# Innate Immune Responses and Chronic Obstructive Pulmonary Disease

## "Terminator" or "Terminator 2"?

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**Innate immune responses appear to be partially responsible for maintaining inflammation and tissue destruction in chronic obstructive pulmonary disease. In the early stages of the disease in smokers, the airways are bombarded with large quantities of particulate material, and activation of phagocytic cells results in the release of many of the mediators believed to remodel the airways. Ironically, failure of the innate immune defense system, either by inherited deficiency or as a result of chronic smoke inhalation, is likely to result in increased susceptibility to infectious disease and exacerbations of chronic obstructive pulmonary disease. It is well known that deficiencies in the production of collectins, pentraxins, and complement can lead to increased infections, and several studies indicate that deficiency in one or another innate defense component is associated with increased exacerbations. Corticosteroids reduce exacerbations in part because of their ability to boost the production of innate host-defense molecules. Therapeutic approaches that stimulate the generation of antimicrobial molecules in the lungs might be able to reduce disease exacerbations.**

**Keywords:** acute phase responses; corticosteroids; exacerbations; inflammation; opsonins

Chronic exposure to cigarette smoke leads to an accumulation of symptoms in a subset of smokers. These symptoms include progressive loss of lung function, destruction of the airways and alveoli, and systemic manifestations that can include weight loss, fluid retention, osteopenia, and depression. Although the pathogenic mechanisms of the loss of lung function are still debated, it is widely believed that persistent inflammation leads to loss of alveoli, secretion of copious quantities of mucus, and mucociliary dysfunction. Of particular relevance to the progression of chronic obstructive pulmonary disease (COPD) is the occurrence of exacerbations during which severe compromise of lung function is associated with infection by viruses or bacteria (1, 2). Disease severity is correlated with frequency of such exacerbations, and the occurrence of exacerbations worsens the course of COPD. Although there is no consensus as to whether patients with COPD have increased susceptibility to viral infection, most evidence suggests that they are more susceptible to bacterial infections in the airways. Whether or not patients with COPD have increased susceptibility to airway infections, it is clear that the consequences of such infections, which are usually minor in normal individuals, are often severe in patients with COPD and can include life-threatening loss of lung function.

Currently available therapeutic approaches to the management of COPD and new strategies and opportunities for development of improved pharmacologic agents for COPD have been well reviewed recently (3–5). This article concentrates on the role that innate immune responses may play in the pathogenesis of COPD, particularly in resistance to infection.

After a brief review of COPD drug development efforts, several underlying hypotheses are discussed. The first hypothesis is that COPD is a disease characterized by inflammation and tissue destruction, which are to a significant extent driven by the innate immune defense system. Innate immunity not only serves to detect and destroy pathogenic organisms but also is centrally involved in removing dead and dying host cells and foreign matter, whether particulate or antigenic, inert or threatening. In the early stages of development of COPD in smokers, the airways are bombarded with large quantities of particulate material. The activation of phagocytic cells, especially alveolar macrophages and recruited neutrophils, results in the release of many of the mediators believed to remodel (and destroy) the airways. Cigarette smoke is also known to increase the rate of apoptotic death of various airway cell types exposed to the gases and resulting solutes, further taxing the reticuloendothelial system or scavenging mechanisms of the lung.

The second hypothesis is that failure of the innate immune defense system as a result of inhalation of smoke is likely to result in increased susceptibility to infection by pathogenic and opportunistic organisms. In fact, development of COPD, which occurs in only one in five dedicated smokers, may be determined in part by underlying, and usually harmless, deficiencies in host defense. In advanced disease, preservation of intact innate host defenses may be essential for survival. This view is supported by several studies indicating that deficiency in one or another innate defense component is associated with increased exacerbations of COPD.

The third hypothesis is that corticosteroids, which have relatively modest antiinflammatory effects in COPD, reduce COPD exacerbations in part by improving the resistance of the airways to infection. This topic was recently reviewed and is discussed only briefly (6).

## CURRENT PHARMACOLOGIC MANAGEMENT OF COPD AND DRUGS UNDER DEVELOPMENT

At present, several classes of drugs are used to dilate and/or dry the airways (e.g., $\beta_2$-agonists, phosphodiesterase inhibitors, anticholinergic drugs). Inhaled and oral corticosteroids and antibiotics are used to manage COPD exacerbations, and corticosteroids are used to reduce the frequency of exacerbations. Unfortunately, smoking avoidance is impossible for the majority of smokers and, in advanced disease, no longer prevents disease progression. The effectiveness of all of these therapies is limited, and there is a need for new therapeutic approaches to manage COPD.

The majority of drugs under development for the treatment of COPD represent approaches to reversal or prevention of the inflammation, injury, and remodeling associated with the disease (3–5). The targeting of proteases (neutrophil elastase; cathepsin

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**TABLE 1. PATHOGEN-BINDING STRUCTURES INVOLVED IN INNATE IMMUNITY**

| |
|---|
| Toll-like receptors 1–12* |
| Nucleotide-binding oligomerization domain proteins 1, 2 |
| CD14 |
| LPS-binding protein* |
| Bacterial permeability–inducing protein |
| Short PLUNC 1–3 |
| Long PLUNC 1–4 |
| CC10* |
| α-Defensins 1–6 |
| β-Defensins 1–4 |
| Cathelicidins |
| Collectins* |
| Pentraxins* |
| Complement* |
| Serum amyloid A* |

*Definition of abbreviation*: PLUNC = palate, lung, and nasal epithelial clone.
* The expression of at least one family member has been shown to be increased by corticosteroids.

G, K, L, and D), matrix metalloproteases, reactive oxygen species (e.g., superoxide dismutase mimetics), cytokines (e.g., interleukin 1 [IL-1], tumor necrosis factor, IL-6, IL-12, granulocyte-macrophage colony–stimulating factor, IFNs), and chemokines involved in the recruitment and activation of neutrophils (e.g., CXCR2), macrophages (CCR1, CCR2, CCR4, and CCR5), dendritic cells (CCR6, CCR7), and $CD8^+$ T cells (CXCR3) has been proposed, because these cells and mediators are elevated in disease. Several signal transduction pathways could be targeted to attempt to achieve this, including pathways using nuclear factor–κB, p38, phosphodiesterase, phosphoinositide-3 kinase, JAK-STAT, and Ras. A challenge will be to inhibit the inflammatory pathways in COPD without excessive compromise of protective innate immune responses.

## INNATE HOST DEFENSE, INFLAMMATION, AND COPD

Several lines of evidence suggest that innate immune responses are important mediators of the host response in COPD and that compromise of innate immunity may ultimately occur in COPD and lead to susceptibility to frequent exacerbations of disease. Innate immune responses are quite complex and involve numerous molecular and cellular systems. Table 1 lists a number of host-defense molecules, most of which are known to be expressed in the airways; these molecules all bind directly to pathogens and/or particulates. Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain proteins (Nod1 and Nod2) are examples of triggering receptors that bind pathogens and particulates. When the TLRs encounter specific pathogen-associated structures, they initiate a signaling cascade that ultimately leads to the activation of nuclear factor–κB and other transcription factors, such as IFN regulatory factors (7). Activation of nuclear factor–κB and IFN regulatory factors triggers expression of numerous cytokines, chemokines, inflammatory enzymes, and host-defense molecules. Individual TLRs can recognize specific peptides, carbohydrates, or lipids from microbes. For example, TLR4, in association with LPS-binding protein (LBP), and CD14, can recognize bacterial endotoxins and trigger inflammation. Interestingly, several TLRs, including TLR4, can also recognize products of tissue damage, including intracellular proteins (e.g., heat shock proteins) and lipid aggregates that might result from cellular debris. Several of the molecules listed in Table 1 are capable of directly killing bacteria, in some cases by increasing their permeability. This includes the bacterial permeability–inducing protein and other members of a family of LPS-binding proteins, including LBP, cholesteryl ester transfer protein, phospholipid transfer protein, and palate, lung, and nasal epithelial clone, or PLUNC (8). Other direct pathogen-binding cytotoxic molecules include CC10, α- and β-defensins, serum amyloid A, and certain chemokines and cathelicidins. Three entries in Table 1, the collectins, pentraxins, and complement, are the focus of much of the remainder of this article. It should be emphasized that Table 1 is not comprehensive, and that it is likely that several of the other molecular families listed in the table are involved in either inflammation or resistance to infection in COPD. The focus here on the collectins, pentraxins, and complement reflects several features that these molecules generally have in common: they bind dead and dying host cells; they bind and kill bacteria; they trigger engulfment by phagocytic cells; and several of them can cause the aggregation of particulates, further enhancing phagocytosis. These characteristics seem to make these molecules particularly relevant in COPD.

## CLEARANCE OF PARTICULATES AND COMPLEMENT RECEPTORS

Several families of molecules have evolved to assist in the clearance of particulate material. The complement, collectin, and pentraxin families are all polymeric proteins that can to bind to a multitude of foreign surfaces and trigger clearance through phagocytosis (9–13). These proteins, and the phagocytic cells that have receptors for them, are likely to be of great importance in maintaining some degree of order in the smoker's lung. When phagocytic cells engulf apoptotic cells or innocuous particles, the normal process of internalization and phagosome–lysosome fusion can take place without further activation of the phagocytic cell. However, when pathogen structures (e.g., endotoxins, bacterial or viral DNA, double-stranded RNA) or products from necrotic cells (e.g., heat shock proteins, cell membrane material, DNA) are present, TLR activation can occur and trigger inflammatory responses (*see above*) as well as immune responses (7). At the extreme, large quantities of carbonaceous combustion products strain the clearance ability of alveolar macrophages. Charcoal particles have been used by immunologists for decades to paralyze the reticuloendothelial system via saturation of mechanisms of phagocytosis. Blockade of the reticuloendothelial system can lead to suppression of both innate and adaptive immune responses and increased numbers of macrophages (14). Smoking may thus simultaneously activate inflammatory pathways involved in removal of pathogens and compromise the ability of such pathways to be specifically directed to pathogens.

## SELECTED PHAGOCYTIC RECEPTORS

Numerous receptors can mediate phagocytosis, including a host of adhesion molecules, receptors for immunoglobulins, and receptors for complement split products. The specificity and heterogeneity of these receptors is beyond the scope of this article, which briefly discusses only one family of receptors for complement, collectins, and pentraxins. Receptors that bind to one or more of the members of these opsonin families include the complement receptor CR1, the collectin receptor (calreticulin, also known as cC1q-R/CR), and the C1q receptors C1q-Rp and gC1qR/p33 (15, 16). These receptors can recognize common structural elements on C1q, mannan-binding lectin (MBL), surfactant protein A (SP-A), and SP-D, and trigger internalization of particulates to which these molecules bind. There is evidence that Fcγ receptors may serve as receptors for the pentraxin C-reactive protein (CRP) (17). It is reasonable to expect that optimal clearance of pathogens and particulates requires adequate presence of opsonins and phagocytic cells bearing these

**TABLE 2. OPSONINS, INFECTIOUS DISEASE, AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

| Scavenger Family | Deficiency? | Deficiency Linked to Infectious Disease? | Deficiency Linked to COPD? |
|---|---|---|---|
| SP-A | Yes | Yes | Yes |
| SP-D | Yes | Yes | Yes |
| MBL | Yes | Yes | Yes |
| C1q | Yes | Yes | Yes |
| Intelectin* | ? | ? | ? |
| CRP | Yes | No | ? |
| SAP | ? | ? | ? |
| PTX-3 | ? | ? | ? |
| C1qrs | Yes | Yes | ? |
| C2 | Yes | Yes | ? |
| C4 | Yes | ? | ? |
| C3 | Yes | Yes | ? |
| C5–C9 | Yes | ? | ? |
| Alternate pathway | Yes | Yes | ? |

*Definiton of abbreviations*: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; MBL = mannan-binding lectin; PTX3 = pentraxin 3; SAP = serum amyloid P; SP = surfactant protein.

* Not strictly classified as a collectin.

receptors. This expectation is supported by studies showing that mice lacking any one of these proteins have compromised bacterial clearance (12).

## RELATIONSHIP BETWEEN COPD AND THE PRESENCE AND ACTIVITY OF OPSONINS

There are several ways in which complement, collectins, and pentraxins may influence the onset and outcomes in COPD. As discussed above, these pathways are capable of triggering an inflammatory response and may thereby contribute to the inflammation in COPD. In particular, activation of complement can lead to the production of C3a and C5a, both of which are potent chemoattractants for inflammatory cells. Recent studies by Marc and coworkers (18), using cytokine bead array assays, indicate that substantial formation of C3a and C5a occurs in both COPD and asthma. There was an inverse correlation between the quantities of C5a detected in the airways and the diffusing capacity of the lungs. These studies suggest that complement is activated in COPD and that the extent of activation is related to disease severity. A study by Kosmas and associates (19) showed a direct relationship between the levels of serum C4 and both emphysema score and frequency of respiratory infections. Strong correlations indicated that those subjects with the lowest levels of circulating complement had the highest rate of infections in the past 3 years and the worst emphysema scores. What is not clear from the study by Kosmas and colleagues is whether lower levels of C4 represent a risk factor for COPD and infections or whether the advancement of disease is characterized by progressive exhaustion of circulating complement. It is not unreasonable to expect that the constant bacterial growth in the airways in late-stage disease would increase the rate of utilization of complement and thereby compromise host defense.

It is well known that deficiencies in the production of members of the complement, collectin, and pentraxin families can lead to increased infections. Table 2 shows the members of these three families and indicates those for which deficiencies have been identified and those for which deficiencies are associated with infectious disease or COPD. The ability of the collectins SP-A and SP-D to assist in the destruction of bacteria is firmly established, as is the increased rate of infections in deficient individuals. Considerably less information is available regarding associations with COPD, however. A study by Guo and coworkers (20) has demonstrated a strong association between microsatellite-based alleles of SP-A and SP-D and COPD. The influence of the microsatellites tested on level of expression or functional activity of the surfactant proteins is unknown, but when both of the two markers tested were present, the odds ratio for COPD was considerably increased (24.3 compared with the instance in which both markers were absent). Another member of the collectin family, MBL, has been strongly implicated in infection and COPD exacerbations (21). Yang and others (21) studied COPD exacerbations in patients with MBL deficiency (a deficiency found in roughly 10% of the population) and found that the odds ratio for developing one or more infective exacerbations was 4.9 compared with patients with normal MBL levels. This study suggests that having low levels of at least one collectin, MBL, is a risk factor for infection and exacerbation of COPD. Studies by Noah and associates (22) in cystic fibrosis showed an inverse relationship between SP-A and SP-D expression and inflammation, and the researchers concluded that local deficiencies in SP-A and SP-D lead to bacterial growth and disease.

Although even less information is available concerning the role of pentraxins (CRP, serum amyloid P, and pentraxin 3) in COPD, these molecules are known to be important in host defense. Mouse knockout studies have shown that deficiency in pentraxin 3 plays an important role in the recognition and elimination of *Aspergillus fumigatus* and *Pseudomonas aeruginosa* (23). CRP is well known as an important antimicrobial defense molecule and has been used recently in COPD as a marker of systemic disease (24, 25). There are genotypes in which CRP levels are found to be relatively deficient, although the author is not aware of studies that have evaluated the influence of CRP deficiency on the incidence and outcome of COPD. Such studies would seem to be worthwhile (26, 27).

## SYSTEMIC AND LOCAL ACUTE PHASE RESPONSES

When infection exceeds the capacity of the local cells and mediators for containment and/or elimination of an organism in a tissue site, a systemic host response can ensue. This response involves release of numerous acute phase proteins from the liver in response to pathogen products (e.g., endotoxins) and cytokines (e.g., IL-1, tumor necrosis factor $\alpha$, and IL-6 generated locally and systemically). The liver produces complement, collectins, and pentraxins together with numerous other classes of molecules involved in host defense, inflammation, clotting, cardiovascular function, and so forth. Probably because of the presence of repeated and severe infections, COPD is characterized by elevations of acute phase proteins, including CRP (24, 25). Systemically, these molecules may contribute to disease, because they can have inflammatory actions caused by activation of leukocytes and activation of complement. Locally, however, the antimicrobial effects of opsonins are likely to be protective. There is a growing realization that local cells in the airways can produce collectins and acute phase proteins, including complement proteins and pentraxins (6, 9, 12, 22, 27). Components of this local acute phase response appear to be induced by cytokines and TLR ligands (6). A recent study showed that CRP is highly expressed by airway epithelium and that CRP in sputum and nasal lavage fluid is capable of killing bacteria (27). Future studies are needed to determine the relative importance of local and systemic acute phase responses in host defense in the airways. A newly recognized family of molecules, the intelectins, has been identified and may play a role similar to that of pentraxins and collectins in the airways (28).

## REGULATION OF INFLAMMATION AND INNATE IMMUNITY BY CORTICOSTEROIDS

It has been known for some time that corticosteroids can potentiate the acute phase response by enhancing hepatic production of acute phase reactants (29, 30). Growing evidence suggests that corticosteroids can exert a number of effects to potentiate innate immune response in the airways, probably including the local acute phase response (6). Pathogen-binding molecules whose expression is known to be enhanced by corticosteroids are indicated in Table 1. In COPD, corticosteroids are not particularly effective in altering the decline of lung function. This may in part reflect the fact that polymorphonuclear neutrophils and alveolar macrophages, which are important effector cells in COPD, are resistant to corticosteroids (31). Corticosteroids reduce exacerbations of COPD, however. This effect may result from both their antiinflammatory effects and their ability to boost the production of numerous innate host-defense molecules, including TLRs, secretory leukocyte protease inhibitor, CC10, CRP, serum amyloid A, C3, factor B, SP-A, and SP-D (6). Other effects of corticosteroids that promote host defense include decreased epithelial permeability, inhibition of bacterial adherence, inhibition of polymorphonuclear neutrophil apoptosis, and enhancement of macrophage phagocytosis and of IgA synthesis. It is important that strategies to be considered for development of new therapies for COPD similarly spare the innate immune responses while they suppress injury and/or inflammation. A recent study by Sin and colleagues (25) demonstrated that treatment with inhaled fluticasone reduces circulating levels of CRP. A likely explanation for this effect is that the antiinflammatory effects of the steroid, which would include inhibition of the generation of tumor necrosis factor $\alpha$, IL-1, and IL-6 in the lungs, would reduce the stimulus responsible for activating production of CRP by the liver (Figure 1). It would be of interest to determine the influence of inhaled corticosteroids on levels of CRP and other opsonins in the airways.

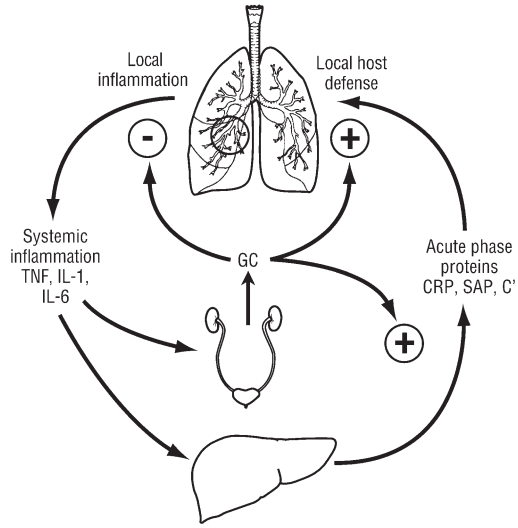


***Figure 1.*** Systemic inflammation and local host defense in the lungs. A complex relationship exists between local host-defense responses, systemic host-defense responses (including elevation of circulating acute phase proteins), local inflammation, and systemic inflammation (mediated in part by elevated levels of inflammatory cytokines in the circulation). Corticosteroids (GC) are generally effective antiinflammatory drugs but have the characteristic that they enhance some innate host defenses (e.g., systemic expression of acute phase proteins and expression of several classes of innate immune effecter molecules locally). Because GC can suppress the release of cytokines that stimulate the acute phase response (interleukin [IL]-1, tumor necrosis $\alpha$ [TNF-$\alpha$], IL-6), they often reduce levels of acute phase proteins despite having a stimulatory effect on hepatic production. CRP = C-reactive protein; SAP = serum amyloid P; C′ = complement.

## TOWARD THE FUTURE

New insight has been gained into the pathogenesis of COPD from recent studies by Hogg and coworkers (32), which show that the most important pathologic feature associated with loss of airway function is the appearance of large lymphoid follicles that compromise airway patency. Strategies to inhibit the proliferation and/or recruitment of B cells should be considered (e.g., inhibiting adhesion, inhibiting chemokine expression or action, inhibiting B-cell proliferation, or inducing B-cell apoptosis). Hogg and coworkers have suggested that repeated infection may lead to the formation of these aggregates. In related studies, Pilette and coworkers (33) showed that the lungs of patients with COPD have a deficiency of polymeric immunoglobulin receptor, the transport receptor for IgA, associated with large reductions of IgA-positive cells. If these studies are to be in agreement, then the B lymphocytes observed by Hogg and coworkers may express an immunoglobulin isotype other than IgA.

If innate immune responses are compromised in COPD, they may allow repeated infections, necessitating the generation of adaptive immune responses that could include large quantities of B lymphocytes. It is imperative that more research be performed to better understand the signaling mechanisms for innate immune responses and the nature of any deficiencies in innate immunity associated with COPD. In particular, approaches that stimulate the generation of host-defense effector (i.e., antimicrobial) molecules in the lungs could possibly have the beneficial effect of reducing disease exacerbations. At the very least, an improved understanding of local innate defenses will facilitate development of selective antiinflammatory approaches that do not compromise protective innate immune responses (34, 35).

Several important issues in the pathogenesis of COPD related to the susceptibility of patients with COPD to colonization of the airways with microorganisms, and their risk of exacerbations induced by infections will need to be resolved before choosing treatment-appropriate strategies. Some remaining questions include the following:

- If COPD results from chronic innate immune activation, will disruption of these processes reduce recruitment of macrophages and polymorphonuclear neutrophils? Targets include complement components, activating enzymes, and receptors.
- What is the extent of paralysis of innate immune mechanisms in early and advanced COPD?
- Are deficiencies in innate immune effectors important determinants of susceptibility to development of COPD? Is there important ethnic variability in expression of effectors relevant to COPD? Will blockers impair innate immunity and accelerate disease progression?
- Do corticosteroids reduce exacerbations by inhibiting inflammation or by enhancing innate defenses (e.g., decreased epithelial permeability, decreased bacterial binding, increased opsonin expression, increased TLR expression)?
- Is the late lymphoproliferative phase of COPD attributable to the collapse of innate immunity? Are the T and B cells monoclonal, polyclonal, or V$\beta$-skewed?
- Will inhibiting proliferation of T and B cells slow or prevent the late lymphoproliferative phase of the disease?

## CONCLUSIONS

Innate immune responses may be partially responsible for maintaining the inflammatory processes that lead to loss of alveoli, chronic bronchitis, degradation of matrix components, and tissue remodeling in COPD. Ironically, it may well be a loss of innate immune responses, either by inherited deficiency or through exhaustion of the responses from repeated insult, that ultimately leads to increased susceptibility to infectious disease and exacerbations. The contrast between the injurious and protective effects of the innate immune system can be likened to the different missions of the character played by Arnold Schwarzenegger in the movies *The Terminator* and *Terminator 2*. Early in the disease process, innate immune responses may play a major destructive role (as the cyborg does in *TheTerminator*); however, something like the cyborg's switch to the role of protector in *Terminator 2*, maintenance of innate immunity may be required for survival late in the disease process.

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