Sialic acid-binding immunoglobulin-like lectin 9 as a potential therapeutic target for chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease (COPD) has become the third-leading cause of death worldwide, which is a severe economic burden to the healthcare system. Chronic bronchitis is the most common condition that contributes to COPD, both locally and systemically. Neutrophilic inflammation predominates in the COPD airway wall and lumen. Logically, repression of neutrophilia is an essential fashion to COPD treatment. However, currently available anti-neutrophilic therapies provide little benefit in COPD patients and may have serious side effects. Thus, there is an urgent need to explore an effective and safe anti-neutrophilic approach that might delay progression of the disease. Sialic acid-binding immunoglobulin-like lectin (Siglec)-9 is a member of the Siglec cell surface immunoglobulin family. It is noteworthy that Siglec-9 is highly expressed on human neutrophils and monocytes. Ligation of Siglec-9 by chemical compounds or synthetic ligands induced apoptosis and autophagic-like cell death in human neutrophils. Furthermore, administration of antibody to Siglec-E, mouse functional ortholog of Siglec-9, restrained recruitment and activation of neutrophils in mouse models of airway inflammation *in vivo*. Given the critical role that neutrophils play in chronic bronchitis and emphysema, targeting Siglec-9 could be beneficial for the treatment of COPD, asthma, fibrosis, and related chronic inflammatory lung diseases.

Keywords: Sialic acid-binding immunoglobulin-like lectin-9 (Siglec-9); Siglec-E; Neutrophils; Chronic obstructive pulmonary disease

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder that causes airflow limitation and breathing-related problems. COPD is a silent killer in developing countries with roughly 328 million people living with COPD.[1] The mortality is expected to reach 3 million in 2016,[2] and it has become the third most common reason for mortality.[3]

Smoking and/or environmental exposure is one of the most common risk factors for COPD.[4,5] After removal of risk factors, the inflammation could continue in self-sustaining fashion which contributes to a gradual deterioration in pulmonary function. Acute exacerbations, usually caused by an infection with bacteria or viruses, are superimposed on this chronic inflammation and result in further cycles of bronchitis and emphysema. However, current therapies have limited effectiveness on chronic bronchitis or emphysematous change.

Neutrophils, the most abundant inflammatory cells, form a vital part of the innate immune system to defend against microbial invasion. They are rapidly recruited to tissues, both infected and damaged, where they ingest and eliminate micro-organisms that have invaded.[6] However, bacterial airway colonization and recurrent colonization may further irritate the development of inflammatory alterations, which have been shown as the cause of emphysematous destruction in COPD.

For decades, researchers have been searching for novel biologic modulators of neutrophils which could potentially serve as potent cell type-specific target agents for the treatment of airway neutrophilia. Sialic acid-binding immunoglobulin-like lectins (Siglecs) belong to the immunoglobulin gene family. Among them, Siglec-9 is mainly expressed by human neutrophils and monocytes, playing a key role in regulating neutrophil recruitment through

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mechanisms of apoptosis and autophagic-like cell death to induce programmed cell death.

This review will summarize the current understanding of airway neutrophilia in COPD, discuss the role of Siglec-9 in immunoregulatory mechanisms in neutrophil recruitment and activation, and Siglec-9 as a potential target for immunotherapy of COPD.

Neutrophils in COPD

Excessive neutrophils are detected in induced sputum and bronchoalveolar lavage fluid as a characteristic profile of COPD sufferers,[7] which have also been reported as a biomarker of disease severity in COPD.[8] The last few years witnessed a new wave of discoveries about the central role of neutrophils in the pathogenesis of COPD [Figure 1]. Exposure to harmful stimuli such as cigarette smoke and pathogenic organisms has a direct stimulatory effect on the generation and emission of neutrophils from the bone marrow, and further extending the lifespan of cells in the airways may be attributed to granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor (GM-CSF) released from alveolar macrophages and endothelial cells.[9] Interestingly, GM-CSF cannot modulate neutrophil apoptosis in COPD in a similar fashion as it regulates this process in healthy subjects.[10] Hence, we have been unable to identify the identical pathway through which GM-CSF acts on pulmonary neutrophils in COPD as it acts in healthy humans. The lifespan of neutrophils in COPD possibly depends on a dynamic balance between pro-apoptotic and anti-apoptotic pathways. The pro-apoptotic *Bac* and *CASP* genes are significantly down-regulated in neutrophils from COPD patients. However, in these subjects, the apoptosis-resistant *Bcl-2* and *Mcl-1* genes were increased in expression.[11,12] In addition, cigarette smoke also affects the phagocytosis of apoptotic neutrophils, leading to secondary necrosis, which triggers subsequent activation of proinflammatory signals.[13]

In COPD patients, an increased neutrophilic infiltration in the airways is closely associated with initial adhesion to endothelial cells though E-selectin which is up-regulated on the surface of endothelium. Adherent neutrophils migrate into the airway and parenchyma under the guiding of multiple neutrophil chemoattractant molecules, such as leukotriene B_4 (LTB_4), chemokine (C–X–C motif) ligand (CXCL) 1, CXCL5, and CXCL8 (interleukin-8 [IL-8]), which are accumulated in COPD respiratory tract.[14] These chemoattractants can be released by activated lung epithelial cells as well as immunocyte-like macrophages and T cells, but neutrophils may be the primary origin of IL-8.[15] In acute exacerbations of COPD, the remarkably

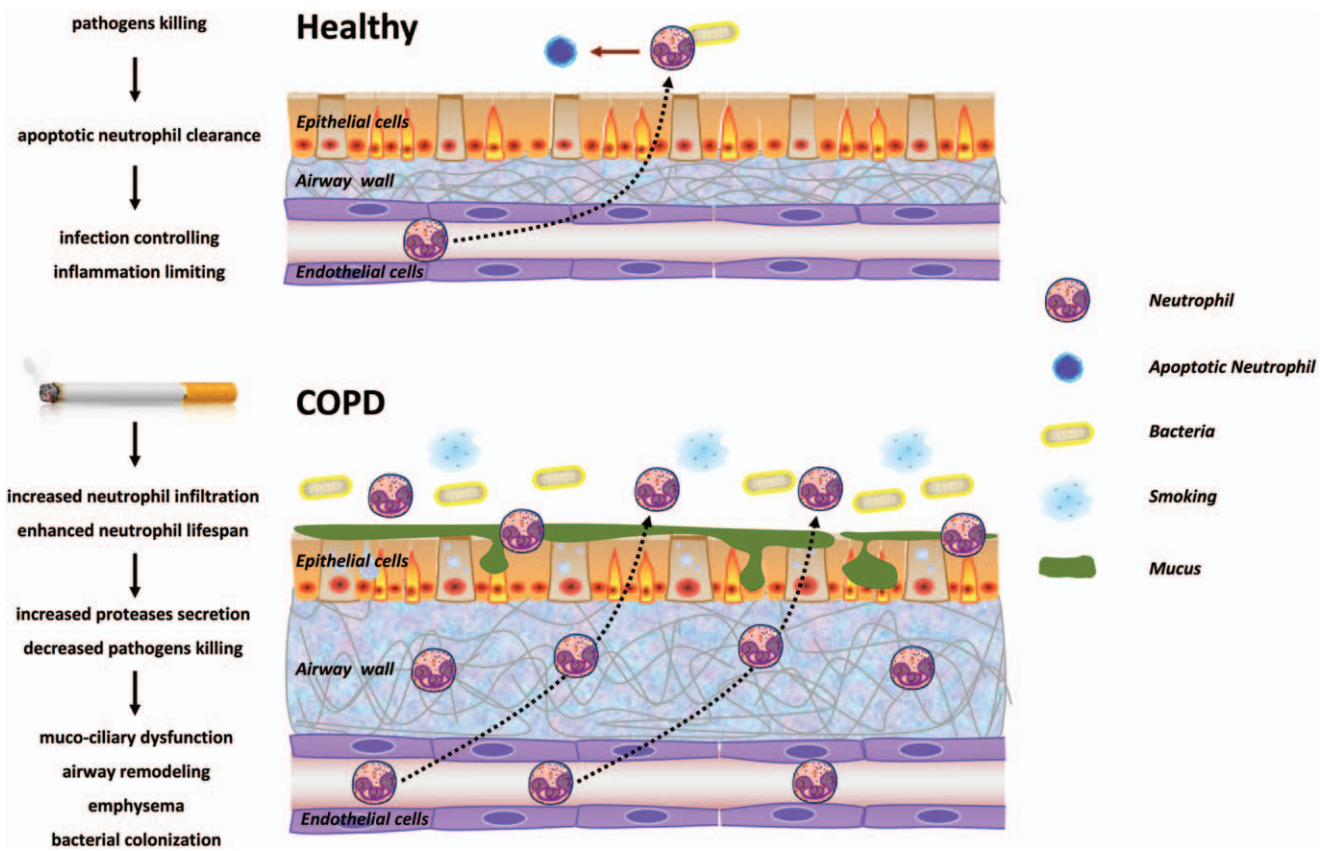

Figure 1: The role of neutrophils in healthy and chronic obstructive pulmonary disease (COPD) airways. In healthy airways, neutrophils play a key role in innate immune system of defense against invading pathogens. Typically, bacteria are trapped and killed by recruited neutrophils, which then undergo apoptosis, controlling infection, and limiting inflammation. In the COPD airways, cigarette smoke and pathogenic organisms trigger the release of chemoattractants, inducing the neutrophilic infiltration. Cigarette smoke or other unknown factors are also capable of increasing neutrophil lifespan and impairing the phagocytosis of apoptotic neutrophils, promoting further proinflammatory signals. Although there is enhanced neutrophil recruitment, local or systemic hypoxia affects leukocyte-mediated pathogen killing and increases the secretion of proteases, resulting in mucociliary dysfunction, airway remodeling and emphysematous destruction.

increased number of neutrophils in the airway accounted for the elevated purulence of sputum, which might present up-regulated secretion of neutrophil chemotactic mediators, consisting of LTB_4 and IL-8.[14]

Neutrophils recruitment to the respiratory tract of COPD patients is activated owing to elevated concentrations of granule proteins including human neutrophil lipocalin and myeloperoxidase (MPO) in respiratory tract secretions.[16] Indeed, partial or global hypoxia compromises antimorphic effect and enhances the production of multiple serine proteases, such as serprocidins and matrix metalloproteinases (MMPs), resulting in further cellular and tissue injury.[17,18] Moreover, several neutrophil-derived inflammatory mediators including neutrophil extracellular traps (NETs), high-mobility group box 1 (HMGB1), and reactive oxygen species (ROS) have been shown to trigger small airway remodeling and alveolar destruction in patients with COPD.[19-22]

MPO is an essential hemoprotein which is found predominantly in the primary granules of neutrophils. It triggers ROS elevation in a state of inflammation, especially in the presence of cigarette smoke, and also accelerates the inflammatory response in smokers.[20] 3-Chlorotyrosine, a product of MPO oxidative activity, was shown to be up-regulated in COPD sputum, implying that it may serve as tissue damage biomarker for MPO-mediated tissue damage in COPD pathogenesis.[23]

Serprocidins, also known as neutrophil serine proteases, include neutrophil elastase, proteinase-3, and cathepsin-G, form three components of azurophilic granules. They have been demonstrated to harbor proteolytic enzymatic activity towards extracellular matrix components, including type IV collagen, elastin, and fibronectin.[24] There is an endogenous association between respiratory tract neutrophilia and mucus hypersecretion, since neutrophil serine protease is a strong stimulus for mucus release from submucosal glands and trabecular cells. In order to avoid excessive harm, the family of serine protease inhibitors known as the serpins could be identified in the plasma, and serine proteases deficiency present protective functions against cigarette smoke exposure-induced emphysema in mice.[25]

MMPs belong to the Zn-dependent protease family that can be released from neutrophils, macrophages, and stromal cells. Collectively, the release of gelatinase MMP-9, metalloelastase MMP-12, and collagenase MMP-1, likely accounts for the majority of elastin and collagen degradation in emphysema pathogenesis.[26] Of these, the gelatinase MMP-9, synthesized exclusively by mature neutrophils, causes elastolysis and stimulates airway neutrophilia via the generation of N-acetyl-proline-glycine-proline.[27]

Formed by activated neutrophils, the NETs are adorned with cytoplasmic proteins, granules, and histones. While NETs have a key function in the innate immune response, excessive formation of NETs cause damage to lung tissue injury.[28] A substantial amount of NETs have been observed in the respiratory tracts of COPD patients in association with the severity of condition and frequency of exacerbation.[29]

HMGB1, a DNA binding protein, is mainly released by necrotic neutrophils involved in neutrophilic inflammation. Patients with COPD exhibit elevated sputum and plasma levels of HMGB1.[22] HMGB1 has significant effects on epithelial injury and reparation through a combined initiation of toll-like receptor 4 (TLR4) and receptor for advanced glycation end signaling, which may provide a potential target for treating neutrophilia and remodeling in patients with COPD.[30]

Anti-neutrophilic Inflammatory Strategies for COPD

Currently, the main therapeutic strategy for COPD consists of bronchodilators and corticosteroids. These agents may temporarily relieve the symptoms, but not considerably postpone disease progression or reduce the frequency of exacerbation. Notably, bronchodilators and corticosteroids are also the mainstay therapy in the management of asthma. Hence, it is important to be wary of the fact that COPD and asthma are two completely distinct diseases, although they have been confused for a long time. In asthma, eosinophils, mast cells, and lymphocytes perform a crucial function, whereas neutrophils have an essential role in only relatively uncommon situations, such as subtype of severe asthma.[31]

However, neutrophils recruitment and activation in the lungs are correlated directly with the severity of COPD.[32] Airway neutrophilia is a driving mechanism for the exacerbations, progression, and probably associated complications of COPD, such as arterial pulmonary hypertension and lung cancer.[3,32] Clinically, corticosteroids are highly effective in treating eosinophilic airway inflammation in asthmatic patients and largely ineffective as an anti-neutrophilic inflammatory therapy in COPD.[33] The treatment of corticosteroids against COPD remains widely practiced, but its side effects have caused a substantial incidence of morbidity.

The recent advances have been exploring the neutrophilic inflammatory mechanisms, particularly a greater understanding of its numerous mediators involved in COPD. Specific blockade of these mediators by either preventing their synthesis or antagonizing their receptors may play a crucial role in efficiently controlling disease progression. Several regulators of neutrophilic inflammatory mediators, such as anti-tumor necrosis factor-α (TNF-α) inhibitors, IL-17 inhibitors, and protease inhibitors are under development for the treatment of COPD.[25,34]

The negative results question the strategy of inhibiting a single mediator in therapy due to the complex of the neutrophilic inflammation in COPD, and so broad-spectrum agents, which directly suppress the cellular components of inflammation, need to be identified. The therapies explored include phosphodiesterase 4 inhibitors, kinase inhibitors, adenosine A2a-receptor agonists, and agents that interfere with adhesion molecules.[35] Still, there are concerns about the immune system dysfunction recently found in COPD patients,[36] because an impaired neutrophilic response may increase the susceptibility to infectious disease.

There is evidence that bacterial colonization of the lower respiratory tracts is found in half of COPD patients,

especially in severe stage, and involves the same bacterial species that contribute to exacerbations.[37] Bacterial colonization is also associated with airway neutrophilia and acquired immunity in the airways. Therefore, the antibiotics for the treatment of lower airway infections should be taken into consideration as a logical therapeutic strategy, albeit concerns on antimicrobial resistance vote against this approach.

Siglecs

Siglecs, the members of immunoregulatory receptors, are primarily located on the surface of hematopoietic cells.[38] The recognition of distinct sialylated glycoconjugates is configurated by an amino-terminal V-set immunoglobulin (Ig)-like domain, which may initiate or inhibit the immune response, depending on the involved Siglecs.[39]

There are 15 different functionally activated Siglecs that have been characterized in humans.[38,39] Conservative Siglecs, comprised of Siglec-1/2/4/15, have genetic homology in diverse mammalian.[38,39] However, CD33-related Siglecs have undergone rapid evolutionary adaptation including Siglec-9.[40] It is not feasible to identify a direct orthologs of human CD33-related Siglecs in mice, but functional paralogs with similar patterns of cellular expression and function can be determined.[40]

Characteristics of Siglec-9 and Siglec-E

Siglec-9 belongs to CD33-related Siglecs and is encoded by the *SIGLEC9* gene.[41,42] Immunoblotting with a specific antibody revealed hyper-expression of Siglec-9 on neutrophils and monocytes in human, and low levels on natural killer cells, and sub-populations of T and B lymphocytes.[41,42] Functionally, Siglec-9 has been demonstrated as an inhibitory receptor. Like the other members of CD33-related Siglecs, Siglec-9 has an immunoreceptor tyrosine-based inhibitory motifs (ITIMs) and ITIM-like domain that rapidly becomes phosphorylated followed by cell activation, which leads to the recruitment and activation of tyrosine phosphatases, including the Src homology-2 domain-containing tyrosine phosphatase (SHP)-1 and SHP-2.[43]

In terms of the murine CD33-related Siglecs expression pattern, Siglec-E is mainly observed in monocytes, neutrophils and dendritic cells, and has been considered to be closest to human Siglec-9.[44] The amino acid sequence of Siglec-E retains approximately 50% to 80% sequence identity to Siglec-9, which comprises three extracellular Ig domains and a cytoplasmic tail with two ITIMs.[45] In line with Siglec-9, Siglec-E ITIMs may recruit and initiate SHP-1 and SHP-2, indicating that Siglec-E negatively modulates the immune response.[45] Recently, elevated tumor cell death was observed in Siglec-E deficiency mice, whereas this phenotype was completely reversed in humanized Siglec-9 transgenic mice,[46] proving the supposition that murine Siglec-E is a functional ortholog of human Siglec-9.[44,45]

Siglec-9 as a Regulator of Neutrophil Apoptosis and Autophagy

In 2005, Von Gunten *et al*[47] first reported that Siglec-9 plays an important role in initiating apoptotic and autophagic-like cell death pathways in neutrophils [Figure 2]. In normal neutrophils, Siglec-9 ligation induced caspase-dependent apoptosis. However, for local micro-environments with proinflammatory cytokines, such as GM-CSF, interferon (IFN)-α, and IFN-γ, Siglec-9 ligation on neutrophils appears to switch from caspase-dependent apoptosis to caspase-independent autophagic-like cell death, which presents more potent cytotoxicity.[47,48] Remarkably, as indicated by additional assays utilizing ROS scavengers or neutrophils unable to produce ROS, the Siglec-9-mediated caspase-dependent and caspase-independent programmed cell death were ROS dependent, and such form of cell death was likely to be even more sensitive and effective in the presence of ROS.[47,48]

There is some existing evidence indicating that engagement of Siglec-9 by natural anti-Siglec-9 autoantibodies occurs on neutrophils after treatment with intravenous immunoglobulin (IVIg) preparations.[49] Intriguingly, this effect dramatically accelerates in a cytokine-rich micro-environment. In parallel with the reported effects of Siglec-9 ligation by specific antibodies, IVIg-mediated neutrophil death also involves ROS, in caspase-dependent and caspase-independent manners.[50] More importantly, there are clinical consequences of the presence of naturally occurring anti-Siglec-9 autoantibodies in IVIg that may have a potential to induce both desired and undesired effects. For instance, the beneficial effect of IVIg may involve the suppression of neutrophilia.[51] Also, an undesired neutropenia has been identified in association with IVIg therapy.[52] The reassuring facts are that IVIg-induced neutropenia is reversible and no severe infectious adverse events have been observed during the neutropenic period.[53] Future work is warranted to explore potential biomarkers to determine those individuals who may benefit from IVIg management for neutrophil dysfunction.

To date, the mechanisms leading to caspases activation in Siglec-9-mediated neutrophil death remain poorly understood. There are only a few studies which reported that tyrosine phosphatase SHP-1 may be involved in the apoptosis-associated caspase activation.[47] Furthermore, phosphoinositide 3 kinase, which participates in anti-apoptotic pathway in neutrophils,[54] would be dephosphorylated by SHP-1 via its association with the regulatory p85 subunit.[55,56] Neutrophil survival is regulated by finely-balanced interactions between pro-apoptotic and survival signals, and SHP-1 could be an important regulator in these processes.[57] Further studies will be awaited to intensively dissect these possible mechanisms.

Siglec-E as a Regulator of Neutrophil Recruitment

As a vital constituent of the innate immune system, neutrophils represent a first cellular line in the defense against bacterial and fungal infections. However, the host immune system and neutrophil recruitment must be precisely regulated to avoid chronic inflammation response and prevent excessive tissue damage. Otherwise, unregulated neutrophil responses and persistent inflammation could lead to entities such as COPD, asthma, and acute lung injury.[31,32,58]

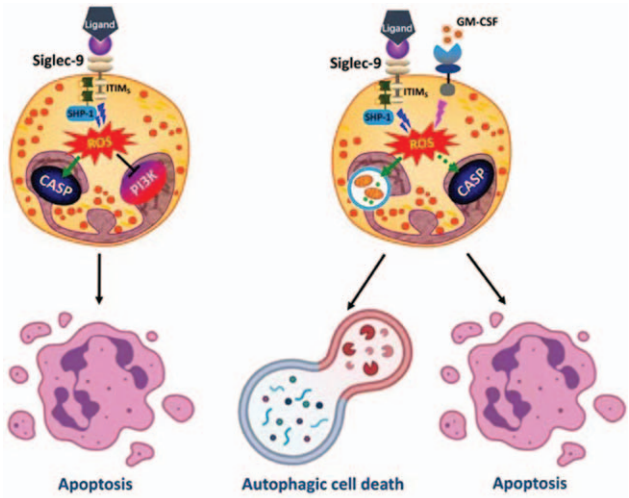

Figure 2: Sialic acid-binding immunoglobulin-like lectin-9 (Siglec-9) as a regulator in neutrophil apoptotic and autophagic-like cell death. The engagement of Siglec-9 by its ligands can recruit tyrosine phosphatase Src homology-2 domain-containing proteins tyrosine phosphatase-1 (SHP-1) to its intracellular immune receptor tyrosine-based inhibitory motifs (ITIMs). Phosphorylation of SHP-1 is followed by reactive oxygen species (ROS) generation in the absence of proinflammatory cytokines, such as granulocyte macrophage colony-stimulating factor (GM-CSF), leading to neutrophil apoptosis in a caspase-dependent fashion. In compensatory pathway, phosphoinositide 3 kinase (PI3K), the anti-apoptotic signal, might be down-regulated by SHP-1 phosphorylation. In the presence of GM-CSF, neutrophils may undergo a caspase-independent cell death, which is also designated as an autophagic-like cell death. CASP: cysteine-aspartic proteases.

In a murine sepsis model, McMillan *et al*[59] found that Siglec-E as an essential inhibitor of CD11b β2-integrin-dependent neutrophil recruitment to the lung after lipopolysaccharide (LPS) exposure. This was linked to a Siglec-E-dependent reduction in phosphorylation of Syk-Tyr^{317} and p38 mitogen-activated protein kinase (MAPK) in neutrophils activated via CD11b β2-integrin ligation to fibrinogen.[59] It has been widely accepted that Syk and p38 MAPK signals are essential for lung neutrophil recruitment.[60,61] Siglec-E in neutrophils was constitutively associated with SHP-1 and thereby dephosphorylation of Syk and p38 MAPK to repress neutrophilic inflammatory responses.[59]

In addition to Syk and MAPK-dependent signals negatively regulated by Siglec-E that dampens neutrophil recruitment, another important compensatory pathway involved is the activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex and production of ROS.[62] NADPH oxidase, a multi-subunit membrane-bound enzyme complex, can be assembled and activated in response to a wide variety of stimulants.[63] Studies targeting NADPH oxidase deficiency revealed a key contribution of the complex in antimicrobial host defense in humans and rodents.[64] Moreover, other studies using NADPH oxidase-deficient mice have validated a phagocyte-derived ROS-mediated anti-inflammatory properties, thereby inhibiting the neutrophils infiltration into the lungs.[65] Thus, the McMillan study provided a novel viewpoint that ROS production by neutrophils following LPS stimulation was dominantly dependent on Siglec-E, which is responsible for the suppression of neutrophils recruitment to the lung.[62]

Given the role of murine Siglec-E as a negative regulator in neutrophil recruitment, the human functional ortholog, Siglec-9 could be a potential therapeutic target in neutrophil-driven inflammatory lung disease.

Natural Ligands of Siglec-9 and Siglec-E in Neutrophilic Disorders

For decades, multiple studies have indicated that ligation of Siglecs-9 or Siglec-E is associated with regulation of neutrophil functions, such as induction of apoptotic and autophagic-like cell death,[47,48] inhibition of recruitment and activation,[59,62] modulation of oxidative stress,[62] repression of inflammatory cytokine secretion,[59] and regulation of tumor immune surveillance.[66] To date, the natural ligands of Siglec-9 and Siglec-E have not been fully identified.

Recent groundbreaking reports have revealed that certain bacteria strains and tumor cells can exploit sialoglycan-Siglec interactions to modulate immune cell function, thereby evading immune surveillance.[66,67] In the field of microbial immunity, Group B Streptococcus (GBS) is a leading cause of Siglec-9-mediated bacterial infections in human newborns.[68] The key virulence agent of GBS is its cystic polysaccharide, mimicking sialic acid that suppresses host immune response and provides a survival benefit to the etiological agent. Therefore, bacterial GBS could bind to Siglec-9 on neutrophils, which is anticipated to inhibit the immunoreactivity of neutrophils. Soluble form of Siglec-9 (sSiglec-9), also known as the extracellular region of Siglec-9, can competitively inhibit binding of GBS to Siglec-9 on neutrophils, leading to antibacterial benefit against GBS infection in the sSiglec-9 transgenic mice.[68]

High-molecular-weight hyaluronan (HMW-HA), a class of glycosaminoglycans, can conjugate to Siglec-9 in a sialic acid-independent fashion and perform immunosuppressive activities on human neutrophils.[69] This interaction between HMW-HA and Siglec-9 may recruit SHP-1 to ITIMs, leading to neutrophil dysfunctions (eg, NETs formation, and oxidative burst) and inducing apoptosis.[69] Group A streptococci utilize this dynamic procedure to escape from neutrophil attack via HMW-HA capsules.[70] Of note, a weaker cross-linking was observed between HMW-HA and murine Siglec-E.[69]

In the fledgling field of tumor immunity, Jia *et al*[71] first demonstrated that LPS-induced increases in Siglec-9 ligand and *MUC5B* expression in Calu-3 human lung adenocarcinoma cells occur via activating the TLR-4/NF-κB signaling pathway. Interestingly, Tomioka *et al*[72] reported that sSiglec-9 competitively antagonizes binding of Mucin1 to its immunomodulatory receptor Siglec-9, leading to the anti-tumor effect on Mucin1-expressing tumor cells *in vivo*, which may down-regulate the negative immunomodulatory function and/or inhibit tumor-associated Mucin1 downstream signal, and subsequent tumor proliferation.

Moreover, a novel sialylated ligand of Siglec-9-N-glycosylated lectin galactoside-binding soluble 3 binding protein (LGALS3BP) was identified in human colorectal and prostate cancers.[73] LGALS3BP binds with high affinity to

Siglec-9 and suppresses neutrophil activation, suggesting a potential mechanism of tumor immune evasion via Siglec-9 ligation. Additionally, LGALS3BP also binds to Siglec-E, while presents a lower affinity.[74]

The Role of Siglec-9 in COPD

Neutrophils obtained from patients with acute septic shock or rheumatoid arthritis showed elevated Siglec-9 expression and vitality.[47] Recent evidence has revealed that imbalance in Siglec-5 and Siglec-14 expression promotes initiation of inflammatory mechanisms in COPD.[75,76] So far, the role of Siglec-9 and its natural ligands in the pathogenesis of COPD has not yet been clearly elucidated.

Recently, Siglec-9 and sSiglelc-9 have been shown to play an important role in excessive and uncontrolled neutrophilic inflammatory airway diseases.[77] In 2017, Zeng *et al*[78] further confirmed that Siglec-9 and sSiglec-9 present a compensatory elevation in COPD patients. *In vitro* studies, cigarette smoke extract and LPS could induce Siglec-9 and sSiglelc-9 expression in peripheral blood neutrophils and culture supernatant, respectively.[78] Notably, dexamethasone could augment neutrophil Siglec-9 expression rather than sSiglec-9 levels in culture supernatant, suggesting that it exerts an anti-inflammatory effect on neutrophils by inducing Siglec-9 expression.[78] Interestingly, sSiglce-9 only enhanced neutrophil chemotaxis toward IL-8 without influence on apoptosis.[78] It was reasonable to postulate that an increased level of sSiglce-9 may lead to severe airway neutrophilia in COPD by inducing neutrophil recruitment. Siglec-9 and Siglec-E are important negative regulators of neutrophil recruitment.[59,62] Therefore, sSiglce-9 increased neutrophil chemotaxis probably via binding with Siglec-9 ligands to inhibit Siglec-9 function.

Influence of Siglec-9 Polymorphisms on COPD Phenotypes

Acute exacerbations are severe events that carry significant consequences for COPD patients. A number of subjects experience frequent exacerbations, designated as the exacerbation susceptible phenotype.[3] These patients are a priority for research and treatment, as exacerbations lead to poorer quality of life and higher mortality.[3] As most of COPD exacerbations are caused by respiratory infections with bacteria or viruses, numerous studies suggest that the aberrant immune response may mechanistically result in exacerbation susceptibility.[79] The initial immune responses against these pathogenic microorganisms frequently involve endogenous glycoproteins, including Siglecs. For instance, a previous study has indicated that non-typeable *Haemophilus* influenza (NTHi), a major trigger of COPD exacerbations, could interact with Siglec-14 to induce proinflammatory cytokine production and secretion from myeloid cells. Consistently, Siglec-14 deficiency resulted in a reduced risk of COPD exacerbations.[75]

It is widely recognized that Siglec-14 ligation can activate innate immune cells. Mostly, Siglecs play a negative modulatory function in innate immune response including Siglec-9. Ishii *et al*[80] demonstrated that two prevalent non-synonymous coding single nucleotide polymorphisms (cSNPs), rs2075803 and rs2258983, in the *SIGLEC9* gene were associated with higher risk of exacerbations and the extent of emphysema in a Japanese population of COPD. Furthermore, a myeloid cell line THP-1 expressing the Siglec-9 variant corresponding to the GA haplotype (rs2075803 = G and rs2258983 = A) induced more TNF-α expression than the control haplotype.[80] In general, Siglec-9 could interact with NTHi and transduce a suppressive signal in myeloid cells. However, a genetic variant of *SIGLEC9* that attenuates the suppressive function of the Siglec-9 protein would promote more severe inflammatory responses, rendering COPD patients more susceptible to exacerbation.

In addition, Läubli *et al*[46] reported that another cSNP (rs16988910) in the *SIGLEC9* gene is associated with emphysematous destruction in the African-Americans. Although rs16988910 is rare among Asian or European populations, the close relationship between this *SIGLEC9* cSNPs and emphysema in different ethnicities appears to support a critical function of Siglec-9 in innate immune responses, in which Siglec-9 variant is a potential risk factor for the development of emphysema in COPD.

Conclusion

COPD is a major cause of chronic morbidity and mortality throughout the world. At present, the pathophysiology of COPD is poorly understood and therapeutic strategy is mainly palliative care. The existing evidence suggests a critical role for neutrophilic inflammation in the pathogenesis of COPD. Human Siglec-9, identified predominantly on neutrophils, is an inhibitory receptor that is potentially able to induce neutrophil apoptosis, suppress neutrophil migration, and reduce exacerbation frequency and the extent of emphysema in COPD. Clinically, high-dose IVIg is now used widely for the treatment of autoimmune and systemic inflammatory diseases. Natural anti-Siglec-9 autoantibodies have been identified in IVIg, suggesting that IVIg might induce caspase-dependent cell death in Siglec-9-sensitive cells. Therefore, treatment for efficient anti-neutrophilic inflammation should be developed via using Siglec-9 relevant ligands or agonistic antibodies. In the future, based on in-depth dissection of the glycobiological characteristics of Siglec-9, a series of targeted therapies will be developed for treatment of COPD, including synthetic ligands, specific antibodies, and small molecule compounds.

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Conflicts of interest

None.

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