Alveolar Macrophages during Inflammation: A Balancing Act

Sepsis is a systemic inflammatory syndrome caused by a dysregulation of host response to infection that can lead to multiple-organ dysfunction and death. Although advances in protocolized sepsis management have substantially decreased early mortality, sepsis survivors can still exhibit protracted clinical courses characterized by recurrent or persistent secondary infections and organ dysfunction (1). The contribution of the primary site of infection, pathogen specificity, and molecular mechanisms underlying this "persistent critical illness" phenotype following sepsis are incompletely understood (2). However, a growing body of literature supports a complex interplay of proinflammatory and immunosuppressive mechanisms causing functional reprogramming of innate and adaptive immune cell subsets to drive immunopathology (1, 3). Specifically, the loss of effector function and increased expression of inhibitory molecules by monocytes, macrophages, and T cells, coupled with decreased expression of activating major histocompatibility complex II molecules by antigen-presenting cells, are among the most prominent features of sepsis-induced immunosuppression (3). Long-lived alveolar macrophages (AM) exert myriad functions to maintain tissue integrity and orchestrate acute responses to lung inflammation, injury, and repair. These specialized phagocytes establish intercellular signaling pathways in the lung microenvironment to effectively clear pathogens and facilitate noninflammatory removal of apoptotic cells following pulmonary infection (4).

In this issue of the *Journal*, Llitjos and colleagues (pp. 689–701) report on a study that used a double-infection experimental model to investigate the contribution of primary sepsis etiology to susceptibility to secondary bacterial pneumonia (5). Notably, they found that mice with cecal ligation and puncture (CLP)–induced polymicrobial peritonitis exhibit worsened mortality and decreased bacterial clearance from secondary *Pseudomonas aeruginosa* (PA) compared with animals initially challenged with *Escherichia coli*–induced pneumonia. Lung-specific immune cell subset analysis throughout the course of primary infection revealed a sequential and significant increase in Ly6C^{hi} classical monocytes and AMs in the *E. coli* pneumonia group compared with the CLP-treated group, respectively. Measurement of the phagocytic and antigen-presenting capacity of AMs, combined with flow-cytometry analysis of activation and antiinflammatory markers and transcriptional profiling of AM following primary and secondary infection, led the authors to hypothesize that changes in AM numbers and function inform the divergent susceptibility to secondary lung PA infection. Functional analysis showed that post–*E. coli* pneumonia AMs exhibit increased expression of lipid metabolic processes compared with post-CLP AMs, whereas the latter downregulated genes are linked to innate immune response, antigen presentation, and cytokine signaling. AMs release prorepair lipid mediators to promote resolution of lung inflammation, and lipid metabolism is required for core AM functions, including efferocytosis.

These findings raise this question: How do macrophage ontogeny and exposure to distinct inflammatory injuries and pathogens modulate their tissue-specific function to initial and subsequent environmental challenges? During homeostatic conditions, tissue-resident AMs (TR-AMs) self-renew by local proliferation, but severe lung injury can deplete the TR-AM pool and lead to recruitment of bone marrow–derived monocytes that differentiate into monocyte-derived AMs (Mo-AMs) (6, 7). Multiple groups of investigators have shown how TR-AMs and Mo-AMs play distinct roles during the acute inflammatory response and resolution phase of lung injury (8, 9). Exposure to specific pathogens or insults induces changes in the functional programs of macrophages/monocytes to enhance host immune responses (priming or trained immunity) or dampen immunity to mitigate pathology (immune tolerance) in secondary challenges (10). Thus, the findings by Llitjos and colleagues raise important questions about which factors or mechanisms dictate the functional adaptability of AMs and bone marrow progenitors to different infectious insults, altering tissue integrity and physiology. Previously, investigators have shown that the inflamed lung microenvironment (following primary injury) plays a pivotal role in providing inductive signals to modulate the response of AM to a secondary challenge (11–14). Notably, the local environment differentially altered the gene-expression profiles of TR-AMs and Mo-AMs (11). A limitation of the study by Llitjos and colleagues is that these distinctive AM populations with unique specialized roles during inflammation were not separately analyzed. Future studies should leverage lineage-tracing systems to identify their adaptive functional changes during infectious challenges and their contribution to organ injury and repair. Moreover, spatially restricted, longitudinal analysis of transcriptional and epigenetic programs over the course of serial environmental challenges could uncover important intercellular signaling and molecular pathways between different AM populations and local progenitors driving lung injury and repair.

Regulatory T cells (Tregs) interact with cells of the innate and adaptive immune system to dampen pulmonary inflammation and promote its resolution (15). In a murine model of zymosan-induced peritonitis, a group of investigators showed that Treg-derived IL-13 promotes AM efferocytosis during resolution of inflammation (16). Interestingly, Llitjos and colleagues show that depletion of Tregs

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increased the total number of phagocytic AMs and improved PA clearance in post–CLP-treated animals, whereas post–*E. coli* mice exhibited impaired PA clearance and no change in the numbers of phagocytic AMs. It remains unclear from the data presented what molecular mechanisms are responsible for driving these cellular changes that affect disease susceptibility in their double-infection model. The type of pathogen, site of injury, and magnitude of inflammatory response have been shown to affect efferocytosis of pathogen-infected and sterile apoptotic cells in host defense (17). Moreover, there is increased recognition that reciprocal interactions between T cells and macrophages at mucosal sites are required to establish trained immunity and enhance host protection against new microbial infections (13). Hence, future studies should better dissect context-specific AM–T-cell interactions that could potentially be leveraged for the development of novel pharmacotherapies to manage patients with sepsis. ■

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