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

DOI: 10.17691/stm2019.11.4.18
Received October 30, 2018

O.Yu. Kytikova, MD, DSc, Researcher, Laboratory of Rehabilitative Treatment;
T.A. Gvozdenko, MD, DSc, Professor of the Russian Academy of Sciences, Chief Researcher, Laboratory of Rehabilitative Treatment;
M.V. Antonyuk, MD, DSc, Professor, Head of the Laboratory of Rehabilitative Treatment;
T.P. Novgorodtseva, DSc, Professor, Deputy Director for Science, Chief Researcher, Laboratory of Biomedical Researchers

Vladivostok Branch of the Far Eastern Scientific Center for Physiology and Pathology of Respiration — Research Institute of Medical Climatology and Rehabilitation Treatment, 73 G Russkaya St., Vladivostok, 690105

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
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, mast cells, 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]. Eosinophilic 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 (FcyRI (CD64+), FcγRII (CD32+), FcγRIII (CD16+)), Fc-IgA (FcaRI (CD89+), Fc-IgE (FceRI, FceRII (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 major 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 Neu5Acα2βn [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]. Sigalycoprotein 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 (FcγRII (CD32+), FcγRIII (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/β2, 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, MUC5AC, 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 siglecgs (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.

**Study funding.** This work was funded by the authors.

**Conflict of interests.** The authors have no conflict of interests to disclose.

**References**

1. European Community Respiratory Health Survey. 2016. URL: http://www.ecrhis.org/.

2. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (GOLD). 2016. URL: http://www.ginasthma.com.

3. NICE. Asthma: diagnosis, monitoring and chronic asthma management. NICE Guideline. 2017. URL: https://www.nice.org.uk/guidance/ng80.

4. Kytkova O.Yu., Gvozdenko T.A. Functional relationships of homeostatic systems in pathological conditions. Uspekhi sovremennogo estestvoznaniya 2014; 5: 211–212.

5. Bogovin L.V., Kolosov V.P., Peref’man Yu.M. Nefarmakologicheskie sposoby dostizheniya kontrolya bronkhal’noy astmy [Non-pharmacological methods for management of bronchial asthma]. Vladivostok: Dal’nauka; 2016: 252 p.

6. Fu J., McDonald V., Gibson P., Simpson J. Systemic inflammation in older adults with asthma-COPD overlap syndrome. Allergy Asthma Immuno Res 2014; 6(4): 316–324, https://doi.org/10.4168/air.2014.6.4.316.

7. Nakawah M., Hawkins C., Barbandi F. Asthma, chronic obstructive pulmonary disease (COPD), and the overlap syndrome. J Am Board Fam Med 2013; 26(4): 470–477, https://doi.org/10.3122/jabfm.2013.04.120256.

8. Lübbers J., Rodríguez E., van Kooyk Y. Modulation of immune tolerance via siglec-sialic acid interactions. Front Immunol 2018; 9: 2807, https://doi.org/10.3389/fimmu.2018.02807.

9. Eakin A.J., Bustard M.J., McGeough C.M., Ahmed T., Bjorson A.J., Gibson D.S. Siglec-1 and -2 as potential biomarkers in autoimmune disease. Proteomics Clin Appl 2016; 10(6): 635–644, https://doi.org/10.1002/prca.201500069.

10. Lehmann F., Gätjhe H., Kelm S., Dietz F. Evolution of sialic acid-binding proteins: molecular cloning and expression of fish Siglec-4. Glycobiology 2014; 14(11): 959–968, https://doi.org/10.1093/glycob/cwh120.

11. Crocker P.R., McMillan S.J., Richards H.E. CD33-related siglecs as potential modulators of inflammatory responses. Ann N Y Acad Sci 2012; 1253: 102–111, https://doi.org/10.1111/j.1749-6632.2011.06449.x.

12. Pillai S., Netravali I.A., Cariappa A., Mattoo H. Siglecs and immune regulation. Annu Rev Immunol 2012; 30: 357–392, https://doi.org/10.1146/annurev-immunol-020711-070518.

13. Wang Y., Neumann H. Alleviation of neurotoxicity by microglial human Siglec-11. J Neurosci 2010; 30(9): 3482–3488, https://doi.org/10.1523/jneurosci.3940-09.2010.

14. Lopez P.H. Role of myelin-associated glycoprotein (Siglec-4a) in the nervous system. Adv Neurobiol 2014; 9: 245–262, https://doi.org/10.1007/978-1-4939-1154-7_11.

15. Delputte P.L., Van Gorp H., Favoreel H.W., Hoebeke I., Delrue I., Dewerchin H., Verdonck F., Verhasselt B., Cox E., Nauwtyck H.J. Porcine sialoadhesin (CD169/Siglec-1) is an endocytic receptor that allows targeted delivery of toxins and antigens to macrophages. PLoS One 2011; 6: e16827, https://doi.org/10.1371/journal.pone.0016827.

16. Chen W.C., Sigal D.S., Saven A., Paulson J.C. Targeting B lymphoma with nanoparticles bearing glycan ligands of CD22. Leuk Lymphoma 2012; 53(2): 208–210, https://doi.org/10.1080/10428194.2011.604755.

17. Álvarez B., Escalonza Z., Uenishi H., Toki D., Revilla C., Yuste M., Del Moral M.G., Alonso F., Ezquerra A., Domínguez J. Molecular and functional characterization of porcine Siglec-3/CD33 and analysis of its expression in blood and tissues. Dev Comp Immunol 2015; 51(2): 238–250, https://doi.org/10.1016/j.dci.2015.04.002.

18. Nordström T., Moterv E., Olin A.I., Ali S.R., Nizet V., Varki A., Areschoug T. Human Siglec-5 inhibitory receptor and immunoglobulin A (IgA) have separate binding sites in streptococcal beta protein. J Biol Chem 2011; 286(39): 33981–33991, https://doi.org/10.1074/jbc.m111.251728.

19. Varchetta S., Brunetta E., Roberto A., Mikulak J., Hudspeth K.P., Mondelli M.U., Mavilio D. Engagement of Siglec-7 receptor induces a pro-inflammatory response selectively in monocytes. PLoS One 2012; 7(9): e45821, https://doi.org/10.1371/journal.pone.0045821.

20. Gao P.S., Shimizu K., Grant A.V., Rafals N., Zhou L.F., Hudson S.A., Konno S., Zimmermann N., Araujo M.I., Ponte E.V., Cruz A.A., Nishimura M., Su S.N., Hizawa N., Beaty T.H., Mathias R.A., Rothenberg M.E., Barnes K.C., Bochner B.S. Polymorphisms in the sialic acid-binding immunoglobulin-like lectin-8 (Siglec-8) gene are associated with susceptibility to asthma. Am J Hum Genet 2010; 86: 392–398, https://doi.org/10.1016/j.ajhg.2010.06.006.

21. Retamal J., Sörensen J., Lubberink M., Suárez-Simpian F., Borges J.B., Feinstein R., Jalkanen S., Antoni G., Hedenstierna G., Roivainen A., Larsson A., Velikyan I. Feasibility of (68)Ga-labeled Siglec-9 peptide for the imaging of acute lung inflammation: a pilot study in a porcine model of acute respiratory distress syndrome. Am J Nucl Med Mol Imaging 2016; 6(1): 18–31.

22. Bandala-Sanchez E., Zhang Y., Reinwald S.,
demographics, disease pattern and response to treatment: report of 12 cases and review of the literature. Int J Dermatol 2008; 47(1): 29–35, https://doi.org/10.1111/j.1365-4632.2007.03544.x.

51. Straumann A., Aceves S.S., Blanchard C., Collins M.H., Furuta G.T., Hirano I., Schoepfer A.M., Simon D., Simon H.U. Pediatric and adult eosinophilic esophagitis: similarities and differences. Allergy 2012; 67(4): 477–490, https://doi.org/10.1111/j.1399-9895.2012.02787.x.

52. Jia Y., Yu H., Fernandes S.M., Wei Y., Gonzalez-Gil A., Motari M.G., Vajn K., Stevens W.W., Peters A.T., Bochner B.S., Kern R.C., Schleimer R.P., Schnaar R.L. Expression of ligands for Siglec-8 and Siglec-9 in human airways and airway cells. J Allergy Clin Immunol 2015; 135(3): 799–810, https://doi.org/10.1016/j.jaci.2015.01.004.

53. Kiwamoto T., Kawasaki N., Paulson J.C., Bochner B.S. Siglec-8 as a druggable target to treat eosinophil and mast cell-associated conditions. Pharmacol Ther 2012; 135(3): 327–336, https://doi.org/10.1016/j.pharmthera.2012.06.005.

54. Nucht E., Aizawa H., Hudson S.A., Bochner B.S. Ligation of Siglec-8: a selective mechanism for induction of human eosinophil apoptosis. Blood 2003; 101(12): 5014–5020, https://doi.org/10.1182/blood-2002-10-3058.

55. Janevksa D., O’Sullivan J., Cao Y., Bochner B.S. Specific subsets of kinases mediate Siglec-8 engagement-induced reactive oxygen species (ROS) production and apoptosis in primary human eosinophils. Glycobiology 2015; 25: 1214.

56. Tateno H., Crocker P.R., Paulson J.C. Mouse Siglec-F and human Siglec-8 are functionally convergent paralogs that are selectively expressed on eosinophils and recognize 6′-sulfo-sialyl Lewis X as a preferred glycan ligand. Glycobiology 2005; 15(11): 1125–1135.

57. Suzukiwata M., Miller M., Rosenthal P., Cho J.Y., Doherty T.A., Varki A., Brodie D. Sialyltransferase ST3Gal-III regulates Siglec-F ligand formation and eosinophilic lung inflammation in mice. J Immunol 2013; 190(12): 5939–5948, https://doi.org/10.4049/jimmunol.1203455.

58. Li N., Zhang W., Wan T., Zhang J., Chen T., Yu Y., Wang J., Cao X. Cloning and characterization of Siglec-10, a novel sialic acid binding member of the Ig superfamily, from human dendritic cells. J Biol Chem 2001; 276(30): 28106–28112, https://doi.org/10.1074/jbc.m100467200.

59. Pfengle F., Macauley M.S., Kawasaki N., Paulson J.C. Copresentation of antigen and ligands of Siglec-G induces B cell tolerance independent of CD22. J Immunol 2013; 191(4): 1724–1731, https://doi.org/10.4049/jimmunol.1300921.

60. Toubai T., Rossi C., Oravecz-Wilson K., Zajac C., Liu C., Braun T., Fujiwara H., Wu J., Sun Y., Brabbs S., Tamaki H., Magenau J., Zheng P., Liu Y., Reddy P. Siglec-G represses DAMP-mediated effects on T cells. JCI Insight 2017; 2(14): 92293, https://doi.org/10.1172/jci.insight.92293.

61. Macauley M.S., Crocker P.R., Paulson J.C. Siglec regulation of immune cell function in disease. Nat Rev Immunol 2014; 14(10): 653–666, https://doi.org/10.1038/nri3737.

62. Escalona Z., Álvarez B., Uenishi H., Toki D., Yuste M., Revilla C., del Moral M.G., Alonso F., Ezquerra A., Domínguez J. Molecular characterization of porcine Siglec-10 and analysis of its expression in blood and tissues. Dev Comp Immunol 2015; 48(1): 116–123, https://doi.org/10.1016/j.devco.2014.09.011.

63. Liu J., Pang Z., Wang G., Guan X., Fang K., Wang Z., Wang F. Advanced role of neutrophils in common respiratory diseases. J Immunol Res 2017; 6710278, https://doi.org/10.1155/2017/6710278.

64. Rosales C., Demaurex N., Lowell C.A., Uribe-Querol E. Neutrophils: their role in innate and adaptive immunity. J Immunol Res 2016; 2016: 1469780, https://doi.org/10.1155/2016/1469780.

65. Guilliams M., Bruhns P., Saey S., Hammad H., Lambrecht B.N. The function of Fcγ receptors in dendritic cells and macrophages. Nat Rev Immunol 2014; 14(2): 94–108, https://doi.org/10.1038/nri3582.

66. Pham D.L., Ban G.Y., Kim S.H., Shin Y.S., Ye Y.M., Chwae Y.J., Park H.S. Neutrophil autophagy and extracellular DNA traps contribute to airway inflammation in severe asthma. Clin Exp Allergy 2017; 47(1): 57–70, https://doi.org/10.1111/cea.12659.

67. Alam R., Good J., Rollins D., Verma M., Chu H., Pham T.H., Martin R.J. Airway and serum biochemical correlates of refractory neutrophilic asthma. J Allergy Clin Immunol 2017; 140(4): 1004–1014.e13, https://doi.org/10.1016/j.jaci.2016.12.963.

68. Hosoki K., Itazawa T., Boldogh I., Sur S. Neutrophil recruitment by allergens contribute to allergic sensitization and allergic inflammation. Curr Opin Allergy Clin Immunol 2016; 16(1): 45–50, https://doi.org/10.1097/ACI.0000000000000231.

69. Freeman C.M., Curtis J.L. Lung dendritic cells: shaping immune responses throughout COPD progression. Am J Respir Cell Mol Biol 2017; 56(2): 152–159, https://doi.org/10.1165/rcmb.2016-0272tr.

70. Walter R.B., Raden B.W., Zeng R., Hausermann P., Bernstein I.D., Cooper J.A. ITIM-dependent endocytosis of CD33-related siglecs: role of intracellular domain, tyrosine phosphorylation, and the tyrosine phosphatases, Shp1 and Shp2. J Leukoc Biol 2008; 83(1): 200–211, https://doi.org/10.1189/jlb.0607388.

71. Hernández-Caselles T., Martínez-Esparza M., Pérez-Oliva A.B., Quintanilla-Cecconi A.M., García-Alonso A., Álvarez-López D.M., García-Peñarrubia P. A study of CD33 (Siglec-3) antigen expression and function on activated human T and NK cells: two isoforms of CD33 are generated by alternative splicing. J Leukoc Biol 2006; 79(1): 46–58, https://doi.org/10.1189/jlcb.0205096.

72. Walter R.B. The role of CD33 as therapeutic target in acute myeloid leukemia. Expert Opin Ther Targets 2014; 18(7): 715–718, https://doi.org/10.1517/14728222.2014.909413.

73. Siddiqui S., Schwarz F., Springer S., Khedri Z., Yu H., Deng L., Verhagen A., Naito-Matsui Y., Jiang W., Kim D., Zhou J., Ding B., Chen X., Varki N., Varki A. Studies on the detection, expression, glycosylation, dimerization, and ligand binding properties of mouse Siglec-E. J Biol Chem 2017; 292(3): 1029–1037, https://doi.org/10.1074/jbc.m116.738351.

74. Ahtinen H., Kulkova J., Lindholm L., Eerola E., Hakanen A.J., Mortiz N., Söderström M., Saanijoki T., Jalkanen M., Rovainen A., Aro H.T. 68Ga-DOTA-Siglec-9 PET/CT imaging of peri-implant tissue responses and staphylococcal infections. EJNNMI Res 2014; 4: 45, https://doi.org/10.1186/s13550-014-0045-3.

75. Jandus C., Boligan K.F., Chijioke O., Liu H., Dahlhaus M., Démosteul T., Schneider C., Wehrli M., Hunger R.E., Baeloche G.M., Simon H.U., Romero P., Münz C., von Gunten S. Interactions between Siglec-7/9 and FcγRIIA on human dendritic cells and macrophages. J Immunol 2014; 193(4): 1810–1820, https://doi.org/10.1111/jec.12659.
Siglec-8 and Siglec-9 binding specificities and endogenous airway ligand distributions and properties. Glycobiology 2017; 27(7): 657–668, https://doi.org/10.1093/glycob/cwx026.

77. Zeng Z., Li M., Wang M., Wu X., Li Q., Ning Q., Zhao J., Xu Y., Xie J. Increased expression of Siglec-9 in chronic obstructive pulmonary disease. Sci Rep 2017; 7(1): 10116, https://doi.org/10.1038/s41598-017-09120-5.

78. McMillan S.J., Sharma R.S., McKenzie E.J., Richards H.E., Zhang J., Prescott A., Crocker P.R. Siglec-E is a negative regulator of acute pulmonary neutrophil inflammation and suppresses CD11b beta2-integrin-dependent signaling. Blood 2013; 121(11): 2084–2094, https://doi.org/10.1182/blood-2012-08-449983.

79. McMillan S.J., Sharma R.S., Richards H.E., Hegde V., Crocker P.R. Siglec-E promotes beta2-integrin-dependent NADPH oxidase activation to suppress neutrophil recruitment to the lung. J Biol Chem 2014; 289(29): 20370–20376, https://doi.org/10.1074/jbc.m114.574624.

80. Schwarz F., Landig C.S., Siddiqui S., Secundino I., Olson J., Varki N., Nizet V., Varki A. Paired siglec receptors generate opposite inflammatory responses to a human-specific pathogen. EMBO J 2017; 36(6): 751–760, https://doi.org/10.15252/embj.201695581.

81. Tanida S., Akiti K., Ishida A., Morii Y., Toda M., Inoue O., Ohta M., Yashiro M., Sawada T., Hirakawa K., Nakada H. Binding of the sialic acid-binding lectin, Siglec-8, to the membrane mucin, MUC1, induces recruitment of β-catenin and subsequent cell growth. J Biol Chem 2013; 288(44): 31842–31852, https://doi.org/10.1074/jbc.m113.471318.

82. Millares L., Martí S., Arduany C., Liñares J., Santos S., Dorca J., García-Nuñez M., Quero S., Monsó E. Specific IgA against Pseudomonas aeruginosa in severe COPD. Int J Chron Obstruct Pulmon Dis 2017; 12: 2907–2911, https://doi.org/10.2147/copd.s141701.

83. Fahy J.V., Dickey B.F. Airway mucus function and dysfunction. N Engl J Med 2010; 363(23): 2233–2247, https://doi.org/10.1056/nejma0910061.

84. Caramori G., Casolari P., Di Gregorio C., Saetta M., Baraldo S., Boschetto P., Ito K., Fabbri L.M., Barnes P.J., Adcock I.M., Cavalcetto G., Chung K.F., Papi A. MUC5AC expression is increased in bronchial submucosal glands of stable COPD patients. Histopathology 2009; 55 (3): 321–331, https://doi.org/10.1111/j.1365-2559.2009.03377.x.

85. Fischer B.M., Wong J.K., Kummarapurugu A.B., Voynow J.A. Neutrophil elastase increases expression of selenocystein blomarkers in normal human bronchial epithelial cells. Am J Respir Crit Care Med 2011; 183: A2434, https://doi.org/10.1164/ajrccm-conference.2011.183.1_meetingabstracts.a2434.

86. Ishikawa N., Hattori N., Tanaka S., Horimasu Y., Horikawa T., Kokno N., Kinnula V.L. Levels of surfactant proteins A and D and KL-6 are elevated in induced sputum of chronic obstructive pulmonary disease patients: a sequential sputum analysis. Respiration 2011; 82(1): 10–18, https://doi.org/10.1159/000324539.

87. Fan H., Bobek L.A. Regulation of human MUC7 Mucin gene expression by cigarette smoke extract or cigarette smoke and Pseudomonas aeruginosa lipopolysaccharide in human airway epithelial cells and in MUC7 transgenic mice. Open Respir J 2010; 4: 63–70, https://doi.org/10.2174/187430 64010040100063.

88. Bottini P., Scatena R. The role of CA 125 as tumor marker: biochemical and clinical aspects. Adv Exp Med Biol 2015; 867: 229–244, https://doi.org/10.1007/978-94-017-7215-0_14.

89. Yilmaz M.B., Zorlu A., Dogan O.T., Karahan O., Tandogan I., Akkurt I. Role of CA-125 in identification of right ventricular failure in chronic obstructive pulmonary disease. Clin Cardiol 2011; 34(4): 244–248, https://doi.org/10.1002/clc.20868.

90. Belisle J.A., Horibata S., Jennifer G.A., Petrie S., Kapur A., André S., Gabius H.J., Rancourt C., Connor J., Paulson J.C., Patankar M.S. Identification of Siglec-9 as the receptor for MUC16 on human NK cells, B cells, and monocytes. Mol Cancer 2010; 9(1): 118, https://doi.org/10.1186/1476-4598-9-118.

91. Angata T., Hayakawa T., Yamanaka M., Variki A., Nakamura M. Discovery of Siglec-14, a novel sialic acid receptor undergoes concerted evolution with Siglec-5 in primates. FASEB J 2006; 20(12): 1964–1973, https://doi.org/10.1096/fj.06-5800com.

92. Yamanaka M., Kato Y., Angata T., Narimatsu H. Deletion polymorphism of Siglec14 and its functional implications. Glycobiology 2009; 19(8): 841–846, https://doi.org/10.1093/glycob/cwp052.

93. Pillai S.G., Kong X., Edwards L.D., Cho M.H., Anderson W.H., Coxson H.O., Lomas D.A., Silverman E.K.; ECLIPSE and ICGN Investigators. Locl identified by genome-wide association studies influence different disease-related phenotypes in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010; 182(12): 1498–1505, https://doi.org/10.1164/rccm.201002-0151OC.

94. Wielgat P., Mroz R.M., Stasiak-Barmuta A., Szepiel P., Chyczewska E., Braszko J.J., Holownia A. Inhaled corticosteroids increase Siglec-5/14 expression in sputum cells of COPD patients. Adv Exp Med Biol 2016; 839: 1–5, https://doi.org/10.1007/978-94-017-89910-0_1.

95. Ishii T., Angata T., Wan E.S., Cho M.H., Motegi T., Gao C., Ohtsubo K., Kitazume S., Gemma A., ParÉ P.D., Lomas D.A., Silverman E.K., Taniguchi N., Kida K. Influence of SIGLEC 9 polymorphisms on COPD phenotypes including exacerbation frequency. Respirology 2017; 22(4): 684–690, https://doi.org/10.1111/resp.12952.

96. Angata T., Ishii T., Motegi T., Oka R., Taylor R.E., Soto P.C., Chang Y.C., Secundino I., Gao C.X., Ohtsubo K., Kitazume S., Nizet V., Variki A., Gemma A., Kida K., Taniguchi N. Loss of Siglec-14 reduces the risk of chronic obstructive pulmonary disease exacerbation. Cell Mol Life Sci 2013; 70(17): 3199–3210, https://doi.org/10.1007/s00018-013-1311-7.

97. Stuble M., Moraitis A., Fortin A., Saragosas A., Kalbaski A., Filion M., Tremblay G.B. Mechanism and function of monoclonal antibodies targeting Siglec-15 for therapeutic inhibition of osteoclastic bone resorption. J Biol Chem 2014; 289(10): 6498–6512, https://doi.org/10.1074/jbc.m113.494542.

98. Kiwamoto S., Takah T., Evans C.M., Janssen ECLIPSE and ICGN Investigators. Loci identified by genome-wide association studies influence different disease-related phenotypes in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013; 188(1): 135(5): 1329–1340, https://doi.org/10.1016/j.jaci.2014.10.027.

99. Hiruma Y., Hirai T., Tsuda E. Siglec-15, a member of the sialic acid-binding lectin, is a novel regulator for osteoclast differentiation. Biochem Biophys Res Commun 2011; 409(3): 424–429, https://doi.org/10.1016/j.bbrc.2011.05.015.

100. Mroz R.M., Holowina A., Wielgat P., Sitko A., Skopinski T., Braszko J.J. Siglec-8 in induced sputum of COPD patients. Adv Exp Med Biol 2013; 788: 19–23, https://doi.org/10.1007/978-94-007-8627-3_3.