Inflammation and infection in cystic fibrosis - hen or egg?

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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 exists 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 Schiødt 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 antiinflammatory 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, piroxicam) 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

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conversion of *Pseudomonas aeruginosa* and tissue damage, it may be indicated to initiate clinical trials where early aggressive 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