GM-CSF: a double dose of protection during pneumonia

Lee J. Quinton
Boston University School of Medicine, The Pulmonary Center, Boston, Massachusetts

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Invading microbes are rapidly recognized in the lower respiratory tract, resulting in robust and often dangerous immune responses. The degree to which innate immunity is launched and maintained largely depends on gene expression programs controlled by pattern recognition receptors and transcriptional hubs such as NF-κB (8, 12). Ultimately, these signals converge to promote innate immunity and, all too often, inflammatory injury. Yet it is teleologically fitting that these same programs encode tissue-protective factors as a means to offset potentially damaging consequences of inflammation. To serve both purposes might seem contradictory, but perhaps not. In this issue, Standiford et al. (13) provide a compelling contribution to an evolving body of evidence implicating granulocyte-macrophage colony-stimulating factor (GM-CSF) as one such gene product, one protective against both infection and lung injury.

GM-CSF is well appreciated for its effects on macrophage biology, surfactant homeostasis, and host defense in the lungs (15). Indeed, pharmacological blockade or genetic deletion of GM-CSF reduces multiple parameters of innate immunity in response to stimuli in the lungs, including gram-negative bacteria or LPS (1, 3). Here, the authors convincingly demonstrate that GM-CSF induction is TLR4 dependent and that it is sufficient to dramatically reduce epithelial cell death and acute lung injury in response to infection with Klebsiella pneumoniae.

By as early as 6 h after the K. pneumoniae challenge, TLR4-deficient mice had significantly higher bacterial burdens in the lungs. Although this may have been expected given the genotype, the approximate 10-fold increase in air space alumin content reflects a surprisingly profound lung injury, one typically correlating with and not against inflammatory signals downstream of TLR4 and other PRRs. These data were also associated with a significant increase in epithelial apoptosis. All too often this phenotype would be dismissed simply as a consequence of increased bacterial burden, which may indeed be the truth, but perhaps not the whole truth. As importantly acknowledged by the authors, this is not the first evidence that TLR4 signaling is protective in the context of acute lung injury. For instance, others have demonstrated that TLR signaling limits injury in response to noninfectious challenges such as bleomycin (6) and hyperoxia (16). Whether and how this possibility extends to lung infections has not been adequately considered, largely because of the challenge of distinguishing between the effects of infection and immunopathology. Results from the current work by Standiford et al. (13) suggest that, during bacterial pneumonia, 1) tissue protective effects of TLR4 exist beyond its influence on antibacterial host defense and 2) GM-CSF itself may serve as an inducible effector molecule responsible for damage control.

Although whole lung GM-CSF levels were only modestly (yet significantly) reduced in the absence of TLR4, protein expression in cultured primary epithelial cells from mutant mice was completely eliminated when stimulated with heat-killed K. pneumoniae. These data support a defect in GM-CSF within the alveolar microenvironment. Yet the gain-of-function studies reported in this communication are perhaps the most compelling. GM-CSF supplementation virtually abolished the effect of TLR4 deficiency on alveolar epithelial apoptosis in vitro and in vivo. Furthermore, GM-CSF treatment completely restored epithelial barrier integrity, as evidenced by air space albumin concentrations, while concomitantly reducing lung and blood bacterial burdens. Thus GM-CSF administration in this setting appears to have promoted both host defense and tissue protection, particularly at the level of alveolar epithelial cells.

These results coincide with a recent study in which prophylactic GM-CSF overexpression (via adenovirus) yielded remarkable improvements in survival and host defense during pneumococcal pneumonia (14). Although effects of GM-CSF on epithelial apoptosis were not explored in this setting, treatment dramatically increased macrophage survival and antibacterial function (14). Similar benefits of GM-CSF therapy have also been reported in mice challenged with influenza (5) and Pneumocystis murina (2). These effects have been identified in noninfectious circumstances as well. For example, overexpression of GM-CSF was shown to reduce epithelial apoptosis and improve barrier function during hyperoxia (10), again distinguishing the influence of this factor on host defense from its effect on tissue protection. Interestingly, Cakarova et al. (4) recently proposed an axis in which macrophage-derived TNF elicited GM-CSF production by alveolar epithelial cells, which in turn improved epithelial barrier function in response to LPS. Therefore, it is possible that TNF signaling coordinates with that from TLR4 to promote maximal GM-CSF expression in vivo.

Although this communication by Standiford et al. (13) sheds new light on GM-CSF biology during pneumonia, many questions remain unanswered, particularly with regard to the contributions of endogenous GM-CSF. It is unclear from these data whether the defect in TLR4-dependent GM-CSF is causally linked to apoptosis and injury. This is particularly notable because of the kinetics of GM-CSF expression, which was unchanged in mutant mice until 24 h, a time by which exaggerated injury was well underway. It is important to consider, however, that whole lung GM-CSF concentrations, as measured here, may not accurately reflect those at the alveolar surface. Lastly, the degree to which GM-CSF’s benefits translate to human therapy remains uncertain. GM-CSF is associated with improved outcome in patients with acute lung injury (7), and early clinical trials interrogating GM-CSF as a therapy suggested that it may improve respiratory function (11). However, a recent trial with a larger patient cohort showed no
significant benefit of GM-CSF delivery (9). As with so many emerging and even established medical approaches, the trick may be to match the right patients with the right therapy. Importantly, these results do not necessarily undermine the potential clinical utility of GM-CSF signaling during pneumonia, which may yet prove an indispensible prophylactic, prognostic, or even therapeutic agent in the right context. The exciting study in this issue of the Journal synergizes with multiple recent lines of evidence to implicate GM-CSF in the lungs as a critical signaling mediator with clinical potential relating to infectious lung injury.

REFERENCES


