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Letter to the editor

ARDS in SARS: cytokine mediators and treatment implications

Dear Sirs,

We wish to draw the reader's attention to the possibility that the severe pulmonary failure in severe adult respiratory syndrome (SARS), associated with a mortality rate of 15–20%, may be secondary to overwhelming inflammatory responses precipitated by the Urbani SARS-coronavirus (SARS-CoV) infection [1] and may be amenable to cytokine-targeted therapy. Soon after the outbreak of the disease, Peiris et al. [2] described how 19 out of 50 SARS patients (38%) progressed, in a short time frame (mean of 8.3 days), to severe pulmonary disease. All the uncomplicated cases recovered, whereas 8 patients deteriorated and, within the short follow-up period, one died. On the other hand, monitoring of serum antibodies shows that seroconversion has occurred by about 10–12 days and, in most instances, the patient's immune defense is effectively intervening by around day 14. Therefore, from the onset of symptoms, 10–12 days is a critical window for active treatment.

Cumulative findings in SARS autopsy material (reference [1] and others) describe a spectrum of pulmonary pathology ranging from desquamation of pneumocytes into alveolar spaces with associated necrotic inflammatory debris, proteinaceous exudates and hyaline membrane formation, intra-alveolar and interstitial mononuclear cell infiltration, to accumulation of multinucleated syncytial cells and macrophages, followed by late-stage fibroblastic and mesenchymal proliferations. This pathological progression is very similar to that seen in acute respiratory distress syndrome (ARDS) induced by other causes.

A substantial body of evidence has shown that inflammatory cytokines play a central role in ARDS. Donnelly et al. [3] found significant levels of macrophage migration inhibitory factor (MIF) in the alveolar spaces of ARDS patients that could activate release of tumor necrosis factor alpha (TNFα) and interleukin 8 (IL-8). Levels of both TNFα and IL-8 were effectively attenuated by anti-MIF [3]. Several other reports have also demonstrated the dominant role of the MIF/NF-κB/TNFα cascade in ARDS, as schematically shown in Fig. 1.

There is early evidence of the role of cytokines in the physiopathology of SARS. Ng et al. [4] showed how, in the pediatric population, SARS patients have a markedly elevated level of circulating IL-1β levels, which may suggest the involvement of a caspase-1-dependent activation pathway. In this study, there was only mild elevation of other cytokines such as IL-6 or TNFα. The Chinese literature, based on a larger number of patients of different ages, highlights the importance of other interleukins such as IL-2, IL-10 and IL-12 [5], indicating the significant elevation of TNFα and IL-6 in late stages of the disease [6]. While these are systemic (not lung-specific) data and thus further experiments must be pursued to investigate the role of inflammatory cytokines in SARS, we propose that therapy targeting TNFα and interleukins should be considered. To be effective, treatment should probably be instituted early before the pathophysiological changes become overwhelming. This may also help to control other extra-pulmonary manifestations in SARS patients that may be cytokine-related, such as the reported intravascular coagulation [7].

There is in vivo [8] and in vitro [9,10] evidence that targeting the cytokines stated before may be of benefit for SARS patients. This may represent treatment with established, multi-purpose drugs such as corticosteroids and ribavirin [10]. New imidazole derivatives have been recently designed as potent anti TNFα and anti-IL-1 compounds [11]. A central aspect of this treatment may involve IL-1, both as a target for therapy [12] and as an indicator of disease progression [13]. Furthermore, a small but growing family of drugs has been shown to exhibit inhibitory effects against macrophage migration

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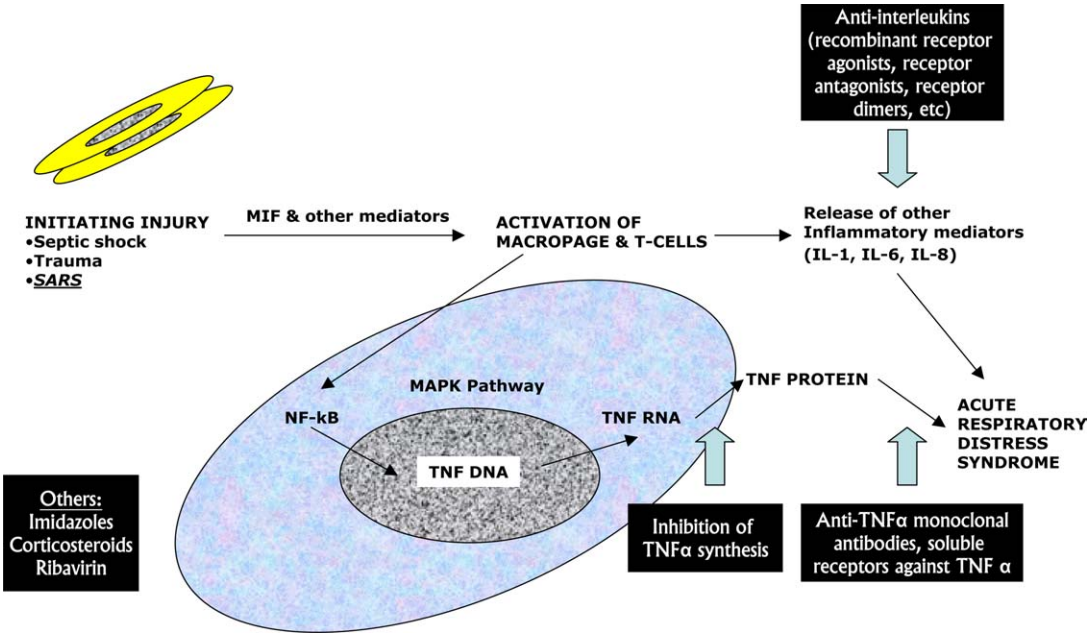

Fig. 1. Hypothetical model for the inflammatory cytokine basis of SARS/ARDS. Cascade of activation of key inflammatory mediators after lung parenchymal injury leading to ARDS is shown. The site of activity of several therapeutic agents is indicated. (MAPK, mitogen activated protein kinase; NF-κB, nuclear factor kappa B).

inhibitory factor (MIF) and TNFα [14]. Monoclonal antibodies and soluble receptors against TNFα, such as infliximab and etanercept, are commonly used in the treatment of chronic inflammatory conditions such as Crohn's disease and rheumatoid arthritis. CNI-149 [15], an inhibitor of TNF translation, has been shown to be effective in protecting animals from severe, acute inflammatory disorders. The promising results from studies with inhibitors of NF-κB should also be exploited [16]. A basic representation of the cytokine activation pathway in the ARDS lung and the possible areas of therapeutic targeting are indicated in Fig. 1.

In summary, the application of new and clinically tested anti-cytokines should be considered in managing the acute phase of SARS. Since there has not been a proper trial of anti-MIF/NF-κB/TNF agents in treating ARDS, we would argue that a future new SARS epidemic would present an excellent opportunity for the scientific and clinical community to do so.

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