Infectious Mechanisms Regulating Susceptibility to Acute Exacerbations of COPD

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Introduction

Acute exacerbations of COPD (AECOPD) are defined by clinical criteria, outlined in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. These include an acute increase in one or more of the following cardinal symptoms, beyond day to day variability: dyspnea, increased frequency or severity of cough and increased volume or change in character of sputum, which represent an acute increase in airway inflammation. The role of infection in the pathogenesis of COPD, acute exacerbation and disease progression has been a clinical and research question for many years, and the pendulum has swung from infection as a major cause of acute exacerbation and COPD (British Hypothesis) [2], to infection as an unrelated epiphomenon in acute exacerbation [3–5], and back again to infection as integral in the development of AECOPD and likely an important contributor to COPD progression [6–19]. Upwards of 80 % of AECOPD are driven by infectious stimuli, with 40–50 % associated with bacterial infection and 30–50 % associated with acute viral infection, with some exacerbations having dual bacterial and viral causation [20]. Much of the advancement in our understanding of the role of infection is AECOPD is due to the advancement of clinical and research tools that have allowed researchers to accurately characterize the microbial pathogens, and better understand the host-pathogen interactions (Table 1).

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Table 1 Microbial pathogens in COPD [139]

Microbe	Role in exacerbations	Role in stable disease
Bacteria		
Haemophilus influenzae	20–30 % of exacerbations	Major pathogen
Streptococcus pneumoniae	10–15 % of exacerbations	Minor role
Moraxella catarrhalis	10–15 % of exacerbations	Minor role
Pseudomonas aeruginosa.	5–10 % of exacerbations, prevalent in advanced disease	Likely important in advanced disease
Enterobacteriaceae	Isolated in advanced disease, pathogenic significance undefined	Undefined
Haemophilus haemolyticus	Isolated frequently, unlikely cause	Unlikely
Haemophilus parainfluenzae	Isolated frequently, unlikely cause	Unlikely
Staphylococcus aureus	Isolated infrequently, unlikely cause	Unlikely
Viruses		
Rhinovirus	20–25 % of exacerbations	Unlikely
Parainfluenza	5–10 % of exacerbations	Unlikely
Influenza	5–10 % of exacerbations	Unlikely
Respiratory syncytial virus	5–10 % of exacerbations	Controversial
Coronavirus	5–10 % of exacerbations	Unlikely
Adenovirus	3–5 % of exacerbations	Latent infection seen, pathogenic significance undefined
Human metapneumovirus	3–5 % of exacerbations	Unlikely
Atypical Bacteria		
Chlamydophila pneumoniae	3–5 % of exacerbations	Commonly detected, pathogenic significance undefined
Mycoplasma pneumoniae	1–2 %	Unlikely
Fungi		
Pneumocystis jiroveci	Undefined	Commonly detected, pathogenic significance undefined

With the more recent scientific acceptance of infectious organisms, both viral and bacterial, as significant players in AECOPD, the host response in patients with COPD must also be questioned. The airways of patients with COPD have significant infiltration of inflammatory cells (polymorphonuclear cells and CD8+ T lymphocytes) and much higher numbers of alveolar macrophages than are seen in healthy persons [21–27]. The nature of the inflammatory infiltrate suggests and supports the findings of both viral and bacterial infections, with recruitment of immune cells pertinent to both the innate and adaptive immune response. Despite the recruitment of appropriate effector immune cells, in many patients with advanced stage COPD (GOLD III-IV), there is persistent presence of pathogens in the airway, rather than eradication [19, 28], suggesting an impaired host response to infection. Numerous studies have delineated impaired macrophage phagocytosis and cytokine secretion [29–31], impaired humoral immune response to infection [32–37] and impaired T-lymphocyte responses [38]. The mechanisms of this impaired responsiveness of both innate and adaptive immune cells to infection has not been clearly delineated, and remains a target of investigation.

Bacterial Etiology of AECOPD

Although the temporal association of bacterial presence in the airway and COPD exacerbation was first recognized in the early 1950s, there was divergence away from bacterial causation of AECOPD during the 1970s and 1980s related to several observations. There were no differences observed in sputum bacterial isolation rates (at a species level) in between stable state and exacerbations, and studies of immune response studies to bacterial pathogens and placebo controlled antibiotic trials showed inconsistent and contradictory results [4, 39]. Beginning in 1992, multiple investigators began to recognize an effect of bacterial infection and colonization in stable COPD [11, 17, 32, 40–45], but a direct association with AECOPD was not initially recognized. The bacterial isolation in these early studies was done predominantly by sputum culture, and as such, most pathogens isolated can be nasopharyngeal commensals in healthy adults, raising the issue of specimen contamination. In addition, the older studies could not differentiate among strains of a pathogenic species, assuming that all strains isolated from sputum over time were identical. Advancing diagnostic techniques of bronchoscopy with protected specimen brushes and bronchoalveolar lavage, as well as molecular bacterial typing allowed identification of bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa* and others at potentially pathogenic concentrations) in the distal airways in stable COPD [9, 17, 28, 40, 41, 46–51], with more severe GOLD stage disease being associated with identification of *Pseudomonas.* Subsequent studies went on to associate colonization with more severe spirometric airflow obstruction [43]. Expanding on the recognition of bacterial colonization during stable COPD, it was recognized that the prevalence of bacteria in the lower respiratory tract increased significantly during AECOPD as compared to stable COPD, when sampled by bronchoscopy [10, 46–48, 52]. Scientific advancement led to the recognition that changes in the overall numbers of potentially pathogenic bacteria in the airways between periods of colonization and acute exacerbation mattered less than the acquisition of a new strain of bacteria [10, 15–17, 28, 47]. Acquisition of a new strain of bacteria (*H. influenzae, M. catarrhalis, S. pneumoniae* or *P. aeruginosa*) was associated with a greater likelihood of symptoms of an exacerbation, increased inflammatory markers both locally and systemically (TNF-α, IL-8, IL-6, CRP, Neutrophil elastase) and development of a specific host immune response to the infecting pathogen [8, 10, 11, 15, 28, 47]. Although some authors have described a link between the presence of *Chlamydia penumoniae, Mycoplasma pneumoniae* and *Legionella* infection and AECOPD [53–55], these studies measured single serologic titers rather than serologic conversion, and an additional respiratory pathogen was often identified. Studies using serologic conversion as a diagnostic criterion or molecular detection to identify the presence of atypical bacterial DNA in sputa [56] during AECOPD indicate only a minor role of these bacteria in exacerbations, often with co-infection with typical bacterial pathogens (Table 1).

The significant role of bacteria in both pathogenesis of COPD and AECOPD, combined with recent data from improved microbiological detection techniques that

the normal lung is not sterile, has led to recent research focused on understanding the microbiome of the lung in stable COPD and during exacerbations. Two groups recently published data using PhyloChip microarray analysis and quantitative PCR and pyrosequencing of the variable regions of the 16S rDNA. The first study identified the bacterial diversity seen during severe AECOPD requiring intubation in eight patients [57], noting significant bacterial richness (as defined by the number of bacterial taxa detected) that waned with prolonged intubation. The common 'core' of 75 bacterial taxa representing 27 classified bacterial families was identified in all patients studied. This group included members of the Pseudomonadaceae, Enterobacteriaceae, Campylobacteraceae and Helicobacteraceae families, among others. The majority of the bacteria belonged to the Proteobacteria phylum, with smaller contributions from Firmicutes and Bacteroidetes. The second study addressed the effects of cigarette smoke on the bacterial diversity in comparing healthy smokers to smokers with COPD to non-smokers [58]. The investigators demonstrated lung resident bacteria in all groups, and the dominant phyla were Proteobacteria, Firmicutes and Bacteroidetes, as noted in the first study. There was heterogeneity in the bacterial communities in the non-smoker, healthy smoker and mild COPD patients, which was lost in the patients with moderate and severe COPD. Within each patient, geographic differences in bacterial heterogeneity were also noted, suggesting micro-anatomic differences in bacterial communities within the lung. Whether the micro-anatomic, spatially distinct bacterial communities within the lung or the overall airway bacterial diversity represent mechanisms of disease progression or contribute to AECOPD remains to be determined.

Viral Infections in AECOPD

Respiratory tract viral infections have long been suspected as capable of inciting inflammation sufficient to generate an acute exacerbation of COPD. The diagnosis of viral infection was initially done by cell culture and serologic methods, with more recent studies detecting viral infection by PCR in either sputa, BAL or nasopharyngeal swabs, with the greatest recovery seen in sputa as compared to nasopharyngeal swabs [59, 60]. The most commonly recovered viruses (varying in prevalence in various studies) in AECOPD using the more sensitive PCR detection methods were influenza, rhinovirus, respiratory synctial virus (RSV), parainfluenza, with the majority of infections due to rhinovirus. These viruses were also found in stable COPD, and it is not clear if those findings were subclinical infection or colonization, as there were no symptoms of active infection in the preceding 30 days [13, 14, 59–62]. Therefore, the presence of viruses in respiratory samples detected by sensitive techniques such as PCR may not always correlate with an acute infection and should be interpreted in its clinical context.

Though there are studies that suggest viral exacerbations are more severe or protracted than non-viral exacerbations [13, 14, 62], these studies did not study bacterial infection concurrently. Virally-induced AECOPD were associated with higher airway levels of IL-6 as compared to AECOPD in which virus was not detected [61,

63, 64]. The presence of eosinophils in sputa samples recovered from AECOPD of viral etiology also differs from the inflammatory cells present during bacterial or non-infectious AECOPD [11]. In studies that have examined viral and bacterial infection simultaneously, presence of dual infections are associated with increased clinical severity of exacerbation [62].

Altered Host Defense to Infectious Challenge in COPD

COPD is now recognized as a state of chronic inflammation, with periods of exacerbation marking acute increases in this inflammation, both locally and systemically. Both pathogenic and host factors determine the outcome of the acquisition of a bacterial strain. Approximately half of the acquisitions of pathogenic bacteria lead to an exacerbation. Pathogen virulence is likely to also play a role in determining which acquisitions lead to acute exacerbations. Strains of *nontypeable H. influenzae* (NTHI) that are associated with exacerbations have more effective adherence to airway epithelium and result in increased IL-6 and IL-8 secretion in in vitro and mouse models, as compared to those strains associated with colonization [48, 65, 66], and demonstrated higher levels of neutrophil recruitment to the airway [9, 10, 65].

There are also significant differences in the host response to different pathogens. Patients with COPD are able to eradicate *Moraxella catarrhalis* and *Streptococcus pneumoniae* from the airway quite well following exacerbations, most likely related to an effective immune response [16, 37]. However, though antibody responses develop to NTHI or *Pseudomonas* following exacerbations, effective clearance is often not seen with these pathogens.

Alterations in Innate Immune Responses to Infectious Pathogens in COPD

The innate immune response is the most immediately responsive immune defense to the invading pathogen, and both anatomic and functional barriers (mucociliary clearance, epithelial tight junctions), as well as cellular immunity (recognition of invading pathogens via germline encoded pathogen recognition receptors (TLR, NOD)) and soluble mediators (SLPI, lysozyme, collectins). This initial innate response is multifaceted, including epithelial cells of the upper and lower airways, airway resident macrophages, dendritic cells and recruited polymorphonuclear cells.

Impaired Macrophage Phagocytosis

Multiple authors have demonstrated an association between increased inflammatory cytokines present in the airways of patients with COPD and bacterial infection and

colonization of the lower airway [7, 9, 52, 67]. The dominant cytokines involved, IL-6, IL-8, TNF-α are also seen in AECOPD due to infection, and suggest a common innate immune response at the time of exacerbation. The source of these cytokines may be from either the airway epithelium, after adhesion and invasion by bacterial or viral pathogens, or from the alveolar macrophage after recognition of pathogen associated molecular patterns (PAMP's) and activation of toll like receptors (TLR). Alveolar macrophages are also less able to phagocytose bacteria in patients with COPD [29, 30, 68] and have a less robust response to bacterial proteins, specifically OMP6 and LOS of NTHI [29], and are less able to clear apoptotic cells from the airway [69]. Both disease and cigarette smoke exposure contribute to this relative hypo-responsiveness, as alveolar macrophages from smokers who had ceased smoking have better phagocytic ability than those who continue to smoke [30, 31], and both were reduced relative to healthy controls. The ongoing presence of apoptotic cells in the airway may function as a source of endogenous ligand for inappropriate self-directed immune responses.

Mucociliary Clearance

Normal mucociliary clearance (MCC) maintains the sterility of the tracheobronchial tree by effectively trapping and clearing inhaled and micro-aspirated particles, including infectious pathogens [70, 71] Smoking disrupts MCC by inducing structural abnormalities in the ciliary apparatus [72]. Other investigators have shown that impairment of MCC is universal, though variable in moderate-to-heavy smokers [73]. Development of chronic bronchitis and airway obstruction in smokers is associated with further deterioration in MCC [71, 73, 74]. Infiltrating neutrophils likely contribute to MCC impairment, probably mediated by increased mucus production (mediated through proteolytic cleavage of TGFα and increased EGF receptor (EGFR) binding), reduced ciliary beating and reduced viscoelastic properties of mucus [75].

Soluble IgA

Tobacco smoke also has effects on airway levels of soluble IgA. The literature has demonstrated conflicting results [76–81], and though these trials were quite heterogenous, they supported the issue of the importance of secreted airway immunity. The more recent trials support geographic changes in the structural integrity of the lung, demonstrating localized areas of IgA deficiency associated with altered epithelial cell integrity, and reduced pIgR expression (polymeric IgG receptor), which is required for trancytosis of the structural components of the IgA molecule from the basolateral to the apical surface of the epithelial cell. The reduction in

expression of the IgA transport system was supported by findings of reduced total IgA in the BAL of patients with COPD [81, 82]. In contrast, the systemic IgA response elicited in the bronchial mucosa seems preserved in COPD, as demonstrated in COPD patients with *Chlamydia pneumoniae* infection [78].

Antimicrobial Peptides

An increasing number of polypeptides with antimicrobial activity have been identified in the airway surface fluid that may play an important role in host defense in the respiratory tract [83–85]. One major group of these peptides is cationic polypeptides. These include lysozyme, which is lytic to many bacterial membranes; lactoferrin, which excludes iron from bacterial metabolism; defensins, which are released from leukocytes and respiratory epithelial cells; and the cathelicidin family of proteins, (of which only LL-37 is found in humans), which are present in specific granules of neutrophils and airway epithelial cells [86–96]. Deficiency in salivary lysozyme and sputum secretory leukocyte protease inhibitor (SLPI) has been related to more frequent exacerbations [15, 97–99]. In patients with normal baseline SLPI levels, these levels drop significantly at the time of infective exacerbations, which return to normal after resolution of the exacerbation [89]. Lower levels of lysozyme and lactoferrin are noted with both colonization and infective exacerbations with NTHI and *Moraxella catarrhalis*, as compared to pre-acquisition levels [89]. In contrast, LL-37 levels have been shown to increase in the presence of airway bacteria, both in states of colonization as well as infection, with greater increases during infective exacerbation, as compared to colonization [89]. The divergent responses of the airway anti-microbial peptides during infective exacerbation underscores the fundamental importance of host-pathogen interactions. Lower levels may be related to consumption in the face of infection, or a mechanism of bacterial evasion of immune clearance. The role of tobacco smoke specifically on the antimicrobial peptides has not been well studied, though murine models suggest that at least with regards to SLPI, the presence of tobacco smoke was deleterious to the protease inhibitory activity [100].

Another important group of antimicrobial polypeptides are the collectins. Surfactant protein-A (SP-A) and surfactant protein-D (SP-D) are collectins with broad spectrum antimicrobial activity that also promote phagocytosis of particulates by alveolar macrophages [101]. Concentrations of SP-A and SP-D are decreased in smokers, and are further decreased in association with emphysema [102, 103], a finding noted in both human and animal models [104]. Mannose binding lectin (MBL) deficiency has been strongly implicated in infection and COPD exacerbations, with an odds ratio of 4.9 for infective exacerbations, as compared to normal MBL levels [105]. Though considerable progress has been made in understanding the basic biology of these polypeptides, their role in response to respiratory infections and in the pathogenesis of COPD is still poorly understood.

Table 2 Bacterial ligands from COPD pathogens that trigger signal transduction pathways in the human respiratory tract through pattern recognition receptors [139]

Pattern recognition receptor	Bacterial ligand	Bacterial species
TLR-1		*S. pneumoniae*
TLR-2	P6	*H. influenzae*
	P2 porin	
	Lipoproteins	
	Lipoteichoic acid	*S. pneumoniae*
	Pneumolysin	
TLR-4	Lipooligosaccharide	*H. influenzae*
		M. catarrhalis
		P. aeruginosa
	Pneumolysin	*S. pneumoniae*
	Lipoteichoic acid	
CD-14	Lipooligosaccharide	*H. influenzae*
LPS binding protein	Lipooligosaccharide	*H. influenzae*
	Peptidoglycan	*S. pneumoniae*
TLR-5	Flagellin	*P. aeruginosa*
TLR-7		*H. influenzae*
TLR-9	CpG dinucleotides	*S. pneumoniae*
Nod1, Nod2	UspA1	*M. catarrhalis*
	Peptidoglycan	*H. influenzae*
		S. pneumoniae
CEACAM1	UspA1	*M. catarrhalis*
Platelet activating factor receptor	Pneumolysin	*S. pneumoniae*
	Lipoteichoic acid	
	UspA2	*M. catarrhalis*
C-reactive protein	Phosphorylcholine	*S. pneumoniae*

TLR toll like receptor
LPS lipopolysaccharide
Nod nucleotide-binding oligomerization domain
UspA Ubiquitous surface protein
CEACAM Carcinoembryonic antigen-related cellular adhesion molecule

Pattern Recognition Receptor Expression

Pattern recognition receptors, of which the transmembrane toll-like receptors (TLR) and cytosolic nucleotide-binding oligomerization domain (NOD) like receptors (NLR) and RIG-I-like receptors predominate, are germline encoded receptors that recognize conserved sequences present on mutiple infectious organisms (pathogen associated molecular patterns, PAMP). This non-specific recognition provides an immediate immune response (innate), without the initial requirement for effector memory responses (Table 2).

Recent evidence suggests that TLR signaling is not restricted to microorganism particles but that TLRs recognize a wide variety of signals such as heat shock proteins [106], hyaluronan fragments [107], oxidative stress [108], and neutrophil

elastase [109, 110]. This non-classical activation (or damage-associated molecular pattern (DAMP) activation), may explain the pro-inflammatory state seen in cigarette smoking healthy controls. Recent data defines a direct effect of cigarette smoke induced MMP and CXCL-8 secretion from epithelial cells that is mediated by activation of TLR4 [111–113], and independent of LPS present in the extract. This was neutralized by the addition of anti-oxidants, suggesting an oxidant stress induced activation of TLR4.

The classical pattern-recognition role for toll-like receptors through PAMP recognition, are affected by both tobacco smoke as well as the development of COPD, both on antigen presenting cells (dendritic cells and alveolar macrophages) as well as the airway epithelium. Decreased levels of TLR2 and TLR4 on both airway epithelial cells as well as alveolar macrophages have been demonstrated in the presence of cigarette smoke as well as in patients with established COPD [114–116]. It has been presumed in the past that lower levels of these TLR's contribute to impaired immune responses to pathogenic bacteria, but in the face of newer data demonstrating activation by reactive oxygen species present in cigarette smoke, these may as yet represent downregulation in an attempt to curb detrimental inflammatory processes, though this has yet to be investigated. The presence of soluble forms of both TLR 2 and TLR4, as well as CD14 are an emerging field of study, and how levels of these proteins factor into the lower levels of cell surface expression is not yet defined.

Natural Killer Cells

Natural killer cells are classified as lymphocytes based on their morphology, their lack of antigen specific receptors puts their responses within the realm of the innate immune response [117]. These cells have been found within the airways as well as the lung parenchyma, and act as cytolytic effector lymphocytes, inducing cell death in infected and structural cells in the lung [118, 119] through secretion of perforins and granzyme B. Increased numbers of $CD3^{-}CD56^{+}$ NK cells and NKT cells ($CD3^{+}CD56^{+}$) have been noted in the induced sputum of patients with COPD as compared to healthy smokers or normal controls [119]. The $CD56^{+}$ cells of patients with COPD expressed greater cytolytic activity, which inversely correlated with FEV1 [119].

Dendritic Cells

Dendritic cells are the canonical antigen presenting cells that link the innate and adaptive immune responses. Dendritic cells act both locally upon antigen recognition (cytokine secretion) and in the lymphoid follicle, after migration from the primary site. Dendritic cells function primarily by promoting differentiation of the $CD4^{+}$ T helper lymphocytes, as well as $CD8^{+}$ cytotoxicity [120].

Tobacco smoke has been associated with an expansion of dendritic cell populations in the lung. Both CD1a Langerhans-like dendritic cells (subepithelial and BAL) and myeloid dendritic cells are selectively recruited into the airways [120–124], and demonstrate increased expression of co-stimulatory markers (CD80, CD86) in smokers as compared to non-smokers [121].

In patients with COPD, all dendritic cell subsets (myeloid and plasmacytoid) demonstrated increased co-stimulatory molecule expression (CD80, CD83 and CD40) that correlated with COPD severity and was not explained by smoking alone [122]. Lung dendritic cells coordinate and co-localize with CD4+ T lymphocytes, and induce Th1 and Th17 responses [122, 125].

The increased number and advanced maturation state of both myeloid and plasmacytoid dendritic cells in the airways of patients with progressive GOLD stage COPD, suggests an enhanced antigen presenting capacity that develops with more severe disease. Whether this develops in response to bacterial colonization and more frequent antigen recognition, leads to self antigen presentation (anti-elastin and anti-endothelin) and progressive auto-immunity or whether these mature dendritic cells are engendering a state of tolerance (via CTLA-4 interaction with T lymphocytes) has not been defined.

Alterations in Adaptive Immune Responses to Infectious Pathogens in COPD

Alterations in Cellular Immunity

Both the innate and adaptive immune responses are altered in COPD and smoking. Antigen specific effector memory responses, of both cell mediated and humoral arms of the adaptive immune response, are required to effectively clear established infection. These effector memory responses respond more slowly than the innate immune response, but are highly specific for the pathogens involved.

The airways of patients with COPD have been noted to retain significant numbers of inflammatory cells of both the innate and adaptive immune responses. Of the adaptive immune response, effector lymphocytes of both CD4+ and CD8+ lineages have been documented in the airways, and subepithelial spaces, with a predominant CD8+ presence [118, 126, 127]. Numbers and cytolytic activity of the CD8+ cells increases substantially in patients with COPD and progressive GOLD stage disease [119, 126]. Elevated levels of interferon gamma have been found in both the BAL and intracellular staining of these lymphocytes, suggesting a Th1 or Tc1 effector phenotype.

Of the CD4+ lymphocytes found in the airways of patients with COPD, there have been two sub-types identified, both Th1 and Th17 cells [128–130]. Lung lymphocytes of the Th1 CD4+ lineage increase with severity of COPD and emphysema and secrete more interferon gamma than control smokers [131].

Th17 cells are a newly recognized CD4+ lymphocyte subset and regulate tissue inflammation by producing IL-17A and IL-17F [132]. Th17 cells regulate immunity to extracellular pathogens, but have also been associated with auto-immunity [132]. IL-17A and IL-17F act on the airway epithelial cells to induce anti-microbial peptides, G-CSF, GM-CSF and chemokine secretion. Recent data may support a geographically restricted role for the two forms of IL-17, with IL-17A localized to the inflammatory hematopoietic cells in the sub-epithelium of small airways, and IL-17F localized to the lymphoid follicles and epithelial cells [129].

Alterations in Humoral Immunity

B cells have been shown to be present in increased numbers in the large and small airways of patients with COPD, organized into lymphoid follicles around the airways and in the parenchyma of patients with COPD with advanced GOLD stage disease [133–137]. These follicles contain memory and naïve B cells, T cells, dendritic cells and follicular dendritic cells, which allow for T and B cell priming and clonal expansion [135, 136]. The B and T cells in the BALT are oligoclonal suggesting antigen specific immunity [134, 138]. The antigens involved in this response have not been identified, but leading candidates include microbial antigens, cigarette smoke-derived antigens, damage-associated antigens from apoptosis or extracellular matrix degradation and auto-antigens.

Despite recruitment of the appropriate effector cell populations, patients with advanced COPD are not able to effectively clear bacterial infection and bacterial colonization results. Whether the breakdown is solely at the level of the innate immune response, at the interface between the innate and adaptive immune response or due to derangements in the adaptive immune response alone, is not clear. It is likely that that with disease progression, there is progressive dysregulation of the immune response to invading pathogens, and downward spiral of inflammation, infection, altered immune response, inflammation and and tissue injury, that is amplified during periods of AECOPD.

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