Chronic Obstructive Pulmonary Disease and Persistent Airflow Limitation: Advances in Prevention and Clinical Management

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Abstract

Global Initiative for Chronic Obstructive Lung Disease (GOLD) research on chronic obstructive pulmonary condition (COPD) characterizes it as a prevalent, preventable, and curable illness with persistent respiratory symptoms and airflow limitation. airway blockage resulting in dyspnoea and air trapping when exercising airflow restriction can be attributed to smoking, ambient tobacco smoke exposure, and the patient's TB history COPD airflow restriction is largely caused by airway tightness, chronic bronchitis, or emphysema. Repeated inhalation of hazardous particles induces chronic inflammatory immune cell infiltration, tissue repair, and airway remodeling, resulting in a 4-to 40-fold increase in airway resistance and bronchiolar constriction. 20% of small airways are bronchi, with the rest being either bronchioles or alveolar ductal gaps. Flow restriction includes alveolar wall disintegration and alveolar support. The modifications worsen the rapid FEV1 fall and contribute to the airway obstruction seen in COPD. COPD, small airway disease (SAD), has been extensively studied. Inflammation, fibrosis, and destruction of bronchioles are all indications of this illness. mixed pulmonary fibrosis and emphysema (CPFE). In fact, fibrosis appears to be involved in the obstruction of small airways.

RAGE participates in several intracellular processes by binding to several ligands. RAGE ligand interactions trigger downstream signaling pathways that have been associated with COPD and other disorders. Thus, inhibitors of RAGE and its signaling pathways also have been found to play a function in other disorders, which suggests that they might be used to treat COPD. There are currently no established biomarkers to diagnose COPD. COPD patients are shown to have altered RAGE and some of its ligands. Despite a lack of agreement on how smoking affects sRAGE levels, greater study is needed to discover whether or not this biomarker is stable. It was discovered that among the North Han Chinese,-429T > C is associated with COPD. COPD vulnerability is furthermore associated with the genetics of RAGE. To get a better diagnosis, population-based studies are needed. Finally, RAGE, AGE-RAGE, and sRAGE all impact COPD, and RAGE may be employed as a biomarker for diagnosis and management of COPD patients if more study supports this hypothesis.

Introduction

According to research conducted by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), chronic obstructive pulmonary disease (COPD) is a pervasive, preventable, and treatable disorder that is characterized by persistent respiratory symptoms and airflow limitation (1). COPD is distinguished by a chronic and irreversible blockage of the airways, which causes air to become trapped and leads to dyspnea during physical activity (2). The most common reasons of airflow restriction are smoking, being exposed to tobacco smoke in the environment, and a previous history of tuberculosis in the patient (2). The restriction in airflow that is characteristic of COPD is typically brought on by one or more of the following conditions: chronic bronchitis, emphysema, or a combination of these diseases (3). Continuous inhalation of toxic particulates causes a cycle of chronic inflammatory immune cell infiltration, tissue repair, and airway remodelling in COPD patients. This cycle ultimately results in a 4–40-fold increase in resistance in small airways (less than 2 mm in diameter) and narrowing of terminal bronchioles (4). Bronchi make up approximately 20% of the microscopic airways that are less than 2 mm in diameter, with bronchioles and alveolar ductal gaps making up the remaining 80% (5). The deterioration of the alveolar walls and the loss of alveolar support are two additional factors that contribute to the restriction of airflow in the lungs (6). These abnormalities make the rapid decline in forced expiratory volume in one second (FEV1) that is characteristic of COPD even more severe and contribute to the condition's airway blockage. Small airway disease (SAD), the most prominent symptom of COPD, has been the subject of extensive investigation. This condition's symptoms include the destruction of tiny bronchioles, inflammation, fibrosis, and mucus plugging up of the airways that are very small. Emphysema, also known as combined pulmonary fibrosis and emphysema (CPFE), is a condition that occurs when both COPD and pulmonary fibrosis are present in the same individual. Emphysema is defined by the loss of alveoli in the lung parenchyma rather than fibrosis. On the other hand, fibrosis seems to play a substantial role in the constriction of small airways (7).

Another important contributor to the development of COPD is the presence of a chronic inflammatory state, which is characterized by the invasion of the lung tissues and small airways by a large number of immune cells including neutrophils and lymphocytes (8). Neutrophils are essential cells in this process and are utilized as an indicator of the severity of COPD in patients (9). Matrix metalloproteinases and other enzymes that are released by neutrophils and macrophages are thought to play a role in the destruction of alveolar tissue (8). As the disease advances, adaptive immunity kicks in, which leads to increasing amounts of B and T lymphocytes (TH1 and cytotoxic T cells) in the lungs, which in turn amplifies neutrophil-mediated inflammation (2). COPD is a severe global public health issue because of its high incidence rate, morbidity, and death rate, as well as its influence on the socioeconomic system. Using a combination of systematic review and meta-analysis, Adeloye et al. (10) came up with an estimate for the global prevalence of the disease in 2010 of 11.7 percent (8.4 percent to 15.0 percent), which corresponded to 384 million cases. The incident presents itself differently depending on where you call home. It is also expected that COPD would take the third spot on the list of main causes of death around the world by the year 2030 (11).

Comorbidities, such as cardiovascular disease, osteoporosis, wasting of skeletal muscle, anemia, and mental problems, are also linked to COPD. These comorbidities are caused by the same underlying condition that causes COPD. Comorbidities produce a deterioration in quality of life, which in turn increases the risk of hospitalization and mortality (12). For this reason, the diagnosis and treatment of comorbidities is essential in the management of this disease. Underdiagnosis of the disease is another issue that needs to be addressed with COPD. The findings of the third National Health and Nutrition Examination Survey (NHANES III) indicate that approximately 63 percent of individuals who have lung function impairment have never been diagnosed with asthma or COPD (13).

If a sizeable fraction of patients with COPD who do not yet have a diagnosis receive one in a timely way, the prognosis will be significantly improved. It has been noted that a history of TB can result in the development of COPD during therapy or, in certain cases, following therapy (14). Other respiratory illnesses, such as tuberculosis, have been linked to an elevated risk of COPD. As a consequence of this, COPD is a complex and multifaceted illness. Despite the fact that FEV1 has been used in the diagnosis and follow-up of patients, it is not an acceptable metric for monitoring illness (15). There is currently a wealth of information available on a number of different biomarkers that can be used to diagnose COPD. These include a number of different biomarkers that can be found in sputum and blood, each of which has its own unique set of limitations (16). The finding of a potent biomarker in COPD patients seems to be of interest to researchers. It has been known for a long time that the receptor for advanced glycation end products, also known as RAGE, plays a role in the signaling of inflammatory diseases like COPD. The RAGE receptor belongs to the immunoglobulin superfamily and has the ability to bind to a wide variety of ligands (17). Since 1992, RAGE has been the subject of a significant amount of research because to the role that it plays in a variety of diseases, including neuronal degeneration in Alzheimer's disease and multiple sclerosis (18), as well as chronic inflammation, tumor progression, and diabetic consequences. According to Wu et al. (19), RAGE staining is significantly increased in formalin-fixed lung tissue from COPD patients who had lobectomy for bronchial cancer. These patients had undergone lobectomy to treat their malignancy. There was an increased staining on the alveolar walls (19), but not in the airways. As a consequence of this, the primary emphasis of this study has been placed on RAGE's likely role in COPD as well as its possible application as a biomarker. There has been a lot of talk on the role RAGE plays in COPD, as well as the AGE-RAGE axis, the soluble form of RAGE (sRAGE), and the RAGE genetics.

Rage's Components, Their Types, and Their Ligands

The Components of RAGE and Their Types

A gene that is located on chromosome 6p21 of the Class III major histocompatibility complex (MHC) in humans is responsible for encoding the RAGE protein. RAGE is a multiligand trans-membrane protein that has 404 amino acids. It has a size of 35 kilodaltons and is divided into three primary regions: extracellular, trans-membrane, and cytoplasmic. A single variable (V) domain and two constant domains (C1 and C2) make up the extracellular region, which is located 22 amino acids away from the signaling area on the N terminal.

These domains, which are analogous to the variable and constant sections of an immunoglobulin, are made up of the extracellular region. RAGE's ability to anchor itself to the cellular membrane is facilitated by its trans-membrane portion, which is composed of 21 amino acids; signal transmission is facilitated by its cytosolic tail, which is composed of 41 amino acids (20). The cytoplasmic portion of RAGE does not share any similarities with any of the recognized signaling domains. The three-dimensional crystal and solution structures of RAGE indicate that the Variable 1 (V1) and Constant 1 (C1) domains work together to generate a compact unit with a wide cationic surface that assists in the binding of RAGE ligands (21).

The RAGE gene contains a binding site for activator protein 1 (AP1), specificity protein 1 (SP1), and many other transcription factors. Among these other transcription factors is nuclear factor-kB (NF-kB), which is known to regulate RAGE gene transcription (21). The expression of RAGE mRNA can be inhibited thanks to a location in its polyadenylated 3'-untranslated region that is suitable for the microRNA (miRNA) known as miR-30 (22). It has been discovered that RAGE may be found in a wide variety of cells and tissues, and that it can be found being created in a constitutive manner during a number of stages of embryonic development. On the other hand, its expression decreases when a person enters adulthood, despite the fact that it has been observed to rise with age, notably in the lungs (23). The three isoforms of RAGE that can be generated by either alternative splicing or membrane-associated proteases are N-truncated RAGE, dominant-negative RAGE, and soluble RAGE. RAGE variations with N-truncated forms are unable to interact with ligands because they lack the V domain; dominant-negative RAGE is missing the cytosolic domain, and RAGE that is missing the trans-membrane domain is known as sRAGE. sRAGE in plasma stops RAGE ligands from interacting with one another, which helps decrease RAGE signals in a number of clinical conditions (24). sRAGE contributes to the neutralization of circulating ligands by competing with RAGE found on the cell surface for the ability to bind ligands (25). The AGEs, the many forms of AGEs, and the signaling cascades that are triggered when AGEs come into contact with receptors are graphically represented in the RAGE. Upper: A variety of exogenous sources of AGEs (including tobacco, cigarette, and dietary AGEs); the majority of pro-inflammatory AGEs are obtained from components of the diet. In the top right corner, some instances of well-studied AGEs are shown. These include CML, pentosidine, MG, and imidazolone. Lower middle: AGEs and their receptors communicate with one another using the RAGE acronym. RAGE is a protein that is 404 amino acids long and is divided into three primary regions: the extracellular area (which is located 22 amino acids away from the signaling area), the trans-membrane region (which is 21 amino acids long), and the cytosolic area (which is 41 amino acids long). TIRAP and MyD88 are responsible for triggering downstream signaling pathways after binding to the cytoplasmic domain of RAGE. Lower left: Other RAGE ligands (HMGB1, Mac1, S-100 proteins, amyloid, sheet fibrils, LPS, HSP70, C3a, and CpG DNA oligos), due to the fact that it detects the three-dimensional structures of the ligands rather than the individual aa.

Signaling that occurs downstream of the interaction between AGE and RAGE, which ultimately results in the development of illness. Mac1, macrophage-antigen-1; TIRAP, Toll-interleukin-1 receptor adapter protein; MyD88, myeloid differentiation main response 88; S-100 proteins, amyloid, sheet fibrils; LPS, lipopolysaccharides; HSP70, heat shock protein 70) TIRAP, Toll-interleukin-1 receptor adapter protein; MyD88, myeloid differentiation main reaction 88; Mac1, macrophage-antigen-1

Complete representation of the image

RAGE Ligands and Their Importance in COPD

RAGE is a multiligand receptor that can recognize three-dimensional configurations of ligands rather than just a single amino acid. It is also known as a pattern recognition receptor (PRR) (26), which is another name for this type of receptor. It has been discovered that both the expression of RAGE and the levels of its ligands are increased in the lungs, which provides evidence that RAGE signaling may play a role in COPD (27). Some examples of traditional and emerging RAGE ligands include advanced glycation end products (AGEs), lipopolysaccharides, high mobility group box protein 1 (HMGB1), heat shock protein (HSP70), macrophage-antigen-1 (Mac1), S-100 proteins, amyloid, C3a, and CpG DNA oligos (28). Depending on the type and nature of the RAGE ligand, signaling arrays can be accelerated. Additionally, RAGE (3) is able to identify a variety of ligands that are produced by cigarette smoke (CS).

The non-enzymatic glycoxidation (Maillard reaction) of lipids, nucleic acids, and proteins produces AGEs (29), which are a diverse group of highly oxidant and irreversibly generated compounds. AGEs are a part of the AGE family of chemicals. AGEs, also known as advanced lipoxidation end products (ALEs), are produced when lipids are subjected to peroxidation, which also results in the formation of these compounds. AGEs, which are N-carboxymethyllysine-modified proteins, were among of the initial RAGE ligands that were discovered (30). N-carboxy methyl-lysine (CML) and methylglyoxal (MG) are two compounds that are well-known to have resulted from interactions between glucose and lipids or between glucose and proteins, and they both function as AGE markers (31). Even though AGEs are produced by the body during normal metabolism, it is possible that high levels of AGEs in various bodily tissues and circulation could be harmful (32). Various heat treatments were utilized in order to improve the food's safety, taste, and bioavailability, which resulted in the Maillard reaction and the development of AGEs (33). AGEs binding to RAGE leads to inflammation because it activates the NF-B pathway. As a consequence of this, it is feasible that AGEs play a part in the progression of COPD through the process of inflammation (19).

Additional Ligands Derived from Other Sources

(Amphoterin) is represented by the hexadecimal code HMGB1.

HMGB1, also known as amphoterin, is a family of high-mobility non-histone nuclear proteins that are a part of the HMGB, HMGN, and HMGA superfamilies (34). This family is part of the HMGB, HMGN, and HMGA superfamilies. The protein, which consists of 215 amino acids, possesses two DNA-binding domains known as the A-box and the B-box, in addition to a highly conserved C-terminal tail that is present in virtually all eukaryotic cells (35). In its extracellular form, the protein functions as a damage-associated molecular pattern molecule (DAMP), which initiates an immune response by activating a variety of receptors, including AGE receptors (36). The COOH-terminal region of HMGB1 is beneficial to the interaction with RAGE. Patients with asthma and COPD have greater levels of HMGB1, which is a target molecule that can be utilized in the treatment of a wide variety of illnesses (37). It is possible for it to generate a positive feedback loop by interacting with RAGE and setting off an increase of the RAGE signal (38). In addition, the activation of the NF-B pathway that results from the interaction of HMGB1 and RAGE is what causes inflammation to continue. According to study conducted on mice with COPD (39), inhibiting NF-B activity by targeting it with a specific drug results in the downregulation of HMGB1 in the lung tissue.

One of the proteins that can be detected on the surface of macrophages is known as Macrophage-Antigen-1 (Mac 1).

Macrophage Ag 1 (Mac-1) is a beta 2 integrin that is present on monocytes, neutrophils, and macrophages. It has a role in adhesion, motility, phagocytosis, and chemotaxis (40). Macrophage Ag 1 is also known as Macrophage Ag 1. Mac-1, also known as M2, is composed of two subunits that are non-covalently coupled and measure 165 kilodaltons and 95 kilodaltons, respectively. These subunits are designated as CD11b or M and CD18 or 2 (165 kD) and CD18 or 2 (95 kD) respectively. Mac-1 has also been related to an oxidative burst in neutrophils, the activation of a phagocytic oxidase (PHOX), and the stimulation of the NF-B signaling pathway (41), among other things. Instead of being necessary on endothelial cells, the presence of RAGE on neutrophils is what's needed for Mac-1-associated neutrophil recruitment that's activated by HMGB1 (42). The interaction between RAGE and the ligand-binding I-domain of Mac-1 results in the formation of a complex that is attractive to leukocytes (43). In a recent investigation (44), researchers found that endothelial RAGE interacts to Mac-1 and intercellular adhesion molecule 1 (ICAM-1), which is necessary for the recruitment of leukocytes in the tissue. The development of RAGE for new therapeutic purposes might benefit from having prior understanding of interactions of this kind.

Proteins S-100

S100 proteins, which are the largest calcium-binding proteins of the EF-hand (helix E-loop-helix F) type, have a molecular weight that ranges from 9 to 13 kilodaltons but are very small. It is comprised of 25 separate components, 45 of which share substantial structural similarities. These control the proliferation of cells, the differentiation of cells, the death of cells, the homeostasis of Ca2+, the metabolic responses, and a number of inflammatory reactions. RAGE is involved in most of these processes (46), including the majority of them. In addition, it has been demonstrated that three S100 proteins—S100A8, S100A9, and S100A12—raise the expression of Mucin 5AC (MUC5AC), which is a major mucin in conducting airways. Excessive MUC5AC production is one of the known critical variables in obstructive airway pathophysiological processes (47), and these three S100 proteins have been proven to promote its expression. It would appear that the synthesis of MUC5AC is initiated upon the interaction of S100 proteins to TLR4 and RAGE receptors. According to the same study, RAGE could not be induced by S100A8 and S100A9 at any point during the experiment. It was shown that inhibiting the binding of S100A12 to RAGE had a selective effect on activation of extracellular signal related kinases (ERK) rather than activation of nuclear factor kappa B (NF-kB), indicating a more flexible relationship between these S100 proteins (47). According to the findings of this experiment (47), there is a connection between persistent neutrophilic inflammation and increased mucin production in airway disease. S100B is expressed in multiple cells of the neurological system and has been associated to respiratory disorders. Increased levels of S100B have been detected in patients with COPD, suggesting that it might be used as a biomarker for brain injury in COPD patients (48). S100B has been linked to a variety of respiratory ailments.

-Amyloid, in addition to -Sheet Fibrils

The amyloid-beta (A) peptide is a 4 kDa peptide that is formed from the larger-amyloid precursor protein (APP). It was initially recognized as the primary component of amyloid deposits in the brains of Alzheimer's disease (AD) patients, as well as persons with Down syndrome and other conditions (49). This interaction between RAGE and amyloid-beta (A) in brain endothelial cells produces signal molecules that lead to monocyte trafficking across the blood-brain barrier (BBB), and RAGE also promotes A transportation over the BBB, which leads to amyloid peptide accumulation in the brain (50). Several studies have found a connection between RAGE and the presence of amyloid in intracellular pathways as well as neurodegenerative diseases such as Alzheimer's disease. Patients with COPD and dementia have a greater rate of hospital mortality and severe sepsis than those without dementia, according to a study that looked at the association between COPD and dementia conducted by Liao et al. (51). In addition, a study conducted in China indicated that adults with cognitively normal COPD had significantly higher levels of blood A when compared to the control group, which suggests that AD-related pathologic abnormalities can be observed in cognitively normal COPD patients (52). It has been shown that hypoxia and respiratory infections can lead to an increase in the amount of A fibril that is deposited in COPD lungs, as well as raised serum levels and an impairment in clearance from the brain (53).

lipopolysaccharides.

The lipid A component of bacterial lipopolysaccharides (LPS) serves as the most prominent immunostimulatory center in a wide variety of eukaryotic species (54), making it one of the most powerful inducers of innate immunity. LPS are found in a wide range of eukaryotic species. In the presence of lipid A and LPS, RAGE is brought into direct contact, which in turn stimulates the generation of tumor necrosis factor (TNF) and activates NF-kB (28). In a model of newborn rats with acute lung damage, the RAGE/NF-B signaling pathway was discovered to have a role in the inflammatory lung damage that was caused by LPS (55). RAGE is also involved in the activation of NF-B, which itself is triggered into action by LPS and the hyperpermeability of endothelial cells (56). It is possible to use different RAGE ligands, such as LPS, as a biomarker because they all have the ability to change crucial biological processes that are associated with the activation of macrophages in a range of diseases.

Heat Shock Protein (HSP70)

HSP70 is a heat shock protein that is recognized by a number of plasma membrane receptors, including TLR4, TLR 2, cluster of differentiation 14 (CD), and CD40 (57). It takes part in the de novo folding and refolding of proteins and is essential for their proper function. This relationship stimulates NF-B signaling, which in turn leads to the generation of cytokines that contribute to inflammation and assists with the phagocytic activity of immune cells (57). According to research, HSP70 binds with RAGE, along with other ligands, and this ligation activates numerous signaling pathways (58). Other ligands also interact with RAGE. The expression of HSP70 in peripheral lung tissue rises with COPD and is made worse by cigarette smoking; this rise in HSP70 expression is subsequently linked to the severity of COPD and IL-8 levels (59). Additionally, in a case-control study on coal miners that included both HSP70 and HSP27, plasma levels of HSP70 were found to be higher, whereas plasma levels of HSP27 were found to be lower (60). According to the findings of the research (60), the source of the elevated plasma HSP70 could very well be the necrotic lung cells.

The Axis of Ageism and Rage

There are several different locations where AGEs can be obtained.

The generation of AGEs is influenced in equal measure by both endogenous and exogenous causes. The ingestion of carbohydrates, particularly fructose, as well as the oxidation of fatty acids and glucose are the two main contributors to the formation of endogenous AGEs. Exogenous AGEs can be created in a variety of ways, including through the use of heat in food preparation activities and through the act of smoking cigarettes (61). Consuming an excessive amount of dietary AGEs has been associated to inflammation as well as oxidative stress, both of which can lead to the development of a variety of different illnesses.

Signaling in the Downstream of the AGE-RAGE Interaction

RAGE is responsible for the activation of a variety of signaling pathways when it binds to its ligands. Because these pathways are reliant on the type of ligand, the environment of the cells, and the environment of the tissues, RAGE ligand binding can mediate a wide variety of cellular responses (58). According to a number of structural and biochemical research, there is a preassembly of RAGE in the plasma membrane in the absence of ligands. When the ligands are bound, RAGE dimerizes, which is necessary for the beginning of RAGE signal transduction (62); nevertheless, there is a RAGE preassembly in the plasma membrane in the absence of ligands. AGEs, cellular receptor RAGE, secretory RAGE, and endogenous secretory RAGE (esRAGE) are the four key components that make up the AGE-RAGE axis (63). In order for NF-B to be activated and for downstream signaling to occur, the intracellular domain of RAGE is required (63). Ras-ERK1/2, NADPH oxidase, stress-activated protein kinase/jun amino-terminal kinases, Ras, Src kinase, and p38 MAPK pathways, as well as PI3K/Akt, small GTPase Cdc42/Rac, RhoA-associated kinase, protein kinase C beta II, and glycogensynthase kin The interaction of AGE and RAGE on the plasma membrane has a negative impact on cellular functioning. It has been shown to induce NF-B, activator protein 1, cyclic AMP response element-binding (CREB) protein, early growth response-1 (EGR-1), signal transducers and activators of transcription 3 (STAT3), and apoptosis in neuronal, endothelial, lung, and muscle cells (58, 64). By interacting with the cytoplasmic domain of RAGE, a number of intracellular adaptor proteins, such as Toll-Interleukin-1 receptor adapter protein (TIRAP) and Myeloid differentiation primary response 88 (MyD88), have been demonstrated to initiate downstream signaling cascades (58). Other intracellular adaptor proteins, including as TIRAP and MyD88, have the same effect. There is no evidence to suggest that the cytoplasmic domain of RAGE contributes in any way to the activation of downstream signaling cascades. The AGE/RAGE signaling pathway has a number of diverse effects on the many different kinds of cells. AGE-RAGE signaling in endothelial cells can modulate apoptosis, oxidative stress, autophagy, inflammatory responses, and the transition of endothelial-mesenchymal cells, while the interaction also promotes the production of reactive oxygen species (ROS), proliferation, and calcification in smooth muscle cells (65). The AGE/RAGE signaling pathway is responsible for the promotion of proliferation, migration, inflammation, and death in lymphocytes and fibroblasts (65). According to research that was carried out on the murine J774 macrophage cell line (66), the production of IL-6 is triggered by the activation of NF-B after cells have been subjected to both AGE and LPS. In addition, exposure to AGE and LPS triggers signaling through RAGE and/or TLR4, which ultimately culminates in the production of ROS. It has also been demonstrated that ROS is required for the generation of IL-6 by J774 macrophages when AGE/LPS is present (66). As a consequence of this, the RAGE signaling pathway is significant in a wide range of human diseases, and its multiple stimulating stimuli have the potential to be utilized as therapeutic approaches or biomarkers for the diagnosis of sickness (20). Both the AGE-RAGE Axis and sRAGE are involved in COPD in some way.

As was indicated earlier, RAGE is a pro-inflammatory PRR. Several studies have identified RAGE as a critical mediator of a range of various diseases and conditions, including asthma, pulmonary fibrosis, allergic airway inflammation (AAI), lung cancer, COPD, and a number of other diseases and conditions (27). RAGE expression and its various ligands are found to be elevated in the lungs, but sRAGE expression is found to be diminished, indicating a potential role in the progression of COPD (27). AGEs cause damage to tissues in two different ways: first, they alter protein structures by covalently cross-linking them, and second, they activate a number of intracellular pathways that result in an increase in the production of inflammatory cytokines as well as the generation of reactive oxygen species (ROS) (23). In addition, the interaction between AGEs and RAGE suppresses the activation of ERK1/2 and SMAD that is caused by TGF, and it also upregulates Egr-1, which is what causes RAGE transcription to be stimulated in COPD (67). The most significant factor in the formation of AGEs is long-term exposure to oxidative stress, which has also been associated with COPD. It has been demonstrated that patients with COPD have an accumulation of AGEs in both the small airways and the lung parenchyma (19). AGEs have also been discovered to be more prevalent in the skin of COPD patients than in the skin of healthy smokers and non-smokers (68). Additional research found no significant variations in skin autofluorescence (SAF) values between COPD severity stages, suggesting that AGE generation during disease progression is not enhanced but may be accelerated during the COPD induction phase (69). It has also been demonstrated that AGEs build up to some degree in people as they age as a result of reactions to oxidative stress, and that the accumulation of these AGEs is enhanced by smoking (69). The development of emphysema brought on by cigarette smoke can be halted, according to the findings of Sanders and colleagues (3), by either deleting RAGE or suppressing its activity. The deletion of the RAGE gene has been shown to have an effect on the expression of a number of other significant genes that are involved in the progression of COPD. They also found that RAGE null animals exhibited lower levels of endoplasmic reticulum stress and oxidative damage, and this was the case even when the mice were subjected to cigarette smoke in a continuous manner.

sRAGE performs the function of a decoy receptor by eliminating circulating AGEs and preventing them from binding to membrane-bound RAGE, hence reducing the amount of damage done to lung tissue (70). In addition, sRAGE inhibits the synthesis of inflammatory cytokines that are dependent on AGE in mononuclear cells, while simultaneously boosting the development of alternatively activated macrophages and regulatory dendritic cells (DCs) (71). Morbini and colleagues (72) made the first observation of increased RAGE expression in the lungs of cigarette smokers with chronic bronchitis and emphysema in 2006. In 2011, Wu et al. (19) discovered higher RAGE expression in the alveolar walls and epithelia of COPD smokers' airways. It was revealed that the levels of AGEs and their receptors in bodily compartments such as bronchial biopsies, sputum, plasma, and skin were higher in the skin of COPD patients; however, the levels of sRAGE were found to be lower, which indicates that sRAGE has a protective impact on the skin (69). In addition, overexpression of RAGE leads to an increase in levels of nitric oxide (NO) and activity of NO synthase in COPD smokers. This phenomenon is accompanied by a decrease in total glutathione levels, which leads to an increase in NF-B activation (73).

In a case-control research on COPD (74), it was found that lower levels of sRAGE were substantially connected to the impairment of diffusing lung capacity as well as the extent of structural emphysema. When the plasma levels of sRAGE and HMGB1 of non-smokers, smokers without COPD, and smokers with COPD were compared, it was shown that smokers with and without COPD had considerably lower sRAGE plasma levels than non-smokers (75). As may be deduced from the above explanation, while the level of RAGE expression is increased in COPD, the level of sRAGE expression is decreased. The ratio of RAGE to sRAGE could be a role in the development of COPD or a biomarker for the disease (76). Both the TESRA (Treatment of Emphysema with a Selective Retinoid Agonist) and the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohorts discovered a correlation between sRAGE and a number of COPD clinical features.

To begin, sRAGE served as a marker that indicated the presence of emphysema in the patient. Lower levels of sRAGE were connected with emphysema, GOLD stage, and COPD status in the ECLIPSE cohort. In the TESRA cohort, lower levels of sRAGE were demonstrated to be a biomarker of lung diffusing capacity for carbon monoxide (DLCO) and lung density. In contrast, the ECLIPSE cohort found that lower levels of sRAGE were linked with emphysema. Even after taking into account all of the potential confounding factors, the associations remained statistically significant (77). According to Szewczyk et al. (78), sRAGE has the potential to be used in the identification of the frequent exacerbator phenotype and in the prediction of COPD exacerbations (ECOPD). Concerning the effect that smoking has on the amounts of circulating sRAGE, there is less agreement. Multiple studies have come to the conclusion that the levels of sRAGE in the blood of smokers and non-smokers are not significantly different from one another (79). Prasad et al. (80) examined the inconsistency of the sRAGE level as a result of the effects of cigarette smoking. According to the findings of one study (81) smoking, on the other hand, leads to a precipitous and significant decrease in serum sRAGE. In addition to this, it has been demonstrated that smoking has a rapid and fleeting affect on the serum sRAGE level (81). A number of writers have reported and advised that additional research is required before sRAGE can be considered a viable biomarker for COPD (82). This is due to the fact that the results of these studies are inconsistent with one another. To elucidate the acute and chronic impacts of smoking and to make it a stable biomarker, additional research is required to discover whether or not there is a consistent increase in serum sRAGE levels as a result of smoking among the different groups of people.

Additional COPD Biomarkers and Risk Factors

When tobacco smoke or other toxic gases are breathed in, a chain reaction of pulmonary inflammation is set off. This chain reaction involves many different types of cells and inflammatory mediators, such as C-reactive protein (CRP), fibrinogen, tumor necrosis factor-alpha, and a large number of interleukins. All of these cells and mediators contribute to tissue damage and alter the structure of the airways (83). In spite of the fact that the FEV1 lung function test is the most popular method for monitoring the progression of COPD, additional circulating biomarkers in the peripheral blood of COPD patients can also be used to evaluate the severity of the condition.

Several research have been conducted to investigate a variety of COPD biomarkers, including the presence of the disease, its several manifestations, and the therapeutic response. Emphysema is associated with lower levels of clara cell secretory protein-16 (CC-16) and sRAGE, whereas COPD exacerbations and death are associated with higher levels of C-reactive protein (CRP), fibrinogen, leucocyte count, and interleukins (84).

Table 1 contains the results of research conducted by Hurst and colleagues (85) about the diagnosis and treatment of COPD using a total of 36 biomarkers. In addition to that, they looked at CRP, which is a pentameric acute phase reactant protein that is produced by the liver. It is produced primarily by IL-6, the amount of which rises in response to inflammation. According to Plata and colleagues (86), CRP levels were found to be higher in individuals with moderate to severe COPD, independent of whether or not they smoked cigarettes. A correlation between CRP and severe COPD clinical outcomes was discovered by Fermont and colleagues in a study that included both a comprehensive review and a meta-analysis (87). According to the findings of another study (88), a correlation exists between CRP and fibrinogen and an elevated risk of mortality in COPD patients. Fibrinogen is an acute phase protein that has a molecular weight of 340 kilodaltons and is a homodimeric glycoprotein. It is primarily produced in hepatocytes and circulates in the bloodstream at a concentration of between 2 and 5 mg/mL (89). Plasma fibrinogen is the most promising COPD measure, and it is also the only blood-based drug development biomarker that has been approved by the FDA for patients who have a high mortality risk (90). There is no evidence that fibrinogen causes a loss in lung function, despite the fact that it has been associated to the severity of COPD. Oral corticosteroids bring about a decrease in fibrinogen during COPD exacerbations, although p38 mitogen-activated protein kinase inhibitors bring about a decrease in fibrinogen in those who have a stable sickness (91). An increased risk of COPD was shown to be associated with high fibrinogen levels, according to the findings of another study (92). Additional important indications of COPD include interleukin-6, interleukin-8, and tumor necrosis factor. T cells, monocytes, fibroblasts, and endothelial cells are all responsible for the production of the cytokine known as interleukin-6 (IL-6), which is a pleiotropic cytokine that helps regulate immune and inflammatory responses. The production of hepatic acute phase protein is increased when IL-6 is present, which is one factor that contributes to a deterioration in health. Patients with COPD reported significantly greater levels of IL-6 in their sputum, bronchoalveolar lavage (BAL), and concentrated exhaled air (93). According to the findings of a study that was carried out by Moraes et al. (83), those who suffered from COPD had greater blood levels of IL-6 and IL-8 than those who were in the control group. Individuals with a body mass index (BMI) of less than 21 kg/m2 who also had a high smoking load and bronchitis had higher levels of IL-6, but IL-8 was only observed in the group with the most COPD exacerbations.

The Genetics of COPD and RAGE

Interactions between genes and the environment play a critical role in the development of airway diseases such as asthma and COPD (94, 95). Several genes have been identified as being important to COPD (96). Alpha-antitrypsin (AAT) insufficiency was discovered to be a genetic risk factor during the early stages of research into the role of genetics in COPD. To this day, it remains the only genetic subtype for which there is a specific treatment (97). Several genome-wide association studies (GWAS) on lung function and airway obstruction illnesses have now found a number of genetic loci connected to these conditions. These loci have been linked to a variety of lung function and airway obstruction illnesses. In 2009, Pillai et al. (98) carried out the first COPD GWAS in a case-control cohort. They discovered a significant association between COPD and the 15q25 region CHRNA3/CHRNA5/IREB2. Three genome-wide association studies (GWASs) were carried out in 2010, 2012, and 2014 by Cho et al. (99,100,101). These studies identified new genetic loci associated to COPD, including the 4q22 regions FAM13A, 1q41, TGFB2, and HHIP spanning the 4q31 region. In the genome-wide association study (GWAS) that Cho et al. (101) carried out in 2014, they combined data from the ECLIPSE study, the National Emphysema Treatment Trial/Normative Aging Study (NETT/NAS), and the GenKOLS study. This allowed them to examine all moderate to severe cases. They confirmed the association between the previously identified loci and a newly discovered locus 14q32 that was close to RIN3. After then, other genome-wide association studies on COPD carried out by Chen et al. (102), Hobbs et al. (103), and Burkart et al. (104) discovered additional loci that are associated to COPD and are significant on a genome-wide scale. In order to gain a deeper understanding of the role that genetics play in COPD, the GWAS loci that have already been revealed are undergoing extensive investigation. In the case of other ailments affecting the airways, such as asthma, putative gene variations have been examined in great detail. In population-based case-control studies (105), it has been shown that a strong correlation exists between the variants in genes that cause asthma and the disease itself. Recent research (96, 106) has shed light on the genetics of COPD as well as the connections between the various loci that have been found by population-based GWAS and meta-analysis studies. GWAS did find some relevant genetic areas connected to COPD, but due to the limitations of this research, additional methods are required to acquire a more thorough understanding of critical genetic areas related to COPD. GWAS did find some important genetic areas related to COPD. In recent years, a variety of approaches that rely on sequencing and network analysis have provided new insights into the genetics of COPD (107). The RAGE gene, which is encoded by the AGER gene and is located at 6p.21.3, is highly polymorphic and has been related with the pathophysiology of COPD (108, 109). This information was reported in a prior study. It is well established that oxidative and inflammatory stresses are responsible for inducing AGER expression. When compared to other tissues, AGER is expressed at a higher level in lung tissues; furthermore, the accumulation of RAGE ligands contributes to an increase in the expression of AGER in COPD (110, 111). In addition to that, different forms of the AGER gene have been associated with a wide variety of other diseases (112). First, in a meta-analysis of substantial population-based GWAS (113, 114), single nucleotide polymorphisms (SNPs) of the AGER gene were found to be associated to lung functions.

According to findings from research that was carried out and published in 2009, the locus known as 6p21 (AGER) is one of five distinct genomic regions that are connected with pulmonary function. In addition, the research discovered a connection between 6p21 and FEV1/FEVC in the DAAM2 gene (113), which stands for the disheveled associated activator of morphogenesis gene. rs2070600 was demonstrated to be a sentinel SNP for FEV1/FVC in the AGER study as well. However, in a further examination, it was shown that AGER did not play a significant role in the case of COPD. This was the case despite the fact that it was found to have a strong correlation with FEV1/FVC but no obvious association with FEV1. One possible explanation for the differences in these results is that the statistical power was insufficient (115).

The 5' flanking region of AGER was cloned, and sequencing it, yielded the discovery of a single major transcriptional start site. It has been discovered that the 1543/587 region of the AGER gene plays a part in the regulation of promoter responsiveness. The regulation of RAGE expression at its various stages was shown to be controlled by two significant NF-kB sites that were found inside the promoter (116). sRAGE levels have been reported to be quite low in COPD patients, according to a number of different analyses. In a study that included two well-characterized, separate, and large cohorts of COPD patients enrolled in TESRA and ECLIPSE (77), sRAGE levels were associated to airflow limitation, CT defined emphysema, and DLCO. In addition, the variants of the AGER gene known as rs2071288 and rs2070600 were found to have a significant relationship with sRAGE levels. Because there were insufficient data for rs2071288 to be analyzed using ECLIPSE, it only showed evidence of interaction in TESRA with the levels of DLCO and sRAGE. It was found that the genetic marker rs2070600 was linked with sRAGE levels in all of these cohorts (77). In order to investigate the possible links between COPD and three different AGER variations, specifically 374T/A, 429T/C, and G82S, 216 Chinese patients participated in a case-control research. Only the G82S form of the protein that AGER produces is associated with COPD. The other two forms are not. They discovered that the G82S variant is responsible for the development of COPD and that the GS genotype is a more significant risk factor among smokers (108). In a case-control research conducted on the Chinese Han population, Guo et al. (117) discovered a connection between the genetic variant rs2070600 and COPD. Later on, Miller et al. (109) used allele-specific RAGE cell models to investigate smokers in the UK. They discovered that the variant rs2070600 (G82S) modifies the ligand-dependent release of sRAGE in the airways. Smokers in the United Kingdom who have the rs2070600T genotype, which correlates to serine82, are less likely to develop COPD than those who do not have this genotype because they have better lung function and lower serum sRAGE levels. It has been demonstrated that the AGER variant known as rs2070600 is connected to COPD in a number of different groups and that it has implications across the genome (103). Using information gathered from GWAS, meta-analyses, and other forms of genetic research, Hall et al. (118) investigated the genetics underlying COPD and asthma. In the same body of study (118), the researchers also revealed how the AGER mutation rs2070600 affected lung function and COPD.

Niu et al. (119) conducted research to determine whether or not certain variants of the AGER gene (rs1800625, rs1800624, rs2070600, rs184003, and rs2071288) are associated with COPD and asthma in the northern Han Chinese population. In the population that was evaluated for COPD, a promoter variant known as rs1800625,-429T > C was found to be associated with an increased risk of developing the disease. On the other hand, the findings of this analysis contrast with those of previous research carried out by Li et al. (108) in the population of southern China. In that earlier examination, rs1800625 did not exhibit a significant link, whereas G82S did. The inconsistencies have been attributed to both the climate and the cultural differences that exist among the people (119). The influence of the AGER splicing process, in addition to the variants, has been examined. A recent study focused on the AGER gene examined the expression of all of its splice sites in relation to overall gene expression in smokers and persons who had never smoked in order to identify the amount of alternative splicing that occurs in each of these groups of people (120). According to the findings of the study, although overall expression of the AGER gene is found to be lower in smokers, the component of AGER that is connected to the production of the anti-inflammatory esRAGE protein is found to be higher (120). This led to the discovery of new information regarding the molecular defense system that the body has against the detrimental effects of smoking.

Conclusion

RAGE plays a significant role in a wide number of intracellular activities, one of which is the binding of RAGE to a wide variety of ligands. Interactions between RAGE and its ligands stimulate downstream signaling pathways that have been connected to a range of diseases, including chronic obstructive pulmonary disease (COPD). In addition, it has been discovered that inhibitors of RAGE and its signaling pathways play a role in the pathophysiology of a range of diseases, which suggests that they could be used to treat COPD (121, 122). COPD is usually diagnosed incorrectly because there are not enough accurate and consistent biomarkers available. Researchers have found that patients with COPD had altered levels of RAGE, sRAGE, and several of its ligands. There is continuing research into sRAGE as a potential biomarker for COPD. However, because the studies that have been done on the subject have come to conflicting conclusions on the effect that smoking has on sRAGE levels, more research is required to establish whether or not this biomarker is reliable. The promoter mutation known as 429T > C was discovered to be associated with COPD in a study that was carried out not too long ago on the northern Han Chinese population (119). There is growing evidence that RAGE genetics play a role in the susceptibility of certain groups to COPD. Additional study that focuses on populations is required so that the illness can be diagnosed more accurately. RAGE might be employed as a biomarker for the diagnosis and management of COPD patients, depending on the outcomes of future research (123-274). Finally, the AGE-RAGE axis, sRAGE, and RAGE genetics all play a role in COPD. RAGE might also be used to treat COPD patients.

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