SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2009; 26; 83-84 © Mattioli 1885

Antioxidant therapy for idiopathic pulmonary fibrosis. A promising therapeutic prospect

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Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disorder of the lung of unknown etiology. Originally, it was speculated that IPF resulted from an unremitting inflammatory response to an exogenous insult, culminating in progressive fibrosis. By targeting the inflammatory response, the belief was that the fibrosis could be limited and/or prevented. However, a growing body of evidence suggests that IPF involves abnormal wound healing in response to multiple, microscopic sites of ongoing alveolar epithelial injury and activation associated with the formation of patchy fibroblast-myofibroblast foci, which evolve into fibrosis. From this new paradigm for the pathogenesis of IPF, new therapies should be directed at controlling alveolar epithelial injury and regulating fibroblast function rather than targeting the inflammatory response *per se* (1).

The lung is exposed to higher oxygen tension than other tissues. *Oxidative stress*, which can be defined as an increased exposure to oxidants and/or decreased antioxidant capacity, is widely recognized as a central feature of many diseases. There is increasing evidence that oxidant-mediated alveolar epithelial cell injury is a pathophysiologically relevant mechanism in pulmonary fibrosis. Glutathione is detected in high concentrations in the extracellular epithelial lining fluid of the lower respiratory tract of those without pulmonary diseases and could act as a first-line scavenger of toxic oxygen intermediates and protect against lung cell damage and injury. From bronchoalveolar lavage studies, IPF is characterized by a severe glutathione deficiency in the epithelial lining fluid of the lower respiratory tract, representing a diminished antioxidant screen at the epithelial surface (2, 3). Furthermore, these low glutathione levels seem to play a major role in the exaggerated lung fibroblast proliferation in IPF, and reestablishment of normal glutathione levels has normalized fibroblast metabolism *in vitro* (4). In this context, one rational approach to therapy for IPF may be to reestablish the antioxidant screen in the lower respiratory tract by the administration of exogenous glutathione.

N-acetylcysteine (NAC), a widely used mucolytic agent, effectively replenishes intracellular glutathione via its metabolism to the glutathione precursor, cysteine. NAC is not only a precursor of glutathione but also has the direct scavenging ability of oxygen free radicals. It has been reported to be effective in animal models of lung fibrosis (5, 6). Furthermore, NAC treatment was reported to be beneficial in IPF patients. A multicenter randomized trial, the IFIGENIA study, tested NAC combined with azathioprine and high-dose corticosteroids versus azathioprine and high-dose corticosteroids alone in a population with rigorously established IPF (7). There was a significant difference in lung function favoring the active treatment arm in this study.

Against this background, in this issue of the Journal, Cui et al. investigated the effect of NAC on the production of several cytokines, which could play an important role in the pathogenesis of IPF (8). They showed that NAC had the potential to downregulate the production of tumor necrosis factor (TNF)-α and their soluble receptors, as well as transforming growth factor (TGF)-β1 and lipopolysaccharide (LPS)-stimulated interleukin (IL)-1β, by alveolar macrophages recovered by bron-

choalveolar lavage in patients with IPF. Of these cytokines, TNF-α is among the early cytokines consistently found in animal models of pulmonary fibrosis to play a cardinal role in the pathogenesis of this disease. With respect to TGF-β, there is substantial evidence to implicate this multifaceted cytokine in the development of IPF. Of the three mammalian TGF-β isoforms, TGF-β1 plays a pivotal role in the regulation of lung fibrosis (9). As noted by these investigators, the importance of these cytokines in the pathogenesis of IPF need not be reiterated. IPF is a complex disease. However, limitations of the model whereby individual mediators of fibrosis or signal pathways were linked to fibrogenesis have been shown by disappointing trials of therapy targeting individual disease pathways. In this context, the investigational value of the study by Cui et al. includes the following points. These are that the antioxidant pathway may influence several cytokines, and that NAC, which has not only anti-fibrotic but also anti-inflammatory effects, down regulates this cytokine network. As stated by Maher et al, IPF develops as a consequence of abnormalities occurring in multiple biological pathways that affect inflammation and wound repair, so the most effective approach to treatment would be to target multiple fibrosis pathways simultaneously (10). Furthermore, individualization of treatment on the basis of each patient's predominant pathogenetic pathway may become possible as a deeper understanding of the balance of abnormalities that result in pulmonary fibrosis is achieved. In fact, it is suggested that disease progression in IPF may be linked to functional polymorphisms such as TNF-α or TGF-β1 gene polymorphisms (11, 12).

Moreover, it is of importance that this study investigated the direct effect of NAC on the production of several cytokines using alveolar macrophages recovered by bronchoalveolar lavage in IPF patients. However, the concentrations of NAC used in these in vitro experiments would not be applicable to the clinical situation, as recognized by Cui et al. as a limitation of the study. After intravenous or oral application, NAC is quickly absorbed and undergoes rapid and extensive metabolism in the gut wall and liver, resulting in bioavailability of about 10% (13). In addition, in contrast to plasma levels, after oral or intravenous administration, only trace amounts of NAC can be expected on the epithelial lining at best (13). In the IFIGENIA study (7), NAC was given as 600-mg effervescent tablets three times daily, which was three to nine times the usual approved dose of acetylcysteine. From this viewpoint, our pilot study (14) is unique in that we investigated inhalation therapy with NAC to maximize drug delivery to the lower respiratory tract. The study by Cui A et al. (8) provides support that inhalation therapy using NAC may be a rational approach to deliver a pharmacologic dose to the lung in IPF. Inhalation therapy is superior to systemic therapies in many other lung diseases, and this is especially important where systemic administration would be toxic.

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