. The authors suggest that Siglec-14 may be an important therapeutic target in COPD.

Recently, there has been described Siglec-15 (Siglec-H), which is highly homologous to Siglec-14 and plays a major role in differentiation of osteoclast precursors [97]. Antibodies and antigen-binding fragments that specifically bind to Siglec-15 have been characterized. All of this is important for the detection and treatment of progressive bone loss due to increased osteoclast activity [98]. The use of Siglec-15 antibodies seems to be promising in the treatment of osteoporosis often associated with COPD [99].

Siglec-8, an inhibitor of eosinophil receptors, participating in BA development mechanisms, is also significant in the pathogenesis of COPD, since it affects the phenotyping of this disease [100]. Analysis of samples obtained from mouse tracheal epithelial cells has shown that MUC5B and MUC4 are ligands for Siglec-F. Finding the ligands and monoclonal antibodies to Siglec-8 (Siglec-F) will provide new approaches to treating COPD.

Conclusion

The balance between pro-inflammatory and anti-inflammatory mediators determines the nature of inflammation in COPD and BA. Its regulators include siglecs, recently regarded as targets for immunotherapy of many diseases. The key role of siglecs in modulating the regulatory activity is associated with their ability to interact with ligands. Since sialic acids are present in all cells, glycan ligands of siglecs are effective markers of pathophysiological targets. Specific selective ligands have been found for a number of siglecs, which makes it possible to transport medicinal substances into the cell for targeted treatment of COPD and BA.

Thus, Siglec-8 (Siglec-F) ligands expressed on epithelial cells of the respiratory tract may be considered as targets in BA treatment. Siglec-8 (Siglec-F) belongs to the group of siglecs whose mechanism of action is associated with the presence of ITIM in the cytoplasmic domain regulating the activation of immune response during inflammation via exogenous (RAMP) and endogenous (DAMP) TLR ligands. At the same time, Siglec-10 is expressed by lung dendritic cells and plays a key role in suppressing DAMP-mediated innate immune responses. However, studies devoted to the use of this siglec in BA pathophysiology are very few and finding its selective ligands is currently an important research area. In BA pathogenesis, studies of Siglec-3, Siglec-5, Siglec-6, and Siglec-14 expressed on mast cells and basophils and finding the specific ligands for these siglecs are also promising. In COPD pathogenesis, attention is paid to the roles of Siglec-3,

Siglec-9, Siglec-14, and Siglec-15. Some of these siglecs (Siglec-14, Siglecs-15) realize their functions through DAP12 able to both enhance and attenuate innate inflammatory responses in infectious and non-infectious processes. Expression of DAP12 in the lung cells regulates transendothelial migration of neutrophils during inflammation. DAP12 deficiency in macrophages is accompanied by the production of inflammatory cytokines. In this regard, discovering ligands selective for these siglecs will also allow for targeted treatment of COPD and BA. Some siglecs are paired receptors (Siglec-5 and Siglec-14, Siglec-11 and Siglec-16) and, if one representative of the pair has ITIM and the other has DAP12, these receptors possess inhibition and activation potential providing signal balance in the interaction with the pathogen. The outlined specific mechanism of the biological action of siglecs allows classifying them as regulators of inflammation levels and promising targets for the treatment of COPD and BA.

Although research on the structure, carbohydrate specificity and biological functions of siglecs in the body has only recently started, the prospects for this research are promising, especially with respect to BA and COPD treatment.

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