A big beautiful wall against infection

Humankind's greatest enemy has always been, and likely will always be, infection. The role of infection in idiopathic pulmonary fibrosis (IPF) is a poorly understood but the emergence of molecular techniques has renewed the focus on this area. Earlier studies of histological sections identified herpes virus DNA and haemophilus species in lung tissue.[1] More recently, studies have used high sensitivity and high throughput techniques to assess bacterial species in bronchoavleoar lavage (BAL). A large number of studies have now identified divergent bacterial species in the BAL and have associated them with mechanistic processes that give biological plausibility to the role of luminal infections promoting the development of IPF.[2–4]

It is therefore somewhat surprising that in the study by Kitsios and colleagues that used the same techniques to assess bacterial species in the lung tissue from 40 patients with IPF but found no evidence of infection.[5] Indeed levels of bacterial reads were so low that they were of the level of reagent controls, lower than negative controls and considerably lower than the samples from patients with cystic fibrosis who, as expected, had evidence of *Pseudomonas* and *Burkholderia* taxa.[5]

So how can the apparent paradox between an apparently sterile fibrotic lung associated with a rich diversity of bacteria in the airways of similar patients be explained? The luminal surface of the lungs and airways is easily colonised by a rich diversity of microbial species, especially when damaged, however the extent that infection may penetrate the periphery of the lung is not known. End-stage fibrotic lung characterised by dense fibrous matrix with varying amounts of cellularity and it is certainly possible that it may not be easily penetrable by microbes. However, if the alveolar space were infected one would expect it to be detectable within explanted lung tissue using the sensitive techniques employed. However, the procedures used to obtain BAL from human subjects do not permit investigators to determine the precise anatomical origin of the samples obtained. Traction change within the airways is a recognised consequence of IPF and it is therefore conceivable that the taxa observed in BAL studies are a consequence of IPF rather than its cause.

Genetic studies have identified that the airway epithelial gene MUC5B is the strongest genetic risk factor for the development of IPF,[6 7] but high levels of MUC5b in mice protect them against infection through altering macrophage function, in contrast mice lacking functional MUC5b proteins die of overwhelming pulmonary infection.[8] So is MUC5b 'walling-off' infection? Certainly the phenomenon of 'walling-off' infection is well described in abdominal infection and tuberculosis, and is thought to be a primitive response to prevent spread of infection through the bloodstream.[9 10] Could it be that the bronchial epithelium acts as both a first line of host defence in the airway and early warning system to the alveoli, promoting fibrosis to aid preventing infection? Certainly the observations that the distal fibrotic lung has evidence of fewer bacterial species that normal lung despite extensive airway colonisation would support this intriguing hypothesis.

Indeed it may be a somewhat cautionary tale that the result of this 'big beautiful wall' may actually be maintaining of a sterile lung, but the cost is the destruction of the organ it was meant to protect.

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