The Role Played by Interleukin-10 in Cytokine and Chemokine Dysregulation during Secondary Pneumococcal Pneumonia after Influenza

To the Editor—In a recent article, Karlström et al. [1] postulated that treatment of secondary pneumococcal pneumonia with protein-synthesis-inhibitor antibiotics, either alone or in combination with a β-lactam, may result in better outcomes by lessening the inflammatory response engendered by lysis of the bacteria. We commend the authors for their work in demonstrating the effectiveness of clindamycin therapy, used either alone or in combination with ampicillin and azithromycin, in such a mouse model.

Karlström et al.’s suggestions are based on a general increase in levels of proinflammatory cytokines and chemokines—including interleukin (IL)–1α, tumor necrosis factor (TNF)–α, IL-6, IL-12p70, KC, and macrophage inflammatory protein (MIP)–1α as well as IL-1β and IL-12p40—in mice treated with ampicillin relative to those in mice treated with clindamycin and, statistically, significant was achieved only for TNF-α and KC. However, Karlström et al. did not determine the level of IL-10 in the lungs of mice after treatment in this model. In fact, IL-10 is an important mediator of the enhanced susceptibility to pneumococcal pneumonia after influenza virus infection. van der Sluijs et al. [2] demonstrated that 50-fold higher pulmonary levels of IL-10 were observed in mice that had recovered from influenza, compared with those in control mice. Treatment with an anti–IL-10 monoclonal antibody before bacterial inoculation resulted in reduced bacterial outgrowth and markedly reduced lethality during secondary bacterial pneumonia, compared with those in control mice. Moreover, influenza-induced expression of indoleamine 2,3-dioxygenase (IDO) could enhance IL-10 production and bacterial outgrowth during secondary pneumococcal pneumonia, and treatment with the IDO inhibitor 1-methyl-DL-tryptophan resulted in a 20-fold reduction in pneumococcal outgrowth after bacterial inoculation and a significant reduction in pulmonary levels of IL-10 and TNF-α [3]. Therefore, IL-10 plays a central role in maintaining a balance between protective immunity and the development of pathology during secondary pneumococcal pneumonia after influenza.

Pneumococcal pneumonia that occurs after influenza is generally considered difficult to treat. Its morbidity and mortality are thought to result from the associated complications caused by an exaggerated cytokine and chemokine response to the combined infection [4]. IL-10 is the master regulator of immunity to infection [5]. Maximal pneumococcal control by means of ampicillin does not necessarily lead to minimal disease, highlighting the essential immunoregulatory role played by IL-10 in limiting pathology. Therefore, to provide more-effective approaches to early therapy, we should consider IL-10 to be a critical mediator of the increased inflammatory responses associated with secondary pneumococcal pneumonia after influenza.

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References

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Reply to Cao et al.

To the Editor—We thank Cao et al. for their response [1] to our recent article [2] on the alternative treatment of secondary bacterial pneumonia after influenza. We agree that interleukin (IL)–10 is an important cytokine in the response to many infections. One poorly understood aspect of severe lung infections is the contribution made by the host inflammatory response to disease and death. In preclinical models, the inflammatory response is needed to control bacterial infections [3], but too much inflammation leads to lung damage and increased mortality [4]. An emerging concept in the study of severe infections is that a balance between anti- and proinflammatory activity is necessary for the resolution of infection and survival [5]. In our preclinical model of secondary pneumococcal pneumonia after influenza, an exaggerated and dysfunctional cytokine response occurs and contributes to mortality [6, 7]. Treatment of these infections with cell wall–active antibi-otics eliminates the infecting organisms, but the inflammatory burst that occurs after lysis of the bacteria can be fatal to the host [2, 8]. An ideal treatment regimen would eliminate bacterial pathogens while limiting inflammatory damage to the host, such that both morbidity and mortality would be reduced [9].

Indeed, in earlier studies using our mouse model, IL-10 levels were found to be strikingly elevated in mice with severe pneumonia [6]. In our recent study [2], IL-10 levels were similarly elevated (mean ± SD, 11,304 ± 2037 pg/mL; n = 5 mice) in the lungs of control mice infected with influenza virus followed 7 days later by Streptococcus pneumoniae. However, IL-10 levels did not change after treatment with either ampicillin (mean ± SD, 11,200 ± 1417 pg/mL; n = 8 mice) or clindamycin (mean ± SD, 11,643 ± 1473 pg/mL; n = 8 mice), as has been demonstrated for other proinflammatory cytokines and chemokines [2]. Therefore, although IL-10 may be important in the pathogenesis of severe lung infections, including those caused by bacterial superinfections after influenza, it is unlikely to be responsible for the difficulties inherent in the effective treatment of this disease.

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