Eur Respir J 2001; 17: 4–5
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

EDITORIAL

Inflammation and infection in cystic fibrosis - hen or egg?

N. Høiby

The noninflammatory defence of the lungs consists of: 1) the primary noninflammatory, nonspecific defence mechanisms, such as the mucociliary escalator, coughing, alveolar macrophages, defensins and surfactant; and 2) the secondary noninflammatory, specific defence mechanisms, such as secretory immunoglobulin A (S-IgA) [1]. The action of these defence mechanisms is silent and very effective in normal subjects, and their activity does not give rise to any symptoms. No tissue damage is mediated through these defence mechanisms. Congenital defects of the primary noninflammatory defence mechanisms comprise cystic fibrosis (CF) (mucus) [2] and ciliary dyskinesia syndrome (cilia). These defects lead to secondary acute or chronic bacterial infections and recruitment of the primary inflammatory defence mechanisms of the lungs, such as polymorphonuclear (PMN) leukocytes, and the secondary inflammatory defence mechanisms of the lungs, such as immunoglobulin G (IgG). The activity of the inflammatory defence mechanisms may lead to successful killing of the offending pathogens, but in addition may give rise to local and systemic symptoms of inflammation such as fever, tissue damage and impaired function. If the infection is not eradicated (persistent or chronic infection) then immunopathological tissue lesions occur, such as immune complex mediated tissue damage [3]. Once the respiratory tract infections persist, most of the viscosity of sputum in CF is due to deoxyribonucleic acid (DNA) from the PMNs [4] as a consequence of the chronic inflammatory response.

When the CF gene was found in 1989 and its product, the cystic fibrosis transmembrane conductance regulator (CFTR) protein, was identified as a chloride channel [5], a search for its pathogenetic involvement in the recurrent and chronic lung infections began. The altered, dehydrated, thick mucus (mucoviscidosis) had traditionally been thought to be the reason why CF patients suffer from recurrent and chronic respiratory infections [6, 7]. Additional explanations have, however, been suggested since the discovery of the CFTR protein: 1) increased sulphation of mucus glycoproteins due to defective acidification of intracellular organelles [8, 9]; 2) defective function of human β-defensin-1 in the fluids of the lower respiratory tract due to the high NaCl concentration in the airway fluid of CF patients [10]; and 3) defective CFTR-mediated uptake of *Pseudomonas aeruginosa* from the respiratory tract [11]. The inflammation present in the lungs of CF patients was originally thought to be caused by infections, but the increased knowledge about the molecules which direct the migration of PMNs, such as adhesion molecules, chemokines, cytokines, complement split products and other chemotactic molecules [12], initiated new explanations. It was shown that an imbalance exsists between interleukin (IL)-8 and IL-10 in the lungs of CF patients in favour of IL-8, which could be responsible for the high concentration of PMNs in these patients [13]. In some CF infants diagnosed by neonatal screening, inflammation dominated by PMNs was present in bronchoalveolar lavage fluid without detectable microorganisms, whereas other noninfected infants did not differ from normal controls in that respect [14, 15].

The question of whether inflammation is present before microbial colonization and infection is addressed in the elegant study by SCHEID *et al.* [16] in this issue of the *European Respiratory Journal*. This involves *ex vivo* studies on nasal epithelial cells and human cell lines from CF patients and controls, as well as tissues from CF mice and control mice. They found no difference in basal IL-8 production or nuclear factor-κB (NF-κB) activation, or in stimulated production after adherence of equal numbers of *P. aeruginosa* bacteria to the CF cells, compared to controls. Their results, therefore, are in accordance with the hypotheses that inflammation in CF patients is triggered by microbial colonization and that inflammation is early, sustained and destructive. Their results are also in accordance with the clinical observation [17] that colonization is accomplished by an inflammatory response.

A consequence of inflammation is the release of proteases and oxygen radicals, which are the main mechanisms of tissue damage in CF [18, 19]. Another consequence of liberated oxygen radicals from PMNs is the induction of mutations in *P. aeruginosa* leading to the characteristic mucoid phenotype and biofilm formation in the lungs, which is a poor prognostic sign in CF [20].

Based on the concept of inflammation-mediated tissue damage, several clinical trials of the use of anti-inflammatory drugs in cystic fibrosis patients have been carried out. Side-effects develop too frequently when systemic prednisone is given [21]. Oral nonsteroid anti-inflammatory agents (ibuprofen, peroxicam) and inhaled budesonide have been shown to be effective in the maintenance of lung function without serious side-effects in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection, and are now used routinely in some cystic fibrosis centres [22–24]. Since inflammation is early and sustained, and leads to both mucoid

Dept of Clinical Microbiology 9301, Rigshospitalet, Juliane Maries Vej 22, DK-2100 Copenhagen, Denmark. Fax: 45 35398331.

convertion of *Pseudomonas aeruginosa* and tissue damage, it may be indicated to initiate clinical trials where early aggresive short-term anti-inflammatory treatment is given together with antibiotics as soon as the initial *Pseudomonas aeruginosa* colonization is diagnosed. The perspective of such trials may be that the initial *Pseudomonas aeruginosa* colonization never continues as chronic infection, which unfortunately is not the situation today in 20% of the patients in whom antibiotics are used alone [25].

References

1. Høiby N, Frederiksen B. Microbiology of cystic fibrosis. *In*: Hodson ME, Geddes D, eds. Cystic Fibrosis. 2nd edn. London, Arnold, 2000; pp. 83–107.
2. Koch C, Høiby N. Pathogenesis of cystic fibrosis. *Lancet* 1993; 341: 1065–1069.
3. Høiby N, Koch C. Maintenance treatment of chronic *Pseudomonas aeruginosa* infection in cystic fibrosis. *Thorax* 2000; 55: 349–350.
4. Shah PL, Scott SF, Knight RA, Marriott C, Ranasinha C, Hodson ME. *In vivo* effects of recombinant human DNase I on sputum in patients with cystic fibrosis. *Thorax* 1996; 51: 119–125.
5. Collins FS. Cystic fibrosis - molecular biology and therapeutic implications. *Science* 1992; 256: 774–779.
6. Boucher RC. Human airway ion transport. Part one. *Am J Respir Crit Care Med* 1994; 150: 271–281.
7. Boucher RC. Human airway ion transport. Part two. *Am J Respir Crit Care Med* 1994; 150: 581–593.
8. Barasch J, Al-Awqati Q. Defective acidification of the biosynthetic pathway in cystic fibrosis. *J Cell Sci* 1993; 17: 229–233.
9. Zhang YL, Doranz B, Yankaskas JR, Engelhardt JF. Genotypic analysis of respiratory mucous sulfation defects in cystic fibrosis. *J Clin Invest* 1995; 96: 2997–3004.
10. Goldman MJ, Anderson GM, Stolzenberg ED, Kari UP, Zasloff M, Wilson JM. Human beta-defensin-l is a salt-sensitive antibiotic in lung that is activated in cystic fibrosis. *Cell* 1997; 88: 553–560.
11. Pier GB, Grout M, Zaidi TS. Cystic fibrosis transmembrane conductance regulator is an epithelial cell receptor for clearance of *Pseudomonas aeruginosa* from the lung. *Proc Natl Acad Sci* 1997; 94: 12088–12093.
12. Adams D, Lloyd A. Chemokines: leucocyte recruitment and activation cytokines. *Lancet* 1997; 349: 490–495.
13. Berger M, Konstan M. Inflammation and anti-inflammatory therapy in CF. *Clin Microbiol Infect* 1999; 5: 63–64.
14. Khan TZ, Wagener JS, Bost T, Martinez J, Accurso FJ, Riches DWH. Early pulmonary inflammation in infants with cystic fibrosis. *Am J Respir Crit Care Med* 1995; 151: 1075–1082.
15. Armstrong DS, Grimwood K, Carzino R, Carlin JB, Olinsky A, Phelan PD. Lower respiratory infection and inflammation in infants with newly diagnosed cystic fibrosis. *BMJ* 1995; 310: 1571–1572.
16. Scheid P, Kempster L, Griesenbach U, *et al.* Inflammation in cystic fibrosis airways: relationship to increased bacterial adherence. *Eur Respir J* 2001; 17: 27–35.
17. Elborn JS, Cordon SM, Shale DJ. Host inflammatory responses to first isolation of *Pseudomonas aeruginosa* from sputum in cystic fibrosis. *Pediatr Pulmonol* 1993; 15: 287–291.
18. Goldstein W, Döring G. Lysosomal enzymes from polymorphonuclear leukocytes and proteinase inhibitors in patients with cystic fibrosis. *Am Rev Respir Dis* 1986; 134: 49–56.
19. Hull J, Vervaart P, Grimwood K, Phelan P. Pulmonary oxidative stress response in young children with cystic fibrosis. *Thorax* 1997; 52: 557–560.
20. Mathee K, Ciofu O, Sternberg C, *et al.* Mucoid conversion of *Pseudomonas aeruginosa* by hydrogen peroxide: a mechanism for virulence activation in the cystic fibrosis lung. *Microbiol* 1999; 145: 1349–1357.
21. Eigen H, Rosenstein BJ, Fitzsimmons S, *et al.* A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. *J Pediatr* 1995; 126: 515–523.
22. Konstan MW, Byard PJ, Hoppel CL, Davis PB. Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med* 1995; 332: 848–854.
23. Sordelli DO, Macri CN, Maillie AJ, Cerquetti MC. A preliminary study on the effect of anti-inflammatory treatment in cystic fibrosis patients with *Pseudomonas aeruginosa* lung infection. *Int J Immunopathol Pharmacol* 1994; 7: 109–117.
24. Bisgaard H, Pedersen SS, Nielsen KG, *et al.* Controlled trial of inhaled budesonide in patients with cystic fibrosis and chronic bronchopulmonary *Pseudomonas aeruginosa* infection. *Am J Respir Crit Care Med* 1997; 156: 1190–1196.
25. Frederiksen B, Koch C, Høiby N. Antibiotic treatment of initial colonization with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. *Pediatr Pulmonol* 1997; 23: 330–335.