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## ADVANCED GLYCATION END-PRODUCTS AS NOVEL BIOMARKERS OF EOSINOPHIL- DERIVED LUNG INFLAMMATORY DISEASES (LITERATURE REVIEW)

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**Ключевые слова:** *конечные продукты гликации, аллергия, эозинофильное воспаление, нейтрофильное воспаление*

**Abstract.** *Advanced glycation end-products as novel biomarkers of eosinophil-derived lung inflammatory diseases (literature review). Gamian A., Zubchenko S.O., Havrylyuk A.M., Kril I.Y., Chopryak V.V. Advanced glycation end-products (AGEs) are created during the process of glycation of cells from various tissues and fluids and are a heterogeneous group of molecules formed from the nonenzymatic reaction of reducing sugars with the amino group of proteins, lipids, and nucleic acid. In normal conditions, they play the immunoregulatory role. In pathologic conditions AGEs activate the receptors for advanced glycation end products (RAGE) and cause long-lasting inflammation. RAGE participates actively in various disorders such as rheumatoid arthritis, diabetes, etc. However, there is relatively small number of scientific studies on the possibility of using the role of AGE in the pathogenesis of allergic diseases. RAGE transcript and protein are expressed in the lung by pulmonary type I alveolar epithelial cells, suggesting that RAGE has an important role in lung pathophysiology. They repress some endogenous autoregulatory functions leading to many diseases, including allergy. Oxidative stress increases the inflammatory reaction in asthma and allergies. Long-lasting inflammation followed by free radicals production are important factors involved in allergic reactions, they negatively influence the incidence and prognosis of allergy. RAGEs are expressed on circulating immune cells, they activate NF kappaB and intracellular oxidative stress also increases the inflammatory reaction in asthma and allergies. The membrane RAGE (mRAGE) signaling is proinflammatory, whereas soluble RAGE (sRAGE), a secreted form of RAGE, is generally anti-inflammatory. The study of AGEs, soluble RAGE, ligands of RAGE HMGB1, and S100A8/A913 and IL-33 is useful in the context of their considering as biomarkers to the differentiation diagnostic between eosinophils-derived and neutrophil-derived asthma/AAD. The mean serum levels of RAGE may be the target of new therapeutic interventions.*

**Реферат.** *Кінцеві продукти глікації як нові біомаркери еозинофільних запальних процесів у легенях (огляд літератури). Гам'ян А. Зубченко С.О., Гаврилюк А.М., Кріль І.Й., Чоп'як В.В. Кінцеві продукти глікації (advanced glycation end-products, AGEs) є гетерогенною групою речовин, що утворюються у процесі неферментативної реакції відновлених цукрів з аміногрупами білків, ліпідів і нуклеїнових кислот з різних тканин і рідин. У нормальному стані вони відіграють імунорегуляторну роль. В умовах патології AGEs активують рецептори для кінцевих продуктів глікації (RAGE) і викликають тривале запалення. RAGE беруть*

активну участь у різних патологічних процесах, таких як ревматоїдний артрит, цукровий діабет тощо. Однак проведена порівняно невелика кількість наукових досліджень щодо можливої ролі AGEs в патогенезі формування алергічних захворювань. RAGE транскрипт і білок експресуються в легенях легеневиими альвеолярними епітеліальними клітинами типу I, відтак – RAGE відіграють важливу роль у патофізіології легень. Виявлено, що RAGE пригнічують деякі ендogenous ауторегуляторні функції, що призводить до формування багатьох захворювань, включаючи алергію. Окиснювальний стрес збільшує запальну реакцію при бронхіальній астмі та іншій алергопатології. Довготривале запалення з подальшим виділенням вільних радикалів є важливими факторами, які беруть участь в алергічних реакціях, вони негативно впливають на частоту загострень і прогноз алергії. RAGE експресуються на циркулюючих імунних клітинах, вони активують капсулу B і внутрішньоклітинний оксидативний стрес, що також підсилює запальну реакцію при астмі та алергії. Передача сигналу через мембранну форму RAGE (mRAGE) спричиняє прозапальний ефект, тоді як розчинна секреторна форма RAGE (sRAGE) зазвичай є антизапальною. Дослідження рівнів AGEs, розчинних RAGE, лігандів RAGE HMGB1 і S100A8 / A913 і IL-33 є важливими в контексті розгляду їх як біомаркерів для диференціальної діагностики між еозинофільною і нейтрофільною / AAD фенотипами астми. Наявність у пацієнта сироваткових RAGE навіть середнього рівня є підставою для вибору нової терапевтичної стратегії лікування.

Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic lung diseases worldwide. They are different from each other in immunological mechanisms and patterns of inflammation [3, 16]. Asthma and chronic obstructive pulmonary disease are two respiratory diseases characterized by the accumulation of inflammatory cells in the respiratory tract, which leads to subsequent airflow obstruction [37]. Asthma/allergic airway disease (AAD) is the main inflammatory condition of modern societies [22]. Atopic asthmatics have other signs of allergy, including eczema, rhinitis, and nasal polyp, immediate skin test responses to antigen, eosinophilia, and elevated IgE levels [37].

The mechanisms underlying the pathophysiology of these two diseases are distinct: the mediators of airway inflammation are different for COPD (neutrophils) and asthma (eosinophils) [37]. The search for biomarkers as substances of the eosinophil-derived inflammatory process is very important for patients with lung diseases combined with allergy.

#### **Advanced glycation end-products: physiological and pathophysiological actions and effects**

Advanced glycation end-products (AGEs) are formed during the process of glycation within and outside the cells from various tissues and biological fluids. AGEs are a heterogeneous group of molecules formed from the non-enzymatic reaction of reducing sugars with the amino group of proteins, lipids, and nucleic acid [27]. Glycation is a non-enzymatic process, where reducing sugars (glucose, fructose, glucose-6-phosphate, and other) react with amino groups of proteins [19]. AGEs are formed by the linkage of glucose usually to lysine residues [21]. In physiological conditions, AGEs play a regulatory role. Normally the proteolytic lysosomal enzymes from circulating phagocytes and Kupffer cells can destroy the AGEs spontaneously. The processes of creating and removing AGEs are well-balanced. AGEs are composed of a heterogeneous

group of bioactive compounds (e.g. pentosidine, carboxymethyl lysine, and imidazoline) that are formed by non-enzymatic glycation of macromolecules. Imidazoline is an inhibitor of histamine release. Thereby, AGEs play a certain role in the pathogenesis of diseases involving oxidative stress and inflammation; the formation and action of AGEs are linked – oxidative stress and inflammation [21]. Oxidative stress decreases immunity, the diminution of IL-1, IL-6 thereby cause immunodepression. Allergens contain numerous free radicals, they oxidize or peroxidize proteins, lipoproteins, DNA, etc. and thus change their properties. AGEs cause lipoperoxidation, cross-bonds, inactivate nitric oxide, costimulate the formation of cytokines, support free-radical creation, cellular proliferation, and support coagulopathy [20]. AGEs increase vascular permeability, inhibit vascular dilatation by blocking nitric oxide (NO), oxidize LDL, cholesterol, support cytokine production, and increase oxidative stress [21]. Endogenous and exogenous (high dietary AGEs, cooking food at high dry heat, elevated pH, and longer period) sources of AGEs have been described in the literature. AGEs formation can be reduced with drugs, vitamins, and cessation of cigarette smoking [27].

Advanced glycation end products and advanced oxidation protein products (AOPPs) are compounds formed by the transformation of macromolecules, including proteins, which can serve as densitometric markers of oxidative stress and inflammation in a number of diseases and their complications. Modified proteins can be used more efficiently than other biomarkers to monitor disease progression and outcome since proteins generally play a key role in various structural and functional aspects of living organisms and their activity and function are strictly dependent on structure, conformation and composition pattern. Thus, modification of the conformation / structure of the polypeptide chain in conditions of

oxidative stress / inflammation can lead to dysfunction / function, of proteins their loss, and inhibition of protein degradation (and, consequently, accumulation) and can also have a wide range of downstream functional consequences, such as cellular dysfunction, tissue damage, and disease onset and progression. These biomarkers also have the advantages over other modified proteins (e.g, carbonylated, and nitrosylated proteins), namely, relative stability and consequent higher blood concentrations [21].

AGEs are also present in foods. AGEs and other signaling substances provoke innate immune system through multiple mechanisms, resulting in the development of allergic phenotypes [30]. High intake of glucose and fat, due to the Western diet, accelerate, the development of chronic diseases [25]. The Western lifestyle and diet promote innate danger signals and immune responses through the production of "alarmins." Alarmins are endogenous molecules secreted from cells undergoing nonprogrammed cell death that signal about tissue and cell damage. High molecular group S (HMGB1) is a major alarmin that binds to the receptor for advanced glycation end-products (RAGE) [12].

Genetic predisposition and increasing amounts of environmental reactive substances (e.g. allergens) also can accelerate chronic diseases, consequently, may be responsible for the modification of biomolecules. Protein glycation, oxidation, and nitration are the most important non-enzymatic protein modifications involved in the formation of endogenous protein aggregates. At present, one of the most studied classes of substances is the heterogeneous group of AGEs. Different precursors are responsible for the formation of AGEs in vivo, for example, elevated levels of reactive oxygen species (ROS) lead to the oxidation of proteins, lipids, and nucleic acids increases [25]. AGEs generate ROS and activate inflammatory signaling cascades. The formation of AGEs is faster than their degradation, which progresses after binding with the receptor of advanced glycation end-products. The major reason for the massive production of ROS is the activation of NADPH-oxidase via complexes of ligand-RAGE. Due to ROS increase, the permeability of cell membranes and the migration of phagocytes into tissues is intensified [26]. Oxidative stress is the result of the imbalance between the endogenous production of free ROS and reduced effectiveness of antioxidant defense mechanisms. This imbalance may exacerbate inflammation and injury by enhancing the release of anti-inflammatory cytokines and altering enzymatic function. Oxidative stress occurs in many allergic and immunologic disorders and has been well documented in patients

with asthma. However, the role of oxidative stress in allergic rhinitis has received little attention, although it is likely to be similar to the role it plays in patients with asthma [21]. Exposure to ozone has been shown to exacerbate allergic rhinitis in experimental animals and humans, and the molecular targets of oxidative stress in allergic rhinitis have been found in blood, nasal mucosa, nasal secretions, nasal cavity, erythrocytes, and in exhaled air and exhaled breath condensate. Reduced serum antioxidant levels have also been recorded in patients with allergic rhinitis and asthma. However, some authors were unable to demonstrate the presence of markers of oxidative stress in patients with allergic rhinitis or demonstrated different degrees of involvement depending on the marker of oxidative stress detected [21].

Recent studies suggest that AGEs contribute to pulmonary diseases [30]. Further larger-scale studies are needed to test the use of AGEs and soluble RAGE (sRAGE) as biomarkers for the prediction of allergy in humans [20]. It has been recently demonstrated that AGEs are involved not only in metabolic abnormalities but also in other various inflammatory disorders through interacting with their AGE receptor, but the direct effects of AGEs on inflammatory cells such as basophils are unknown [33].

Basophils are thought to play pivotal roles in the pathogenesis of allergic reactions, but their roles in inflammation associated with systemic abnormalities such as metabolic disorders remain largely unknown. Advanced glycation end products are potentially important substances produced in high-glucose disease conditions [13]. Apoptosis of basophils was induced by high concentrations of glycated albumin. Although glycated albumin triggers degranulation or production of IL-4 and IL-13 in basophils, it dose-dependently induced IL-6 and IL-8 secretion [13, 33]. AGEs are known to affect human basophils; they inhibit cell longevity but enhance the secretion of inflammatory cytokines. So, basophils may play a role in inflammatory conditions associated with metabolic disorders that present elevated levels of AGEs [13].

#### **The key functions of a receptor of advanced glycation end-products in lung pathology development**

AGEs activate the receptor of advanced glycation end product receptors and cause longlasting inflammation [20]. RAGE, a member of the immunoglobulin superfamily of cell surface molecules, is involved in the signal transduction from pathogen substrates to cell activation during the onset and continuation of inflammation. RAGE were first identified in lung tissue, they are located on the basolateral membranes of alveolar epithelial type I and II cells [16].

RAGE in the pulmonary compartment (epithelial or endothelial cells) is important for allergic pulmonary inflammation. RAGE is necessary for both IL-33 release and group 2 innate lymphoid cells (ILC2s) accumulation in the lungs to promote chronic and acute allergic airway disease. Due to the unique role of RAGE both before and after the course of IL-33 in patients with allergic asthma, blocking RAGE can alleviate a wide range of symptoms associated with allergic airway inflammation (AAI), including mucus hypersecretion, airway hyper response, and eosinophilic inflammation. A small-molecule inhibitor of RAGE could be an attractive new treatment option for asthmatic patients [22].

Generally, RAGE is an inflammation perpetuating receptor and has many additional ligands, including S100 proteins, high-mobility group protein B1 (HMGB1), amyloid  $\beta$  peptide, and heparin [22]. Two known RAGE ligands, S100A8/A9, and HMGB1 are associated with asthma pathogenesis in human subjects [24]. Preferential localization of RAGE is at cell-cell contacts [2, 25]. This receptor, by binding AGEs, contributes to allergies. The link between AGEs and allergies goes beyond discussion. There are various theories about pathogenetic roles of AGE (RAGE): 1) mast cells produce AGE-binding protein, receptor to AGE (RAGE), apoptosis of mast cells contributes to the formation of inflammation; 2) glycated albumin supports the extracellular release of superoxides from mitochondria, and thus damages calcium homeostasis; 3) some AGEs have innate catalytic oxidative capacity; stimulation of NAD(P)H oxidase through the activation of RAGE and damage to mitochondrial proteins leads to mitochondrial dysfunction and induces oxidative stress [20].

Prolonged inflammation, accompanied by the production of free radicals, is an important factor involved in allergic reactions, affecting the incidence and prognosis of allergies. RAGE, activate nuclear factor NF kappa B formation and intracellular oxidative stress. Besides, they inhibit some endogenous autoregulatory functions leading to allergies. Oxidative stress increases the inflammatory reaction in asthma and allergies. As it is our knowledge, there are no published articles regarding AGEs responses or the association between AGEs groups and IgE concentrations in allergic patients.

The cytokines such as IL-5 and IL-13 are mediators of eosinophil involvement and airway remodeling, suggesting that RAGE probably acts as a proximal mediator one or more pro-inflammatory pathways. Because of the multivalence that RAGE has, it is reasonable to conclude that RAGE acts

below antigen recognition; thus, its ligands in asthma/AAI are likely to be endogenous and not derived from the initial antigenic stimulus. Finally, although RAGE is predominantly expressed on alveolar type I epithelial cells, some studies have suggested that it is expressed on hematopoietic cells and endothelium as well. Characterization of the cell type(s) responsible for the effect seen in these studies, as well as the elucidation of the molecular pathways between RAGE and the T-cell cytokines IL-5 and IL-13, will constitute key aims of future studies [22].

Exogenous IL-33 induces IL-5 and IL-13 expression independent of allergen. Lack of IL-33 leads to attenuated Th2 immune responses to the allergen, indicating that this cytokine is critical in the development of a competent allergic response. IL-33 expression is increased in the lungs of patients with severe asthma. IL-13 expressing cells were able to reconstitute bronchial hyperresponsiveness and pulmonary inflammation in response to exogenous IL-25. These data suggest that IL-13 signaling is sufficient for Th2-mediated disease [24]. Despite these discoveries, the tissue-specific mechanisms that cause the release of the epithelium-derived cytokines are incompletely understood. Recent investigations have suggested a role of the receptor of advanced glycation end-products in mediating of development of allergic airway disease in experimental animal models [1, 22, 35].

RAGE is highly expressed in the lung and binds multiple ligands, suggesting that it might act as a pattern recognition receptor to promote lung inflammation. The role for RAGE in the pathogenesis of human asthma has recently been supported by two genome-wide association studies that have identified a single nucleotide polymorphism in domain binding of RAGE ligand (G82S), which correlates with altered FEV1, a key parameter of pulmonary function in asthma [14, 28]. RAGE is implicated as a potential mediator of ILC2 (the major producers of IL-5 and IL-13) accumulation in the lung [18]. RAGE is necessary for increased production of IL-33 from pulmonary cells in response to the allergen. RAGE is highly expressed on type I alveolar epithelial cells [8, 10], whereas IL-33 localizes to nuclei and is released by type II alveolar epithelial cells in response to damage. How RAGE activation might direct increased IL-33 expression is unclear, but it is known that type I and type II alveolar epithelial cells communicate through multiple paracrine and juxtacrine signaling pathways [5, 15]. RAGE was found to drive AAI by promoting IL-33 expression in response to allergen and by coordinating the inflammatory response downstream of

IL-33 [24]. The absence of RAGE impedes pulmonary accumulation of ILC2s in experimental models of AAI. IL-33 is a potent stimulator of a novel class of innate lymphoid cells that secrete copious amounts of the Th2 cytokines IL-5 and IL-13. ILC2s lack a T-cell receptor but express other markers suggestive of lymphoid origin - CD45 and CD90. ILC2s, which bear receptors for IL-10, IL-12, IL-17, IL-25, and IL-33 (ST2), have been found to play a crucial role in the evolution of type 2 inflammation in animal models of pulmonary disease [24].

RAGE activation on endothelium, mononuclear phagocytes, and lymphocytes triggers cellular activation with the release of key pro-inflammatory mediators [16, 26]. The molecules of integrin Mac-1 of leukocytes bind to RAGEs on endothelial cells and contribute its migration to the inflammation area. Anti-RAGE antibodies can block the activation of lymphocytes and phagocytes [26], but autoantibodies IgG-AGE in patients with early synovitis play an important role in protein turnover, tissue remodeling, and the pathologies of different diseases [31]. The expression of RAGE is significantly decreased in COPD lung, especially in severe disease [16].

#### **Advanced glycation end-products and immune response to allergens**

The modern role of fundamental processes of innate and acquired immunity in the pathogenesis of atopic dermatitis, allergic rhinitis, and bronchial asthma has been demonstrated [34]. The capacity of RAGE to bind many pro-inflammatory ligands indicates that RAGE is an important component in the propagation of immune responses. Like most components of the innate immune system, the gene encoding RAGE (Ager) is localized within the major histocompatibility class (MHC) of class III [26].

Interaction of AGEs with its cell-bound receptor (RAGE) results in the generation of oxygen radicals, NF- $\kappa$ B, pro-inflammatory cytokines, and cell adhesion molecules [27]. The promoter of gene encoding of RAGE has the property to bind to NF- $\kappa$ B. NF- $\kappa$ B is a common activator of lymphocytes and has been identified as being capable to regulate RAGE synthesis [26]. The interaction of RAGE on leukocytes results in the activation of sustained NF- $\kappa$ B-dependent gene expression. NF- $\kappa$ B is a key point of immune reactions; they activate the genes and encode regulation of apoptosis and cell proliferation [17, 34]. The onset of cellular signaling pathways leads to the activation of the transcription factor NF- $\kappa$ B. It migrates to the cell nucleus and activates the expression of cytokine genes (TNF- $\alpha$ , IL-1, IL-6), chemokines (IL-8, MIP1, RANTES), adhesive molecules (VCAM-1, ICAM-1), and enzymes (iNOS) and support the inflammation process [26].

It should be noted that RAGE has been identified as capable of complexing with TLR9 (the principal DNA-recognizing receptor). This RAGE-TLR9 complex can detect pathogen DNA. RAGE has been shown to reduce immune recognition and promote DNA uptake by endosomes in the lungs [29]. TLRs are involved in the pathogenesis of asthma. Allergen recognition can activate TLR4 and subsequently allergen-specific Th2 cells. TLR2 stimulates the Th2-mediated immune response, which may be correlated with the Th1/Th2 imbalance in asthma. Increased expression of TLR2, TLR3, and TLR4 plays a potential role in the development of asthmatic exacerbations [37].

RAGE is found in many cells, including lung tissue cells, and RAGE is expressed on circulating T lymphocytes, monocytes, and macrophages [20]. The membrane RAGE (mRAGE) signaling is pro-inflammatory, whereas soluble RAGE (sRAGE), a secreted form of RAGE, is generally anti-inflammatory because it scavenges pro-inflammatory ligands [16]. Circulating soluble forms of RAGE (sRAGE) and endo-secretory RAGE (esRAGE) compete with RAGE for ligand binding and function as a decoy [27].

In pulmonary diseases, soluble RAGE causes activation and maturation of B cells, which leads to a higher secretion of IgM and IgG and leads to activation of T cells, which is confirmed by increased production of cytokines [6]. The absence is manifested by reduced activation of T-cells to antigens. RAGE is involved in the differentiation of T-cells along with a Th1 phenotype and RAGE mRNA is more abundant in Th1 compared with Th2 cells [7]. Although T-lymphocytes are thought to be the main source of IL-4, IL-5, and IL-13, other cell types have been linked to the production of one or more members of this triad. Thus, IL-4 induction in the absence of the other two typical Th2 cytokines could be reflective of either uncoupling in the cytokine response at the T-cell level or the recruitment of other cell types that may produce IL-4, such as macrophages or basophils. The fact that immunoglobulin production in response to antigens occurs in the absence of RAGE, despite the lack of other features associated with allergic airway disease, is consistent with prior studies suggesting that B-cell deficiency (and hence immunoglobulin production) does not affect the physiologic and pathological changes seen in response to allergen sensitization and challenge in an experimental mouse model of asthma/AAD. Furthermore, the fact that in the presence of high hypersensitivity, eosinophilia, or remodeling would seem to indicate that IgE alone is not playing a central mechanistic role in this model of asthma, although it must be noted that changes in



airway physiology were assayed with graded doses of methacholine rather than allergen [22].

The mucosal T-cells play important roles in asthma but activated IL-2R<sup>+</sup> CD4<sup>+</sup> T-cells in the broncho-alveolar lavage (BAL) of asthmatics. The Th-2 cytokine pathway, which links IL-4/IL-5 production to IgE synthesis, is associated with the accumulation of eosinophils and mast cells in lung tissues. Interleukin-13 (IL-13), which is a Th2 marker, is known to be important in eosinophilic inflammation and asthma too [11]. IgE binds to receptors found on the surface of mast cells, thus initiating an allergic response. Therefore, activated mast cells subsequently degranulate to release histamine, leading to the development of bronchial constriction. In most asthma cases, there is a predominant expression of Th2-type cytokines, including IL-4, IL-5, IL-13, these cytokines result in the increased migration of eosinophils and mast cells [37].

IL-17 has been suggested to play a role in allergy and asthma; it is upregulated in response to allergen sensitization. RAGE plays a role in IL-17 regulation. RAGE may actively inhibit the secretion of IL-17, directly or by disrupting precursor cytokines, such as IL-23. Conversely, the absence of RAGE may lead to compensatory induction of other factors that in turn drive the IL-23/IL-17 axis [36]. Although IL-17 has been shown to play a role in neutrophilic asthma, it has also been shown to be a negative regulator of established allergic asthma. The baseline elevation of IL-17 may thus impede the initiation of a primary asthmatic response [22].

#### **The changes of expression of advanced glycation end-products and its receptors in lung inflammatory diseases**

Persistent inflammation and airflow obstruction are the major characteristics of asthma and COPD. However, the patterns of inflammation and the immunological mechanisms that lead to the airway structural alterations are different for the respective diseases. Inflammation in the larger conducting airways is mainly observed in asthma [38]. In contrast, COPD predominantly affects the lung parenchyma and smaller airways [13]. In investigation Iwamoto et al. [16] found that the blood level of RAGE was higher in asthmatic subjects compared with patients suffering from the chronic obstructive pulmonary disease and control group. Another experimental study [22] has shown that RAGE is more expressed in asthmatic airways and giving RAGE inhibitors markedly decreased inflammation in an animal model of asthma. El-Seify et al. [9] found that serum level of sRAGE correlated with the severity of bronchial asthma clinically and functionally. More multicenter studies are needed on a

larger number of asthmatic children to detect the effect of anti-asthma medications on serum RAGE. Serum RAGE is elevated during acute childhood asthma exacerbation in comparison with control subjects [3]. In newborns of allergic parents higher levels of IgE and AGEs in umbilical blood are revealed. We believe that the probability of future allergic reactions in children, whose mothers have an allergy, maybe higher when the level of AGEs and IgE in umbilical cord blood is significantly increased. Because the levels of glucose in two groups did not differ significantly, we can conclude that potentially allergic children have increased oxidative stress [20].

Another possible explanation is that reduction in sRAGE might modify neutrophilic airway inflammation, as sRAGE has anti-inflammatory properties by capturing RAGE ligands. This concept is in agreement with the fact that reduced plasma sRAGE levels is accompanied with transition of COPD in asthma with neutrophilic airway inflammation. Moreover, the recent study by Sukkar et al. [32] has demonstrated a clear association between broncho-alveolar lavage fluid sRAGE and airway neutrophilic inflammation. Therefore, the present results indicate that peripheral lung destruction might be associated with decreased plasma sRAGE in patients with COPD-asthma transition and COPD, but further investigations are needed to clarify its mechanisms and potential role of modulating the lung inflammation [16].

Bronchodilators and corticosteroids remain the mainstays of therapy, but they are ineffective or inadequate for some groups of patients. New therapies that use ancillary mechanisms of the disease and have fewer side effects than chronic corticosteroid treatment are urgently needed. A few studies in humans have suggested that there is an increase in the levels of RAGE ligands HMGB1 and S100A8/A913 in samples from patients with asthma compared with controls, suggesting that RAGE may contribute to asthma/AAD pathogenesis. Although one recent study suggested that sRAGE is increased concomitantly with HMGB1 in patients with asthma, another suggested a decrease in sRAGE and no change in HMGB1 in patients with neutrophilic asthma. Apart from the potential inconsistency between the latter two results, those studies have not provided mechanistic insight as to the role of mRAGE versus sRAGE in asthma, nor have they elucidated how cytokines and chemokines key to allergic disease are differentially regulated in the presence or absence of RAGE [22].

Soluble receptor of advanced glycation end products (sRAGE) acts as a decoy receptor for RAGE which has several distinct pro-inflammatory ligands in the extracellular compartment and is believed to

protect against inflammation and cell injury. Plasma levels of sRAGE showed statistically significant lower levels in asthmatic patients compared to the control group [9] and were similarly decreased in COPD groups, but not in asthma [23]. RAGE is primarily expressed on alveolar type I pneumocytes and could assist these cells in acquiring a spreading morphology [9]. Therefore, RAGE might have a role in alveolar integrity, and decreased sRAGE levels could be associated with disrupted alveolar structures [16]. Increased levels of RAGE were demonstrated in bronchoalveolar lavage fluid in various direct models of lung injury induced separately by intratracheal instillation of hydrochloric acid,

lipopolysaccharide (LPS), or *Escherichia coli* as well as exposure to hyperoxia [3].

#### CONCLUSIONS

1. The patterns of inflammation and the immunological mechanisms that lead to the airway structural alterations are different for the various lung diseases.

2. A few studies in humans have suggested that the use of AGEs, soluble RAGE, ligands of RAGE HMGB1, and S100A8/A913 and IL-33 as biomarkers are necessary for the differential diagnosis between eosinophil-derived and neutrophil-derived asthma/AAD.

Conflict of interests. The authors declare no conflict of interest.

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