Reply to Roux and Ricard

To the Editor—In response to Roux and Ricard [1], we wish to highlight a few facts regarding the use of granulocyte-macrophage colony-stimulating factor (GM-CSF) for preventing microbial pneumonia. Recent studies by us and others show that overexpression of GM-CSF in the lungs protects mice against secondary bacterial pneumonia following sublethal influenza A virus infection [2, 3]. We demonstrated that GM-CSF mediates protection against secondary bacterial pneumonia through enhanced function of alveolar macrophages and neutrophils. However, our previous study indicated that overexpression of pulmonary GM-CSF provides 100% protection against lethal influenza virus infection and that alveolar macrophages, not neutrophils, play a vital role in protection [4].

Bacterial pneumonia significantly contributes to complications and mortality during influenza virus infection [5–8] and ventilator-associated pneumonia (VAP). VAP is a common infectious disease in intensive care units, and Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus, and other bacterial species have been isolated from patients with VAP. Studies have shown an association between Candida albicans and P. aeruginosa in VAP [9], indicating that prior infections or insults to the lung increase the predisposition to secondary bacterial pneumonia. GM-CSF has been shown to reverse the immunosuppressive effect and restore the fungicidal activity against Aspergillus conidia in mice [10], and prophylactic use of GM-CSF in patients who are neutropenic or undergoing chemotherapy for acute myeloid leukemia led to significant reduction in the incidence of fatal fungal infections [10, 11]. Other studies have shown that GM-CSF increases neutrophil recruitment and reduces the fungal burden [11, 12] and that C. albicans impairs macrophage function, which enhances the susceptibility to P. aeruginosa pneumonia [13]. Richardson et al demonstrated that GM-CSF–treated human neutrophils significantly enhance the phagocytic ability and intracellular killing of C. albicans [14]. GM-CSF helps maturation of mononuclear phagocytic cells and alveolar macrophages and enhances the life span of phagocytic cells by inhibiting apoptosis [15–17]. Therefore, pulmonary GM-CSF would increase the phagocytic activity and the number of functional phagocytes in the lung that, in turn, will increase antimicrobial activity and facilitate lung maintenance and homeostasis.

The issue of lung damage and capacity of tissue repair and maintenance, as well as lung homeostasis, are of crucial importance in the propensity of a host to secondary bacterial infections [18]. GM-CSF protects lungs by increasing amphiregulin production, which promotes the growth of epithelial cells and the homeostasis of surfactant proteins [2, 19, 20]. We speculate that delivery of GM-CSF to the alveolar space likely protects against VAP and/or alleviates VAP complications by stimulating the pulmonary innate immune system and by increasing the capacity of lung repair, maintenance, and homeostasis.

From a practical standpoint, GM-CSF is approved by the Food and Drug Administration to treat neutropenia and bone marrow suppression, minimizing the need for extensive preclinical toxicity studies. Aerosolized ribavirin and pentamidine are used to treat pneumonia due to respiratory syncytial virus and Pneumocystis carinii, respectively, and aerosolized GM-CSF is also used to treat alveolar proteinosis [21–23], indicating the feasibility of delivering GM-CSF via the aerosol route.

Finally, GM-CSF stimulates innate immune responses, and, unlike the adaptive immune responses, innate immunity is not specific to a particular pathogen. Therefore, it is reasonable to believe that boosting the innate immune system of the lung by GM-CSF could act against multiple pathogens, including drug-resistant strains, and may remain effective against multiple infectious agents for many years.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Renuka Subramaniam and Homayoun Shams
Center for Pulmonary and Infectious Disease Control,
University of Texas Health Science Center at Tyler

References

Limitations of Staphylocinase as a Marker for Staphylococcus aureus Invasive Infections in Humans

TO THE EDITOR—We read with great interest the article by Kwiecinski et al [1] concerning the role of staphylocinase (Sak) in promoting the establishment of Staphylococcus aureus skin infections while decreasing disease severity. In their study, the authors used a combination of in vitro, ex vivo and in vivo approaches to show that the congenic strain secreting high levels of Sak (LS-1spa-sak) has a greater ability to invade skin and soft tissues than those secreting less or no Sak (LS-1 sak and LS-1EP, respectively). In addition, they clearly established that the activation of plasminogen by Sak does not promote systemic spread from skin infections but helps drainage of skin lesions over time. To assess the clinical significance of their findings, they compared sak gene frequency and Sak secretion between uncomplicated skin infections and invasive S. aureus infections. They noted that there was no difference between groups in the frequency of isolates secreting Sak, but that isolates from invasive infections secreted less Sak than isolates from uncomplicated infections, which suggests that high Sak secretion might predict a less invasive course of S. aureus infection in humans.

We attempted to confirm this hypothesis by analyzing unrelated and well-characterized clinical strains of Staphylococcus aureus collected throughout the whole French territory and sent to the National Reference Center for Staphylococci. Strains were isolated from patients with nasal carriage (n = 30), uncomplicated skin infection (n = 19), cellulitis (n = 9), community-acquired pneumonia (n = 30), bacteremia without endocarditis (n = 8), and infective endocarditis (modified Duke criteria, [2]) (n = 8). Seventy-seven strains (74%) harbored the sak gene and were identified by DNA microarray (Alere) [3], a higher prevalence than observed by Kwiecinski et al [46.6%] [2]. Consistent with their findings, we observed no significant difference when comparing the presence of the sak gene between invasive infections (including cellulitis, community-acquired pneumonia, bacteremia, and endocarditis) and noninvasive infections (uncomplicated skin infections; Figure 1A). We then determined the level of Sak secretion with a chromogenic assay, as described earlier by Kwiecinski et al [4].

Contrary to the report of Kwiecinski et al [1], our results did not show a significant difference in Sak secretion levels between invasive and noninvasive groups, or between infection isolates and nasal carriage isolates (Figure 1B). Because every strain from our collection had the genetic background (clonal complex [CC]) determined by DNA microarray, we could show that the frequency of sak gene depends on CC; for instance, most CC398 or CC15 isolates lack sak gene (Figure 1C). Moreover, the Sak production level was variable, depending on the CC (Figure 1D). This indicates that the level of Sak production in invasive versus noninvasive infection isolates strongly depends on sampling. Because the genetic background of the strain collection tested by Kwiecinski et al [1] is not available, it is difficult to assess whether the higher level of Sak secretion observed in invasive isolates could be explained by sampling bias. Therefore, their conclusion that higher Sak secretion might predict less invasive S. aureus infection in humans should be approached with caution. This limitation of their study does not preclude their conclusions concerning their in vitro and animal experiments, but it weakens the potential translation of their work into clinical settings. It is very likely that S. aureus invasiveness is a complex phenomenon involving multifactorial issues, wherein Sak is one player among many.


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Correspondence: Homayoun Shams, DVM, PhD, Center for Pulmonary and Infectious Disease Control, University of Texas Health Science Center at Tyler, 11937 US Hwy 271, Tyler, TX 75708-3154 (homayoun.shams@uthct.edu).

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