Cystic Fibrosis Lung Disease: Interplay of a Microbial Microcosm and Extremes of Inflammation

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In this issue of *IMAJ*, two articles discuss and review the roles of chronic airway infection [1] and inflammation [2] respectively in cystic fibrosis lung disease.

The thought-provoking views presented by Daniel Katznelson [1] embrace a topic of central importance in the pathophysiology of lung disease in CF. Airway infection and subsequent destruction of lung tissue is the cause of mortality in most patients with this fatal disease. The inability to eradicate pathogens entrapped within viscous mucus plugs and secreting biofilms, which limit access to phagocytes, are central to CF lung disease, and long-term oral, inhaled and intravenous antibiotics remain one of the mainstays of treatment [3].

While this commentary does not present new findings, it provides an important and novel perspective of great importance. The point of view presented is unusual and does not support the commonly held view that forms the basis of present management in cystic fibrosis centers. In particular, it contests the central focus on P*seudomonas aeruginosa* as the main 'culprit' with the resultant need to combat acquisition of infection with this organism by means of draconian measures to avoid cross-infection [4]. The latter opinion now dictates management of CF worldwide, including patient cohorting in clinics, cessation of patient summer camps and support groups, etc. The alternative view suggested by Katznelson [1] is far more holistic, wherein Pseudomonas, which proliferates most readily using conventional culture techniques may by no means be the main pathogen within the complex microenvironment of the CF airway with its multiplicity of microorganisms. Thus, the article has implications for the concept of disease, the practical issue of cross-infection and acquisition of flora within CF airways and, most importantly, the rationale for planning management and choice of antibiotic therapy – which is the mainstay of treatment in this disease.

The jury is still out on many of these issues, and the controversies remain [5,6], Notably, recent studies are beginning to support Katzenelson's view [7], including one study showing that antibiotic therapy guided by painstaking synergistic *in vitro* sensitivity studies of resistant Pseudomonas from patients' sputum did not improve outcomes compared to empiric therapy [8]. It is difficult to change preconceived ideas that have dictated care for so long. However, it cannot be ignored that the survival of CF patients once they acquire chronic Pseudomonas infection is significantly decreased [9]. Furthermore, as conceded by Katznelson, the recent reports of alarming epidemic strains of P*seudomonas aeruginosa* as well as B*urkholderia cepacia* would strongly support the need for patient cohorting and measures to avoid cross-infection [10].

Changing focus, the role of host response in determining the severity of CF lung disease has become a central issue in understanding pathogenesis as well as planning new therapeutic measures in recent years. The complex dysregulation of the inflammatory response and the main players in these inflammatory cascades are elegantly presented in the review of the immunopathophysiology of CF by Ruth Soferman in this issue of *IMAJ* [2].

Over two decades ago, the possibility was raised that this host response to infection rather than the infection per se may be central to CF lung destruction. Extreme neutrophilic inflammation is indeed the hallmark of CF lung disease [11]. An early trial of oral steroid therapy reduced deterioration of lung function but was stopped due to unacceptable side effects [12]. Similarly, a study of long-term ibuprofen slowed the progress of CF lung disease [13].

Recently the question was raised whether the hyperinflammatory state in CF is the "chicken or the egg," i.e., whether it is merely a response to the chronic airway infection or in fact directly related to the mutation in the CFTR protein. Supporting the former are bronchoalveolar lavage studies in young CF infants showing marked signs of inflammation clearly associated with infection [14]. However, as described by Soferman in this journal [2], *in vitro* culture of CF airway epithelial cells compared to stably CFTR-corrected cells, when exposed to tumor necrosis factor-alpha without an infectious stimulus, showed increased interleukin-8 secretion and up-regulation of intracellular signaling molecules and nuclear factor-kappa B, responsible for expression of multiple inflammatory mediators [15]. There is even evidence for a direct role of mutated CFTR in this process [16]. As a result of this cascade, large numbers of neutrophils (both dead and alive) release high levels of oxidants and neutrophil elastase, destroying airway walls and lung connective tissue [17].

The role of modifer genes effecting the CF phenotype is a

CF = cystic fibrosis
TNF = tumor necrosis factor

field of intensive study and has focused on polymorphisms in genes affecting lung inflammation, as detailed by Soferman [2]. The most significant to date appears to be the gene for TGF-β, important in lung repair and fibrosis [18].

Strategies to decrease CF lung inflammation are changing the approach to CF care today. Recently, inhaled corticosteroids have become very popular, although controlled multicenter trials are awaited. Long-term azithromycin has been successful clinically, and a large trial showed reduced pulmonary exacerbations and improved pulmonary function possibly due to immunomodulation [19]. Pulmozyme, part of CF standard-of-care today, breaks down extracellular DNA from apoptotic neutrophils, enhancing airway clearance and lung function and reducing pulmonary exacerbations with associated reduced elastase and IL-8 levels [20]. Modulation of cytokines and transcription factors could be a more targeted approach, although signaling pathway redundancy may prevent effectiveness.

In summary, awareness of the central role of an exaggerated inflammatory response in CF lung disease as presented in the review by Soferman in this issue of *IMAJ* [2] has changed much of the clinical approach to treatment and affords new hope for future therapies for this life-threatening disease. Infection with an ever-increasing multiplicity of organisms, as described by Katznelson [1], is probably still the major trigger of this inflammatory response, and choice of antibmicrobial therapy remains more of an art than a science for the CF clinician.

TGF-β = transforming growth factor-beta
IL = interleukin

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The meeting of two personalities is like the contact of two chemical substances: if there is any reaction, both are transformed

Carl Jung (1875-1961), Swiss psychiatrist and pioneer psychoanalyst who originated the concept of introvert and extrovert personalities and conducted valuable studies of mental diseases, including schizophrenia. He collaborated with Freud until their differences became irreconcilable.