Herpesviruses: a cofactor in the pathogenesis of idiopathic pulmonary fibrosis?

Peter Doran1 and Jim J. Egan2
1Department of Medicine and Therapeutics, Genome Resource Unit, and 2Advanced Lung Disease and Irish National Lung Transplant Program, Mater Misericordiae Hospital, St. Vincent’s University Hospital and Our Lady’s Hospital For Sick Children, Dublin Molecular Medicine Center, University College Dublin, Dublin, Ireland

Traditionally, idiopathic pulmonary fibrosis (IPF) has been seen as an inflammatory disease progressing to pulmonary fibrosis, and consequently, patients have been exposed to corticosteroid therapy. However, anti-inflammatory therapy has failed to have any meaningful impact on this condition. Recent histological studies have challenged the concept that inflammation is central to the pathogenesis of IPF (4). The studies demonstrated that the outcome was determined by the burden of fibroblastic foci, collections of immature fibroblasts, and not the extent of histological inflammation. Consequently, the emerging hypothesis underlying the pathogenesis of IPF is that repeated microscopic injury of alveolar epithelial cells results in dysregulated repair mediated by fibroblastic foci (9).

The source of epithelial cell injury has received little attention. It is probable that no single mechanism initiates the disease response in the lung; rather, a combination of injuries potentially contributes to the emergence of IPF. Endogenous herpesviruses may be an important source of injury. Although Epstein-Barr virus (EBV) normally infects the upper respiratory tract, it has also been shown to infect and replicate in the lower respiratory tract (6). Both EBV protein and DNA expression have been identified in lung tissue of patients with IPF (3, 10). In surgically acquired lung tissue, EBV glycoprotein 340/220 and viral capsid antigen viral proteins expressed during the lytic phase of EBV infection have been localized to alveolar epithelial cells (3). The putative role of EBV in the development of IPF has been expanded by findings that the expression of EBV latent membrane protein 1 in alveolar epithelial cells is associated with a poor prognosis in IPF patients (12). Further studies have suggested a pathogenic role for herpes viral infection by demonstrating clinical stability in two patients following oral antiviral therapy (11).

However, an association between EBV and IPF does not establish a causal relationship. The acquisition of human lung tissue to explore the proof of concept is clinically difficult because the majority of patients are unsuitable for lung biopsy. Therefore, animal models provide an opportunity to improve our understanding of the relationship between EBV and IPF.

Lok et al. (5) have demonstrated that murine γ-herpesvirus 68 (MHV68), which is biologically equivalent to human EBV, may act as a cofactor in the development of pulmonary fibrosis. BALB/c mice primed with MHV68 and injured with bleomycin, to which they are normally resistant, were seen to develop pulmonary fibrosis. In contrast, there was no evidence of pulmonary fibrosis in those mice exposed to MHV68 in isolation. This suggests that herpesvirus infection alone does not result in pulmonary fibrosis and that an exogenous injury may result in pulmonary fibrosis if the host has been primed with infection. The finding that this infection was not in itself sufficient to induce pulmonary fibrosis in an immunocompetent host emphasizes that the impact of the virus may be influenced by the local cellular environment.

The pathological hallmark of IPF is the deposition of extracellular matrix by way of enhanced matrix production or decreased matrix degradation. The deposition of extracellular matrix is propagated through inappropriate activation of both lung epithelial cells and fibroblasts. These cellular alterations are influenced by an imbalance between local mediators of pro- and antifibrotic activity. This imbalance has been demonstrated in the lungs of IPF patients, as evidenced by enhanced levels of T helper type 2 (Th2) cytokines over their antifibrotic Th1 counterparts (13). Th2 cytokines, such as IL-4 and IL-13, have been demonstrated to activate lung fibroblasts resulting in extracellular matrix deposition. Th1 cytokines, on the other hand, abrogate activation of fibroblasts in IPF. Thus it has been proposed that the predominance of Th2 over Th1 cytokines is a key event in the pathogenesis of IPF.

IFN-γ is a Th1 cytokine that has been implicated in the protective immune response to several herpesviruses. MHV68 is recognized as inducing elevated IFN-γ during the acute phase of infection, and low-level IFN-γ is associated with a recrudescence of MHV infection. After MHV68 infection, excessive collagen deposition and splenic atrophy have been observed in IFN-γR−/− mice. This would suggest a cytokine imbalance in favor of IL-4, IL-1β, and transforming growth factor (TGF)-β1. Consequently, Ebrahimi et al. (1) studied the impact of MHV68 infection in IFN-γR−/− mice, and they observed the development of pulmonary fibrosis in animals at 14 days following infection.

A novel extension of these observations is the report by Mora et al., one of the current articles in focus (Ref. 7, see p. L711 in this issue), in which they explore the interplay between viral infection and cytokine imbalance. Infection of both wild-type and IFN-γR-deficient mice resulted in the establishment of acute lung inflammation, which resolved after 45 days in wild-type animals. This inflammation was more pronounced in receptor-deficient mice compared with their wild-type counterparts, reflecting the role of Th1 cytokines in the resolution of inflammation. Of note was the observation that the infection of receptor-deficient mice resulted in a much more persistent inflammatory response compared with the infection in wild-type animals. Furthermore, chronic infection of Th2-biased animals resulted in a pronounced fibrotic injury at day 45 when subpleural fibrosis was established as demonstrated by immunohistochemistry. This initial fibrosis had progressed to interstitial disease, with marked thickening of
the alveolar walls and pleura and enhanced collagen deposition. The propagation of the fibrotic response was evidenced by the appearance of myofibroblasts in areas of interstitial thickening. Immunolocalization indicates that the herpesvirus resides in alveolar epithelial cells in a fashion similar to that shown in human studies. The transdifferentiation of resident epithelial cells to a fibroblastic phenotype has been increasingly recognized as a source of fibroblasts. The observation of enhanced numbers of such cells in fibrotic areas further underpins the hypothesis that the synergistic activity of Th2 cytokine dominance and herpesvirus infection may result in the development of de novo fibrosis.

The finding of enhanced expression of the profibrotic cytokine TGF-β1 in IFN-γR-deficient infected mice may provide a common pathway for the evolution of fibrosis. TGF-β1 is a critical mediator of lung fibrosis in animal models. Although targeted overproduction of TGF-β1 is associated with an increase in pulmonary fibrosis, antagonizing its action is effective in preventing the fibrotic process. The finding of enhanced TGF-β1 expression in response to herpesvirus infection in the setting of INF-γ-deficient mice has clinical relevance.

The clinical relevance of the synergistic activity of both herpesvirus infection and local cytokine milieu of pulmonary fibrosis is in the context of emerging treatment of IPF. IFN-γ-1b replacement therapy is a potential therapeutic strategy for the treatment of IPF. It is believed that an imbalance between IFN-γ and TGF-β in IPF may contribute to the disease process. IFN-γ inhibits transcription of the TGF-β gene and inhibits TGF-β-induced gene expression through the induction of Smad7.

In an open randomized pilot study, patients receiving IFN-γ demonstrated a statistically significant improvement in total lung capacity over 1 year and a reduction in TGF-β expression in tissue obtained by serial transbronchial biopsy (14). The IPF patients were carefully selected on the basis of two criteria: first, a failure to respond to steroids over 1 year, and second, histological evidence of usual interstitial pneumonia acquired by open lung biopsy. An important factor to acknowledge is that the steroid-only control group that clearly had steroid unresponsive disease were persistently exposed to oral corticosteroids (10–50 mg), potentially worsening lung function by promoting of EBV replication (2). However, in the treatment group, the patients who responded to INF-γ therapy appeared to have impaired levels of INF-γ transcription.

This pilot study led to a large, randomized, double-blinded, placebo-controlled trial of IFN-γ-1b in 330 IPF patients (8). With death or disease progression as trial endpoints, there was no significant advantage to those patients receiving IFN-γ. Subgroup analysis showed a statistically significant advantage to patients with limited disease defined as a baseline forced vital capacity of >55%. In this setting, death occurred in 3.3% of the IFN-γ group compared with 13.0% of the placebo group. This suggests that INF-γ therapy in IPF patients with limited disease may confer a survival advantage. However, INF-γ therapy had no impact on estimates of lung function. The absence of a direct effect on lung function tests suggests that IFN-γ may be effective in ways other than having a direct antifibrotic effect. Restoring the Th1-Th2 balance and protecting against herpesvirus-mediated respiratory dec ompensation may be clinically relevant. Therefore, the characterization of IPF patients in terms of physiological status and IFN-γ deficiency/host predisposition may be critical in identifying patients most likely to benefit from IFN-γ therapy.

The data presented by Mora et al. (7) support the role of multiple pathogenic mediators acting synergistically, in the evolution of pulmonary fibrosis. Their study further provides evidence for a central role for herpesvirus infection in the initiation and progression of pulmonary fibrosis. Importantly, this study demonstrates that herpesvirus infection exploits the local cellular milieu capitalizing on the predisposition of the host. This may explain why viral infection may only impact on certain individuals. A challenge for the future would be to utilize an animal model to determine the impact of abolishing herpes infection in the setting of established pulmonary fibrosis. The current study by Mora et al. (7) coupled with ongoing determination of the molecular mechanisms of IPF will most certainly provide novel avenues for exploitation in our efforts to treat patients with this devastating disease.

DISCLOSURES

J. Egan is an investigator involved in a study of IFN-γ therapy sponsored by Intermune Incorporated (Brisbane, CA).

REFERENCES

10. Stewart JP, Egan JJ, Ross AJ, Kelly BG, Lok SS, Hasleton PS, and Woodcock AA. The detection of Epstein Barr virus DNA in lung tissue from patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 159: 1336–1341, 1999.