

Mechanisms of airway inflammation in cystic fibrosis

Döring G. Mechanisms of airway inflammation in cystic fibrosis.
Pediatr Allergy Immunol 1996; 7 (suppl 9): 63–66. © Munksgaard 1996.

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Key words: cystic fibrosis; children; airway inflam-
mation; lung infection; phagocytosis; cytokines

Bacterial lung colonization

Although the primary genetic defect has been detected in cystic fibrosis (CF) in 1989 (1) and lung inflammation in CF has been described for several decades, we still know very little about how mutations in the CF transmembrane conductance regulator gene are related to infection and inflammation. Two major hypotheses which recall the paradox of the hen and the egg (Fig. 1) are currently discussed. The classic conception is that the primary genetic defect causes abnormal intracellular chloride retention and increased sodium reabsorption leading to abnormal thick secretions in the airways. Viscous secretions could impair the mucociliary clearance and thus enable opportunistic pathogens such as *Staphylococcus aureus* or *Pseudomonas aeruginosa* to colonize the CF airways. Hence, the metabolic defect leads to lung infection in a noninflamed lung. As a consequence of infection, inflammation will be triggered and since the bacteria persist, inflammation becomes chronic and causes long-term lung destruction.

Based on histological and immunological investigations in CF patients, a second hypothesis was recently offered which implies that lung inflammation precedes lung infection in CF. This hypothesis is supported by findings which show that obstructive mucous plugging and epithelial metaplasia occur already in patients under four months of age (2). Furthermore, activated neutrophils which release lysosomal enzymes as well as cytokines which trigger neutrophil chemotaxis (3) are present in bronchoalveolar lavage samples of very young CF children without any trace of bacteria. Since bacterial clearance is normally reduced when inflammation is enhanced (4, 5), the consequences of continuous in-

flammation due to the primary gene defect could well result in facilitated colonization of the CF airways.

Inflammation occurs very early in life in CF patients and immature neutrophils may not be able to protect the airways sufficiently. Studies in human newborns have shown that neutrophils express reduced C3bi receptors on their surfaces and exhibit decreased chemotaxis which remains markedly depressed through the age of 2 (6). When groups of 12 DBA/2J cri mice aged 10 and 35 days were each challenged with an aerosol containing 10^6 colony forming units of the *P. aeruginosa* strain PAO1, clearance of the bacterial organisms from the airways was significantly lower in the younger animals compared to the older animal group. Correspondingly, neutrophil numbers were significantly higher in older animals compared to younger animals (7). Taking together, several mechanisms including abnormal mucus secretion, impaired mucociliary clearance, focal obstruction, lung inflammation and immature neutrophil functions may act together and cause the increased colonization and reduced clearance of microorganisms in the CF lungs.

Host response

A vigorous host response is seen in CF patients after onset of *P. aeruginosa* infection, characterized by a rapid production of antibody titers to a large number of *P. aeruginosa* antigens and the formation of immune complexes in the airways (8). These immune complexes are thought to play an important role in the immunopathology of CF and, thus, high antibody titers and immune complex levels correlate with poor clinical status. Despite this response, the bacteria persist. In the case of *P. aeruginosa*, a phe-

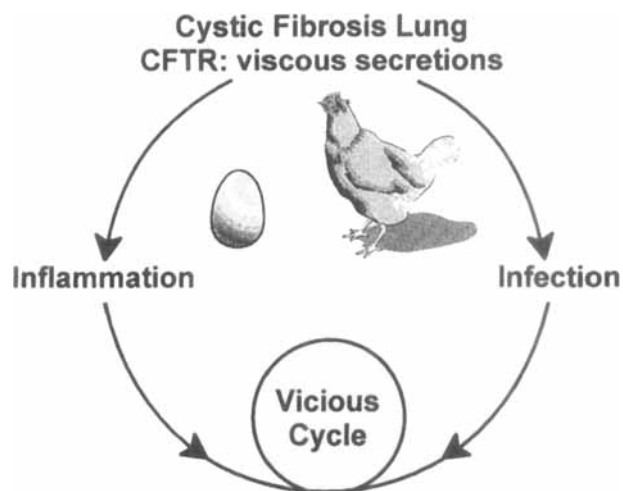


Fig. 1. Two mechanistic conceptions leading to a vicious cycle of inflammation in cystic fibrosis patients.

notypical switch to a mucoid growth in macrocolonies (9, 10), impairing successful phagocytosis, is thought to be the most important persistence mechanism. The chronic nature of the bacterial infection leads to the functional impairment of the local inflammatory response by factors derived largely from the inflammatory response itself rather than bacterial products. This, in turn, contributes to the chronicity of bacterial infection.

Neutrophils are the predominant phagocytic cells in bacterial lung infection in CF patients which are attracted from the bloodstream to the site of infection by various chemoattractants (11–13) including IL-8. Once the neutrophil has reached the airways it will not return to the circulation. Apparently, neutrophil apoptosis (programmed cell death), a mechanism by which apoptotic neutrophils are recognised and engulfed by macrophages without release of their contents (14) does not function sufficiently and high levels of lysosomal enzymes such as myeloperoxidase, elastase, collagenase and cathepsin G are released into the surrounding of the cells (8). The reason why such high levels of free neutrophil elastase are present in the inflamed CF airways is the local inactivation of about 90% of endogenous α_1 -proteinase inhibitor by neutrophil elastase (15).

Neutrophil proteinases

Neutrophil elastase plays a major role in the pathophysiology of chronic inflammation in CF (reviewed in 8) by cleaving immunoglobulins, cell receptors and complement components, thus having an important impact on opsonophagocytosis. It also stimulates airway gland secretion and cleaves lung elastin. When the balance between proteinases and proteinase inhibitors is disturbed, free host protein-

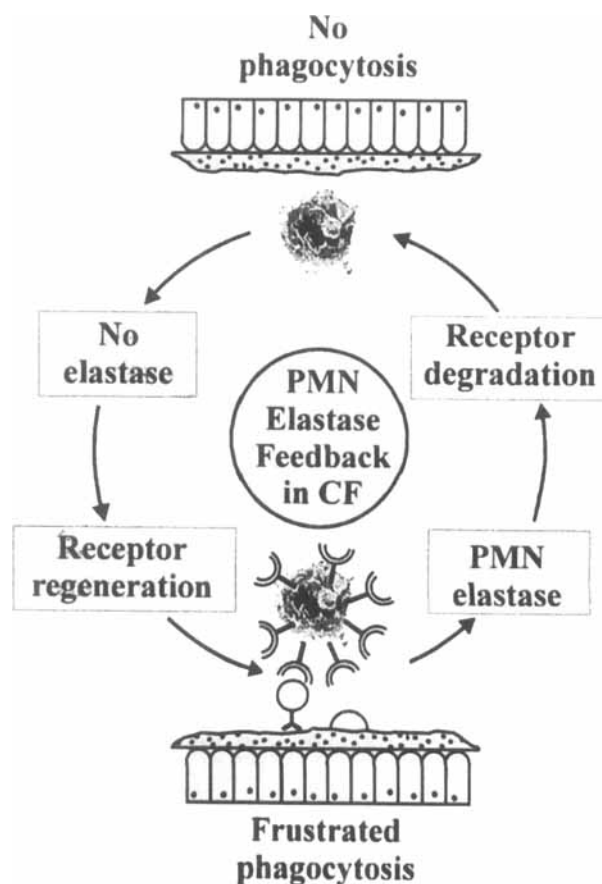


Fig. 2. Negative feedback mechanism of neutrophil elastase release and neutrophil stimulation.

ases may damage epithelial cells by cleaving fibronectin or cilia and leading to enhanced *P. aeruginosa* adhesion *in vitro* or *in vivo*.

Once neutrophil elastase activity in the CF airways has reached a certain level, the enzyme controls in a negative feedback mechanism its own release (8, 16), since neutrophils entering the airway lumen from the tissues, cannot be stimulated due to the cleavage of the complement receptor 1 (17), complement components (18), immunoglobulins and immune complexes (19) (Fig. 2). Such an immunosuppressive effect of neutrophil elastase was also demonstrated on T lymphocytes present in the airway lumen of CF patients (20).

Reactive oxygen species

Neutrophils respond to stimulation with a burst of oxygen consumption and the production of reactive oxygen species such as superoxide anion, hydrogen peroxide, hydroxyl radical and singlet oxygen. As with lysosomal proteinases, these species are not only released into the phagolysosome but also outside of the phagocyte, where they may be toxic to the host. It is not yet certain whether toxic oxygen

metabolites produced by stimulated PMN also contribute to lung injury in CF, as has been suggested in other airway diseases. However, indirect evidence may support this hypothesis; high sputum concentrations of extracellular myeloperoxidase (MPO), a PMN-derived enzyme which transforms hydrogen peroxide (H_2O_2) into highly reactive oxygen metabolites, have been detected in CF patients (15, 21–23), and lung function has been inversely correlated with MPO levels (21–23). The presence of endogenous scavengers such as superoxide dismutase, which dismutates superoxide anion to hydrogen peroxide, or catalase, which changes hydrogen peroxide to water and oxygen, has not been investigated in CF sputum or bronchoalveolar lavage samples until now.

Nevertheless, the amount of tissue damage and degree of protein inactivation by oxidative attack in CF and other disorders has not been clearly defined. Of considerable interest is whether α_1 -proteinase inhibitor undergoes oxidative inactivation. A number of studies have shown that Met³⁵⁸, an important residue of the serine proteinase binding site, is particularly susceptible to oxidative attack, the result being a substantial reduction in the ability of the inhibitor to bind neutrophil elastase (24).

Cytokines

Due to continuous inflammation cytokines such as interleukin (IL)-1 β , tumor necrosis factor α (25, 26), IL-8 (12, 26) and IL-6 (26) have been detected in CF sputum or bronchoalveolar lavage samples. Cytokine levels are higher in CF patients infected with *P. aeruginosa* than in noninfected patients (25). Interestingly, CF bronchial epithelial cells contained much less IL-10, a cytokine which decreases inflammatory responses and T-cell stimulation, than those from normal healthy individuals (27).

Anti-inflammatory therapy

The importance of host factors, especially the neutrophil with its lysosomal proteinases, in the progressive pathological processes in the respiratory tract in CF patients has led to the current approach of combining anti-inflammatory therapy with effective antibiotic treatment, including steroids (28), nonsteroidal anti-inflammatory drugs such as ibuprofen (29) and proteinase inhibitors (30, 31).

Conclusion

Chronic airway inflammation is a consistent finding in patients with the hereditary disease cystic fibrosis (CF). The consequences of chronic inflammation are decreasing lung function and premature death of

CF patients. The mechanisms leading to inflammation and/or infection with opportunistic pathogens including *Pseudomonas aeruginosa* in the immuno-competent CF patients are complex and far from being understood. Neutrophils are the predominant phagocytic cells and released lysosomal enzymes and the formation of reactive oxygen species during neutrophil activation is thought to be mainly responsible for tissue destruction and impairment of host defense mechanisms. Besides a proteinase-antiproteinase imbalance also the balance between pro-inflammatory cytokines and cytokines which downregulate inflammation in the airways of infected CF patients seems to be disturbed. The importance of host factors in the progressive pathological processes in the respiratory tract in CF patients has led to the approach of combining anti-inflammatory therapy with effective antibiotic treatment.

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